"Do as I say!" : parenting and the biology of child self-regulation

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Title: "Do as I say!" : parenting and the biology of child self-regulation
Issue Date: 2013-03-21

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Printed by Uitgeverij BOXPress
Cover design and layout by Studio Teekens

"Do as I say!"
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Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C. J. J. M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 21 maart 2013
klokke 13:45 uur

door

Rianne Kok

geboren te Zaanstad
in 1985

Promotiecommissie

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The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam. We gratefully acknowledge the contribution of general practitioners, hospitals, midwives and pharmacies in Rotterdam. The first phase of the Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development (ZonMw). The present study was supported by additional grants from the Netherlands Organization for Scientific Research, grant no. 452-04-306 (VIDI), grant no. 453-09-003 (VICI), grant no. 017.106.370 (VIDI), and NWO SPINOZA prize.

Contents

1

Introduction

Introduction

The development of self-regulation is one of the major challenges of a child's healthy and adaptive development (Colman, Hardy, Myesha, Raffaelli, & Crockett, 2006; McClelland & Cameron, 2011a). Unlike many other species, humans are not at the mercy of automatic, stimulus-response associations, but with the help of others develop the ability to inhibit dominant responses and actively select alternative behaviors (Conway & Stifter, 2012). Self-regulation develops over an extended period starting already in infancy (Bernier, Carlson, & Whipple, 2010), with a rapid developmental spurt in early childhood (Anderson, 2002), and further maturation in adolescence (Crone, 2009). Though children are innately inclined to strive for self-regulation (Bronson, 2000) and many intrinsic factors such as child temperament and neurological development are key to early self-regulation, extrinsic factors such as high quality interactions with caregivers are essential to nourish and channel self-regulatory development (Bronson, 2000; Fox & Calkins, 2003). In the current thesis, the contribution and interplay of parental and biological factors in the development of self-regulation in the preschool period are studied.

Self-regulation of behavior and emotions

It was long assumed that young children had little capacity to regulate their behavior and emotions. In the last decades, however, evidence accumulated that early indicators of self-regulation are already developing in the preschool years (Bernier et al., 2010; Eisenberg & Sulik, 2012). The foundation for self-regulation is laid in infancy. First, the regulation of autonomic arousal and sleep-wake cycles and primitive emotion and behavior regulation are developed (Calkins, Smith, Gill, & Johnson, 1998; Kopp, 1982). In this early period regulation is primarily reactive and externally regulated. During the toddler and preschool years, regulation becomes more proactive, planful, and conscious, and the locus of control of regulation moves from external to internal (Bronson, 2000; Kopp, 1982). At the end of the toddler period demands and expectations about self-regulation increase and it is expected that children are capable of basic self-regulation in behavioral, physiological, and emotional domains (Kopp, 1982). However, individual differences exist in the extent to which children demonstrate competent self-regulation, even in non-clinical populations (Calkins et al., 1998).

Research on the development of self-regulation has been conducted from different theoretical frameworks (Bridgett, Oddi, Laake, Murdock, & Bachmann, 2012) and therefore a variety of concepts and definitions have been formulated. In general, self-regulation refers to the capacity to control and direct one's attention, thoughts, emotions, and behavior (McClelland & Cameron, 2011b) and to utilize and adapt this capacity to different contextual and personal demands (Colman et al., 2006). Developmental researchers have studied self-regulation from a framework of *effortful control,* which is defined as the ability to inhibit a dominant response in order to activate a subdominant response (Kochanska, Murray, & Harlan, 2000; Rothbart, 1989a, 1989b; Rothbart & Ahadi, 1994; Rothbart & Bates, 1998). Other developmental studies have focused specifically on emotion-related self-regulation which includes the temperamental processes to monitor, manage, and change the experience and expression of emotions (Eisenberg & Sulik, 2012; Silk, Steinberg, & Morris, 2003). Neuroscientists and cognitive psychologists investigating self-regulation often use the term *executive function* to indicate the set of higher-level cognitive processes needed to regulate behavior and emotions (Bridgett et al., 2012). Socialization research has focused on self-regulated, *committed compliance* as a marker of development of behavioral regulation in early childhood (e.g., Denham, Warren-Khot, Bassett, Wyatt, & Perna, 2011; Kochanska, Coy, & Murray, 2001). The parsing of the construct into unique processes has led to greater understanding of how specific self-regulatory processes relate to specific consequences (Conway & Stifter, 2012) but the variation in definitions and frameworks applied in these studies has also hindered research in this field (McClelland & Cameron, 2011b). Recently, scholars have attempted to integrate the various frameworks and have found that there is substantial overlap between the constructs used in the different research traditions (Bridgett et al., 2012; McClelland & Cameron, 2011b; Zhou, Chen, & Main, 2012). For this reason, in the current thesis we approach self-regulation as a broad construct, including aspects of behavioral regulation such as child compliance behaviors and executive function, and an aspect of emotion regulation in the form of internalizing problems.

Determinants of self-regulation

Studies on the origins of self-regulation in children have focused on a broad array of possible determinants, including biological factors such as brain development, genetic heritability, and child temperament, but also environmental factors such as the quality of the early attachment relationship, parenting, and contextual factors.

The upsurge of methods to image brain structures and activity and to study the contribution of molecular genetic determinants of development has resulted in an increase in studies on the biological nature of the higher-order cognitive skills involved in self-regulation. For example, children born very preterm or with very low birth weight with abnormalities in white matter maturation in the brain show higher levels of cognitive and executive function problems in childhood and adolescence (Skranes et al., 2009; Woodward, Clark, Pritchard, Anderson, & Inder, 2011). Neuroscientists have long thought that mainly the prefrontal cortex is involved in self-regulatory capacities, but recent evidence indicates that integrity of the entire brain is necessary for optimal executive function skills (Alvarez & Emory, 2006; Jacobs, Harvey, & Anderson, 2011; Skranes et al., 2009). Individual differences in self-regulatory capacity may also be due to genetic variation. Studies on the heritability and familiarity of executive function have found evidence for a heritable, genetic basis varying in size depending on the specific measure of executive function and on the nature of the sample (Friedman et al., 2008; Jester et al., 2009; Polderman et al., 2007; Yamagata et al., 2005).

From a socialization perspective, the quality of parenting may be an important predictor of self-regulation. Because of the protracted development of self-regulation and the fact that children rely on their parents to help them regulate behavior and emotions in infancy, parents may play a crucial role in self-regulation development (Bernier, Carlson, Deschênes, & Matte-Gagné, 2012; Conway & Stifter, 2012; Kopp, 1982). Positive parenting in toddlerhood, characterized by maternal warmth, praise, and guidance, has been found to be concurrently associated with higher levels of compliance (Calkins et al., 1998) and to predict better self-regulation in preschool and school-aged children (Colman et al., 2006; Jennings et al., 2008). However, a meta-analysis on the concurrent association between maternal responsiveness and self-regulation in preschool indicated that they were not related (Karreman, Van Tuijl, Van Aken, & Dekovic, 2006). Also, more global measures of positive parenting, such as calm maternal responses to transgressions, were not found to be longitudinally related to executive function development in preschool (Hughes & Ensor, 2009). In contrast, maternal positive discipline and control strategies, such as distraction and appropriate limit setting, were concurrently and longitudinally related to higher levels of compliance (Karreman et al., 2006), better ability to delay gratification (LeCuyer & Houck, 2006), and more advanced executive function abilities (Schroeder & Kelley, 2010). Negative discipline which is characterized by negative control strategies and physically punitive behavior was concurrently and longitudinally related to less advanced levels of self-regulatory functions such as compliance and emotion regulation (Calkins et al., 1998; Colman et al., 2006; Karreman et al., 2006).

Recently, researchers have attempted to combine the biological and socialization perspectives to better explain differences in child development. Studies focusing on genetics and studies focusing on brain development showed that not all children might be equally affected by environmental factors due to biological or genetic differences. The buffering potential of positive parenting has been demonstrated in a study on the association between low birth weight and the risk of externalizing and internalizing problems in childhood (Laucht, Esser, & Schmidt, 2001). Similarly, the development of self-regulation was more hampered by early negative parenting for preterm or low birth weight infants with a difficult temperament than in those without biological and temperamental risk (Poehlmann et al., 2011). In addition, an intervention study aimed to enhance maternal sensitive discipline found that in children with a 7-repeat allele of the DRD4 gene whose mothers showed the largest increase in sensitive discipline, externalizing problems declined the most (Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008). These findings are congruent with the theories of *differential susceptibility* and *biological sensitivity to context* which state that variation in susceptibility to environmental influences such as parenting has an evolutionary advantage (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). It is therefore important to investigate the interplay of both biological and parental determinants in the study of the development of self-regulation.

Consequences of self-regulation

Self-regulatory capacity has been implied in various aspects of child and adult well-being. Self-regulation deficits are related to psychopathologies, such as autism and ADHD (Pennington & Ozonoff, 1996). On the other hand, higher levels of self-regulation lead to more social competence (Eisenberg & Sulik, 2012), more advanced moral development and empathy in childhood and adolescence (Feldman, 2007; Kochanska, Murray, & Coy, 1997), and higher levels of academic achievement and school success (McClelland et al., 2007; Obradovic, 2010). Because early self-regulation is involved in a variety of developmental consequences from childhood up to adolescence and adulthood, it is important to study the origins of individual differences in self-regulation across children.

The current study

The role of parental and biological factors in the development of self-regulation was studied in the Generation R Study. The Generation R Study was designed to identify early environmental and genetic determinants of growth, development, and health from fetal life onwards, in Rotterdam, the Netherlands (Jaddoe et al., 2012). Detailed measurements were obtained in a subgroup of children of Dutch national origin, meaning that the children, their parents, and their grandparents were all born in the Netherlands to reduce confounding and effect modification by ethnicity. The participating children were born between February 2003 and August 2005. Children and their parents visited the research centre regularly for various behavioral and somatic measurements. The measurements used in the current thesis are summarized in Figure 1.

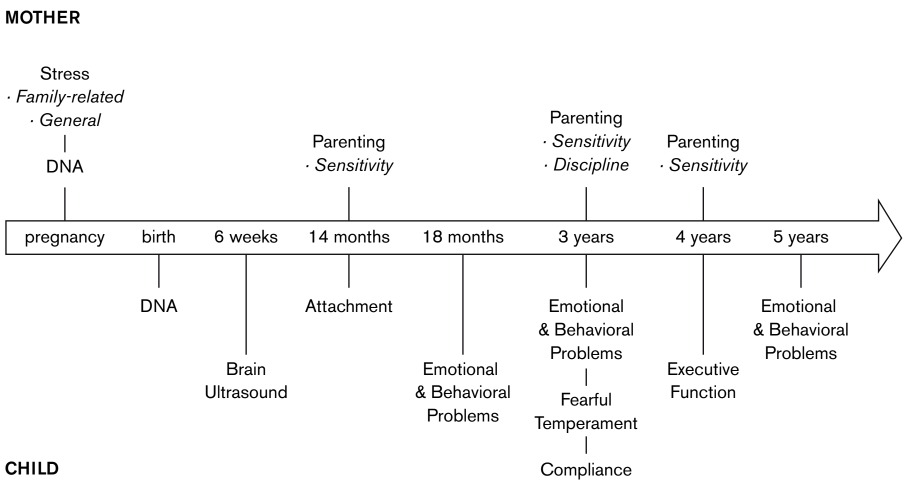

Figure 1. Measurements in Generation R used in current thesis.

Aim of this thesis

The general aim of the studies presented in this thesis is to provide more insight into the influence of biological and parental factors in the development of self-regulation in the preschool years. Observational measures, parental reports, and biological measures were used to assess these associations.

The main focus of Chapter 2 is the association between infant-mother attachment quality and toddlers' compliance and active resistance during a clean-up task. In Chapter 3 we examine the role of maternal stress during pregnancy, maternal discipline, and child dopamine-related gene polymorphisms in the development of compliance. A mediation model is tested with maternal discipline as the mediator in the association between maternal stress during pregnancy and child compliance. In addition, the moderating effect of child COMT rs4680 genotype and DRD4 polymorphism in the association between maternal discipline and compliance is explored. In Chapter 4 we study whether parenting influences executive function at preschool age independently or in interplay with corpus callosum length in infancy. Chapter 5 concerns the association between maternal sensitivity and child internalizing problems in the preschool period. We examine longitudinal and bidirectional associations between maternal sensitivity and child internalizing problems in two large population-based studies. In Chapter 6 the effect of maternal 5-HTTLPR on sensitive parenting is studied. Moreover, the moderating effect of child fearful temperament in the association between 5-HTTLPR and maternal sensitivity is examined. Against the background of our results, parental and biological determinants in the development of child self-regulation are discussed in Chapter 7.

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2

Attachment insecurity predicts child active resistance to parental requests in a compliance task

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Abstract

Aim We studied the effects of early mother-child relationship quality and child temperament on the development of child compliance and active resistance in a large population-based cohort study (*N* = 534).
Background Parenting and the quality of the parent-child relationship can either hamper or support the development of child compliance directly or in interplay with child temperament.
Method Mother-infant dyads were observed at 14 and 36 months and maternal and child behaviours were independently coded. The quality of compliance was assessed at 36 months in a clean-up task. Child behaviour was coded using a system differentiating between two dimensions: Compliance and Active Resistance.
Results Controlling for concurrent maternal sensitivity, child temperament, and gender children with a more insecure attachment relationship showed higher levels of active resistance during Clean-Up than more securely attached children. The effect was stronger for boys than for girls and mainly driven by attachment avoidance.

Introduction

Young children's *compliance* is related to better developmental outcomes at later ages, such as empathy and internalization (e.g., Feldman, 2007; Kochanska, 2002). Defiance or *active resistance* against requests has been found to result in less optimal developmental outcomes (e.g., Patterson, 2002). However, defiance can also be viewed as part of the development of autonomy and therefore an immature but healthy attempt to control events (Dix et al., 2007). It is important to investigate which factors affect the development of compliance or defiance in young children. The parent-child relationship is one of the factors that may play a role in fostering children's compliance with parental requests (Laible & Thompson, 2000; Van IJzendoorn, 1997). Though many scholars have emphasized the importance of parent-child *relationship quality* in the development of moral behaviour, interest has shifted towards interactive processes between parenting and child temperament as a result of equivocal empirical evidence for a substantial main effect of parenting (e.g., Kochanska et al., 2004). Recently this view has been broadly adopted and research is focused on the additive or interactive effects of relationship quality and temperament on child development (Vaughn et al., 2008). In the current study we investigate the influence of the early mother-child relationship and temperament on active resistance and compliance.

In infancy and the pre-school period, children gradually develop the ability to comply with parental requests and prohibitions and to show altruistic behaviours and empathy (e.g., Kochanska et al., 2010; Warneken & Tomasello, 2007; Zahn-Waxler & Radke-Yarrow, 1990), but there are large individual differences in when and whether they reach these milestones. Some children seem more inclined to show prosocial or moral behaviour, whereas others seem more prone to be disobedient and defiant (National Institute of Child Health and Human Development Early Child Care

Research Network [NICHD ECCRN], 1998). The gender of the child can explain some of these differences, as in most studies girls show more advanced levels of moral behaviour than boys (e.g., Kochanska et al., 2010; Silverman, 2003). Compliance to parental requests and prohibitions is often described as a precursor of later moral development (e.g., Feldman, 2007; Kochanska et al., 1995). Compliance that is internally motivated has been found to predict more advanced moral behaviour at later ages, whereas externally controlled compliance or noncompliance resulted in less optimal moral development (Kochanska, 2002).

The quality of the parent-child relationship is an important influence on moral development in children (Kochanska et al., 2005; Londerville & Main, 1981). The quality of the relationship can be indexed in various ways, such as through *attachment security* or *sensitive parenting*. Children are securely attached when they seek proximity to the attachment figure, for example the mother, in times of stress, illness or distress, and feel comforted by the attachment figure (Bowlby, 1969). Parental sensitivity is one of the predictors of attachment security and is defined as the sensitive responsiveness to the child's signals and communications (Ainsworth et al., 1978). Relationship quality can influence the development of compliance in three different ways. First, a responsive caregiver models social norms within a relationship and thereby teaches the child to be compliant. Second, children are better able to regulate their emotions and behaviour within a secure parent-child relationship and are hence in a better position to comply. Finally, children might also be more inclined to comply with a responsive caregiver because of the reciprocal positive relationship they have with this caregiver (Grusec & Davidov, 2010; Thompson & Meyer, 2007; Van IJzendoorn, 1997).

Studies on the effect of mother-child relationship quality on the development of compliance are inconsistent (e.g., Feldman, 2007; Kochanska & Aksan, 1995; Laible & Thompson, 2000; NICHD ECCRN, 1998; Van der Mark et al., 2002; Volling et al., 2006). Not all studies found an association between relationship quality and compliance. This may be because of differences in the way relationship quality was defined. Different measures of attachment security were used (Strange Situation Procedure or Attachment Q Sort), as well as other indicators of relationship quality, such as mutual positive affect, dyadic synchrony, or maternal sensitivity. These studies also focused on varying aspects of compliance as outcome measures. The taxonomy developed by Kochanska and Aksan (1995) has often been used to distinguish five categories of child behaviour: *committed compliance, situational compliance, passive noncompliance, resistant noncompliance,* and *defiant noncompliance*. Committed compliance is defined as a genuine eagerness and internal commitment in the child to comply with the parent's agenda. In the case of situational compliance the child is essentially cooperative but does not seem to embrace the parent's agenda and does not show sincere commitment. Passive noncompliance refers to the child's ignoring of the parent because of reluctance to accept parental requests or prohibitions. Resistant noncompliance is defined as an overt form of resisting the parent's request by simply refusing or negotiating with the parent. Defiant noncompliance refers to overt rejection of the parent's request by defiant physical or verbal behaviours. Some studies reported on the first category only (e.g., Feldman & Klein, 2003; Kochanska et al., 2010), whereas other studies included several categories, either as separate variables or aggregated into one or more variables (e.g., Kochanska, 2002; NICHD ECCRN, 1998).

Child characteristics such as temperament can also contribute to the development of moral behaviour. Temperament refers to constitutionally based individual differences in the reactivity to and the regulation of domains of attention, emotions, and behaviour (Rothbart & Posner, 2006). Many different temperamental dimensions have been studied in the context of the development of moral behaviour. Regulatory capacities of the child (also referred to as *effortful control*) have been described as an important underpinning of compliance because to be compliant a child needs to be able to suppress a dominant response and/or initiate a subdominant response (Kochanska et al., 2001). Also, negative reactivity of the child, manifested in anger proneness or fearfulness, has been found to be related to lower levels of compliance (Braungart-Rieker et al., 1997; Kochanska et al., 2001; Kotler & MacMahon, 2004). Most recent studies moved away from studying main effects of temperament to investigating the interplay between parental and child determinants in predicting moral development. Grazyna Kochanska and her colleagues, for example, have conducted several studies on the combined effects of attachment security, parenting, and child temperament (e.g., Kochanska, 1997; Kochanska et al., 2001, 2007). She proposed and tested a model in which interactions between difficult temperament and attachment security, and between difficult temperament and parenting style predicted moral development. Kochanska (1997) reported that in fearful children gentle discipline elicited an appropriate level of arousal that fostered internalization of norms. For fearless children she found a different pathway, emphasizing the importance of the quality of the relationship between parent and child, in which the positive emotions led to internalized conscience. This model was replicated with different measures of relationship quality (Kochanska et al., 2007) and similar results were found with anger proneness as a moderator (Kochanska et al., 2001).

In the current study we examined all categories of compliance-related child behaviour as described by Kochanska and Aksan (1995) in a clean-up task in a large population-based cohort study of 534 children. We analysed the underlying correlation structure of these behaviours with categorical principal components analysis (CATPCA) to reduce the categorical ratings to a smaller number of dimensions. This analysis showed that the categories of compliance are best described by two dimensions, representing *compliance* and *active resistance*. Next, we investigated the influence of mother-child relationship quality at 14 months on compliance and active resistance at 36 months, controlling for concurrent relationship quality. We expected that early relationship experiences remain important in explaining child behaviour at later ages. We also tested the moderating role of fearful temperament in the association between relationship quality and compliance or active resistance, because variation in fearfulness is one of the temperamental domains implicated in the development of moral behaviour (e.g., Fowles & Kochanska, 2000; Kochanska et al., 2007). Gender of the child was taken into account as (small) gender differences in the ability to inhibit responses and the ability to comply have been previously reported (e.g., Kochanska et al., 2010; Silverman, 2003).

Method

Setting

The current investigation is embedded within the Generation R Study, a prospective cohort study investigating growth, development, and health from fetal life onwards in Rotterdam, the Netherlands (Jaddoe et al., 2010). Detailed measurements were obtained in a subgroup of children of Dutch national origin, meaning that the children, their parents, and their grandparents were all born in the Netherlands. Further eligibility criteria were enrolment before a gestational age of 25 weeks and a delivery date between February 2003 and August 2005. Data were collected with questionnaires and visits to the research centre for behavioural assessments. All measures were approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants.

Study population

In the current study, data of the visits at the age of 14 and 36 months are presented. Infant-mother attachment classification was available for 721 dyads. One of these children could not be assigned an attachment status because of a ‘cannot rate’ classification, thus information on the security of the attachment relationship with the mother was available for 720 children. Of these remaining mother-child dyads, 552 also participated in the 36-month visit. Eighteen children were excluded because of procedural or technical difficulties during the clean-up task. The sample therefore consisted of 534 mother-child dyads. Non-response analyses on the 187 children excluded from the analyses or with missing data on compliance and active resistance indicated that these children did not differ from the participating children on most background variables, temperament, attachment security, or maternal sensitivity. A significant difference was found only for ‘experience with cleaning-up’: children excluded from analyses had more experience with cleaning-up than children included in the analyses, χ^2 (1, $N = 721$) = 5.26, $p < .05$.

Of the 534 mother-child dyads participating in this study we had full data available for gender of the child, gestational age at birth, attachment security, and active resistance and compliance during Clean-Up. Information on the amount of experience the child had with cleaning-up was available for 524 children. Maternal sensitivity scores at 36 months were available for 533 children. A rating for temperamental fearfulness was available for 492 children. Reasons for missing data on predictor variables and covariates were procedural or technical difficulties. Missings were imputed by the mean as multiple imputation generally does not add information if missings are less than 10% (Steyerberg, 1996).

The sample consisted of 49% girls; and 60% of all children were firstborn. The average weight at birth was 3511 g ($SD = 523$) and the average age of the child when compliance was assessed was 37.5 months ($SD = 1.4$). The mean age of mother at intake was 31.8 years ($SD = 3.7$); 64% of mothers had a high level of education (at least higher vocational training or a bachelor's degree).

Central measures

Compliance and active resistance during Clean-Up

Compliance was assessed around 36 months in a disciplinary context ("Clean-Up") of 4 min in which the parent asked the child to clean-up toys. Child behaviour was coded every 20 s using a coding system based on Kochanska and Aksan (1995) and Kuczynski and colleagues (1987). The predominant behaviour of the child in the 12 segments of 20 s was coded in five mutually exclusive categories. Committed compliance was coded if the child eagerly cleaned up the toys, needed no prompting by the parent, and/or showed positive affect during cleaning-up. Situational compliance was coded when the child needed regular prompting and/or showed difficulty in complying. Passive noncompliance was coded if the child ignored the mother's request. Resistant noncompliance was coded when a child actively resisted the mother, i.e. protesting or whining. Defiant noncompliance was coded if the child reacted angrily through physical or verbal behaviours. Child behaviour was independently coded from DVD recordings by one of four trained coders. Coders were extensively trained and regularly supervised. Reliability of the coders was assessed directly after the training and at the end of the coding process to detect possible rater drift. The intercoder reliability (intraclass correlation coefficients, ICC) for the four coders was .75 on average for both reliability measurements (range .56 - .85, $n = 48$).

Categorical principal components analysis (Meulman, Heiser, & SPSS, 2010; see also Linting et al., 2007) was used to investigate the correlation structure of the data, accounting for categorical measurement levels and possible non-linearity in relations between the variables. With this analytical procedure the interrelations between the categorical ratings were investigated and the variables were reduced to a limited number of dimensions. A solution with all variables on nominal scaling level was compared with a solution with all variables treated numerically (which equals the standard PCA solution) to investigate whether there was substantial non-linearity in the relations across variables. The difference between nominal and numerical solutions was only 7% in variance accounted for, so non-linearity did not have much influence on the solution and the numerical solution was selected. The two-dimensional structure explained 59% of variance compared with 31% in the one-dimensional structure. The second dimension was therefore maintained in the solution. For interpretation purposes an oblique rotation was performed in standard principal components analysis on the transformed variables from the CATPCA, because the category scores are mutually exclusive and thus not independent. Factor scores were extracted by regression method, and were used for all further analyses. The first dimension, labelled *Compliance*, indicates whether the child complies with the request of the parent and contrasts committed and situational compliance with passive noncompliance. The second dimension, representing *Active Resistance*, indicates the amount of active resistance against the request of the parent, which contrasts resistant noncompliance and defiant noncompliance with the other categories. Factor loadings per variable and per dimension are presented in Table 1. The two dimensions were not correlated, $r\,(532) = -.04$, $p = .36$. Factor scores for Active Resistance were log transformed to approach normality.

Table 1. *Factor loadings of category scores for the two dimensions Compliance and Active Resistance.*

	Dimensions Principal Components Analysis	
Categories coding system	Compliance	Active Resistance
Committed compliance	.44	.00
Situational compliance	.68	-.45
Passive noncompliance	-.95	-.33
Resistant noncompliance	-.03	.87
Defiant noncompliance	.06	.56

Attachment security

Attachment quality was assessed in the Strange Situation Procedure (SSP, Ainsworth et al., 1978) when the infant was about 14 months of age ($M = 14.6$; $SD = 0.9$). The SSP is a widely used and well-validated procedure to measure the quality of the attachment relationship. The procedure consists of seven episodes of 3 min each and is designed to evoke mild stress in the infant to trigger attachment behaviour evoked by the unfamiliar lab environment, a female stranger entering the room and engaging with the infant, and the parent leaving the room twice (see Ainsworth et al., 1978, for the protocol). The SSP used in the current study included all these stimuli but to make it fit into a tight time schedule, we shortened the (pre)separation episodes with 1 min keeping the critical reunion episodes intact (see also Luijk et al., 2010a, 2010b; Tharner et al., 2011). Attachment behaviour was coded from DVD recordings according to the Ainsworth and colleagues (1978) and Main and Solomon (1990) coding systems by two reliable coders, trained at the University of Minnesota. Coders were extensively trained and regularly supervised. Reliability of the coders was assessed directly after the training and at the end of the coding process to detect possible rater drift. Intercoder agreement was calculated on a total of 70 SSPs that were coded by both coders. For ABCD classification, intercoder agreement was 77% ($\kappa = .63$); agreement on disorganization was 87% ($\kappa = .64$). Continuous scores for avoidance and resistance were used in the analyses, which were the means of the scores of the two reunion episodes (one for avoidance in the two reunions, and one for resistance in the two reunions). The scores were square root transformed to approach normality.

Richters and colleagues (1988) developed a series of classification functions to score infants' attachments in a continuous way on the basis of the interactive scales (proximity seeking, contact maintaining, avoidance, and resistance) and crying behaviour in the two Strange Situation reunion episodes. Van IJzendoorn and Kroonenberg (1990) adapted the algorithm by leaving out the crying episodes, producing a valid Attachment Security Scale. Higher security scores indicate a more secure attachment relationship. In the Generation R Study the ICC for the continuous attachment security was .88 ($n = 70$).

Maternal sensitivity

At 36 months maternal sensitivity was observed when mother and child performed two 3-min tasks that were too difficult for the child: building a tower and an etch-a-sketch task. Mothers were instructed to help their child as usual. Maternal sensitivity was coded from DVD recordings with the revised Erickson 7-point rating scales for *Supportive Presence* and *Intrusiveness* (Egeland et al., 1990). The subscales Supportive Presence and Intrusiveness were coded for each task. An overall sensitivity score was created by reversing the Intrusiveness scales, standardizing the scores on the subscales, and creating an average over both subscales and both tasks. The two tasks were independently coded by 13 trained coders. Coders were extensively trained and regularly supervised. Reliability of the coders was assessed directly after the training and at the end of the coding process to detect possible rater drift. Total ICCs for the subscales were .75 on average for the tower task (range .73 - .77, $n = 53$) and .79 on average for the etch-a-sketch task (range .65 - .93, $n = 55$).

Fearful temperament

Fearful temperament was measured at the age of 36 months with the Stranger Approach (SA) episode of the Laboratory Temperament Assessment Battery Preschool Version (Lab-TAB, Goldsmith et al., 1999). The Lab-TAB is a widely used, standardized instrument for laboratory assessment of early temperament. In the SA episode the child deals with social fear when a novel, slightly threatening stranger approaches. The situation is modelled after real-life events. The child is left alone in a room. After 10 s a female stranger entered the room and asks standard questions from the child in a neutral tone of voice. In the original Lab-TAB protocol a male stranger enters the room in the Stranger Approach episode. For practical reasons we chose to have a female stranger who controlled the cameras during the visit in an adjacent room and thus had not been interacting with the child. We made the person more male appearing by a baseball cap, sunglasses, and a dark coat. This also ensured that the stranger was as uniform as possible for all children.

The episode is divided in nine epochs. Episodes were coded from DVD recordings according to the original coding system provided in the manual for the Lab-TAB Preschool Version. Regular checks were conducted to make sure that episodes closely followed the procedure as described in the manual. Intensities of fear expressions, distress vocalizations, activity decrease, approach, avoidance, gaze aversion, verbal hesitancy, and nervous fidgeting were scored in each epoch by coders, who were blind to all other measures. Coders were extensively trained and reliability was established before data were coded. For each parameter (e.g., intensity of fear expressions), average scores were calculated by dividing the child's overall score for that parameter across the nine epochs. The mean ICC for these average scores was .84 (range .71 - .97, $n = 25$). Then each average score was divided by the maximum attainable score for that parameter per epoch. This was done to ensure that scores for each parameter were standardized along the same scale to range between 0 and 1. Finally, one overall 'fearfulness' score was created by taking the mean of the standardized average scores for the different parameters. This fearfulness score ranged from 0 to 1 with higher scores indicating a more fearful temperament.

Covariates

Gender, gestational age at birth, and experience with cleaning-up

Gender and gestational age at birth were obtained from community midwife and hospital registries at birth. Gestational age at birth is included as an indicator of the biological risk of developmental delays (MacKay et al., 2010; Yang et al., 2010). Information on the amount of experience the child had with cleaning-up was provided by the mother at the 36-month visit prior to the clean-up task and dichotomized as "often" ($n = 360$) or "not often" ($n = 164$).

Statistical analyses

First, the bivariate associations among covariates, attachment quality, maternal sensitivity, fearful temperament, and compliance and active resistance during Clean-Up were explored with Pearson's correlations, *t*-tests, and chi-squared analyses. A linear regression analysis was performed to test the association between attachment quality and child behaviour during Clean-Up, controlling for gender, child temperament, gestational age at birth, concurrent maternal sensitivity, and the amount of experience the child had with cleaning-up. Interaction terms between gender, child temperament, and attachment security were computed after centering. Non-significant interaction terms were removed from the model before interpreting the main effects. As gender differences in the child's ability to inhibit responses and the ability to comply have been found (e.g., Kochanska et al., 2010; Silverman, 2003), and because some studies used samples with only one gender (e.g., girls, Van der Mark et al., 2002), we decided to explore possible differences between boys and girls by rerunning the same regression models for boys and girls separately.

Results

None of the demographic variables were associated with both attachment security and compliance or active resistance during Clean-Up. Children of older mothers showed less compliance during Clean-Up, r (532) = -.10, $p < .05$, and more active resistance during Clean-Up, r (532) = .09, $p < .05$. Children of mothers with a high educational level were less compliant during Clean-Up than children of mothers with a low or medium educational level, t (532) = 2.45, $p < .05$.

Bivariate correlations between the factor scores of the two dimensions derived from the CATPCA and the relative frequencies of categorical ratings were investigated to compare our new outcome measures with measures used in previous research. The relative frequency of the categories defiant and resistant noncompliance and the factor scores for the dimension active resistance were strongly correlated, r (532) = .92, $p < .01$. The relative frequency of the categories committed and situational compliance was also significantly correlated with the factor scores for the dimension compliance, $r(532) = .90$, $p < .01$.

Attachment security and active resistance

Attachment security and active resistance during Clean-Up were significantly correlated: more securely attached children showed less active resistance, $r(532) = -.09$, $p < .05$. A linear regression analysis was performed to control for gender of the child, fearful temperament, the amount of experience the child had with cleaning-up toys, maternal sensitivity at 36 months, and gestational age at birth. Interaction terms were not significant and therefore excluded from the analysis. Table 2 shows that more experience with cleaning-up predicted less active resistance during Clean-Up. After controlling for the other predictors and covariates attachment security again predicted less active resistance during Clean-Up.

The linear regression analysis was repeated with the continuous resistance score and with the continuous avoidance score of the children to investigate whether the association between attachment insecurity and higher levels of active resistance was accounted for by avoidant or resistant attachment behaviour. After controlling for the other predictors and covariates attachment resistance score did not predict active resistance ($\beta = -.01$, $p = .81$). However, a higher attachment avoidance score did predict more active resistance ($\beta = .09$, $p < .05$).

We repeated the analyses after stratification by gender. The association between attachment security and active resistance during Clean-Up reached significance only in boys, $r(270) = -.12$, $p < .05$; but not in girls, $r(260) = -.05$, $p = .47$, although the results were in the same direction. Linear regression analyses (presented in Table 2) showed that a more secure attachment relationship predicted less active resistance in boys. No effects of the covariates and other predictors were found. More experience with cleaning-up predicted less active resistance during Clean-Up in girls. Attachment security and the other predictors and covariates were not significantly associated with active resistance of girls during Clean-Up. Similar results were found when attachment avoidance scores or attachment resistance scores were entered as predictors.

Table 2. *Regression analysis predicting active resistance from attachment security.*

	B	*SE*	β	*t*	*p*	*F*	R^2	R^2change
Total group ($N = 534$)								
Step 1:						2.47*	.02	.02
Gender	-0.01	0.01	-.05	-1.10	.27			
Fearfulness	-0.12	0.11	-.04	-1.03	.30			
Gestational age at birth	-0.01	0.01	-.08	-1.88	.06			
Experience cleaning-up	-0.04	0.02	-.09*	-2.17	.03			
Step 2:						1.98	.02	.00
Sensitivity at 36 months	0.00	0.01	.01	0.29	.77			
Step 3:						2.34*	.03	.01
Attachment security	-0.01	0.00	-.09*	-2.02	.04			
Boys ($n = 272$)								
Step 1:						0.56	.01	.01
Fearfulness	-0.02	0.15	-.01	-0.14	.89			
Gestational age at birth	-0.01	0.01	-.09	-1.46	.15			
Experience cleaning-up	-0.01	0.03	-.01	-0.21	.84			
Step 2:						0.51	.01	.00
Sensitivity at 36 months	0.01	0.02	.03	0.56	.58			
Step 3:						1.31	.02	.02
Attachment security	-0.01	0.00	-.13*	-2.12	.04			
Girls ($n = 262$)								
Step 1:						4.13**	.05	.05
Fearfulness	-0.28	0.17	-.10	-1.61	.11			
Gestational age at birth	-0.01	0.01	-.07	-1.18	.24			
Experience cleaning-up	-0.07	0.02	-.18**	-2.99	<.01			
Step 2:						3.14*	.05	.00
Sensitivity at 36 months	-0.01	0.02	-.03	-0.40	.69			
Step 3:						2.57*	.05	.00
Attachment security	0.00	0.00	-.04	-0.58	.56			

* $p < .05$, ** $p < .01$.

Note. Betas are taken from the final models

Attachment security and compliance

The bivariate correlation between attachment security at 14 months and compliance during Clean-Up at 36 months was not significant, r (532) = .02, p = .67. In a linear regression analysis controlling for other predictors and covariates (gender of the child, fearful temperament, the amount of experience the child had with cleaning-up toys, maternal sensitivity at 36 months, and gestational age at birth) interaction terms were not significant and therefore removed from the analysis. Attachment security did not significantly predict compliance during Clean-Up (β = .02, p = .65), and none of the covariates were significantly associated with compliance. The results were similar for boys and girls.

The linear regression analysis was again repeated with the continuous resistance score and with the continuous avoidance score of the children to investigate whether there was an association with compliance. After controlling for the other predictors and covariates resistance (β = .06, p = .20) and avoidance (β = -.07, p = .09) did not significantly predict compliance.

Discussion

A more secure attachment relationship between mother and infant predicted less active resistance during Clean-Up at toddler age. The security of the mother-infant relationship did not predict compliance in toddlerhood. The findings from this large sample are in concordance with previous studies that found an association between relationship quality and defiance in children (e.g., Kochanska & Aksan, 1995), but do not converge with studies that found an effect of relationship quality on compliance in children (e.g., Feldman & Klein, 2003). An important difference between our study and previous studies was the use of the empirically derived two-dimensional structure of child compliance behaviour: compliance and active resistance. The correlations between these newly derived measures and the categorical ratings which they were based on were, however, strong. Indeed there is no inherent contradiction between the empirical dimensions used in the present study and the a priori defined dimensions because we used Kochanska's taxonomy to score the child's behaviour. However, our empirical approach to derive dimensions yielded fewer dimensions (factors) that were only slightly interrelated and that were based on all compliance related behavioural patterns observed in the children. One dimension, compliance, indicates the distinction between compliance and noncompliance, whereas the dimension active resistance indicates whether the child actively resists the mother's demand. Given the oblique rotation, the second dimension might represent more extreme noncompliant behaviours than the first dimension, which we found to be more common in children with an insecure attachment relationship. Noncompliance without active resistance might be the more normative behaviour that all toddlers display now and again, regardless of the quality of the relationship with their mother.

The association between attachment insecurity and the level of active resistance during Clean-Up at 36 months was specific for children who showed more avoidance during the Strange Situation Procedure at 14 months of age. This finding is in concordance with previous studies that found an association between avoidance and externalizing behaviour manifested already during toddlerhood (Keller et al., 2005; Munson et al., 2001). A recent meta-analysis indicated a significant but small association between avoidant attachment and externalizing behaviour (Fearon et al., 2010).

Besides the influence of a secure relationship we found that less experience with cleaning-up was also predictive of more active resistance in toddlerhood. Practising with cleaning-up seems to result in less resistance to this request in the future. Socializing children in cleaning-up may effectively reduce their resistance against this task. Although we did not find significant gender interactions, analyses were performed separately for boys and girls because in many respects they represent two different populations, and previous studies found evidence for gender differences in child compliance behaviours (e.g., Kochanska et al., 2010; Silverman, 2003). The association between less attachment security and more active resistance was largely accounted for by boys, as for girls the extent to which they had experience with cleaning-up was the only significant predictor for their level of active resistance. Because there were no gender differences in the amount of active resistance, these findings could indicate that for this aspect of their development boys are more susceptible to the influence of relationship quality than girls. This is in line with a study by Shaw and colleagues (1998) in which maternal unresponsiveness resulted in an increased risk for externalizing problems in boys but not in girls.

Further research is needed to complement these findings with the examination of the effect of the *father*-child relationship on compliance. Differences might exist between fathers and mothers in expectations and parental behaviour towards boys and girls in disciplinary contexts. Furthermore, the behaviour of boys and girls during Clean-Up might be different towards their mother and father. Previous studies found that fathers use more warm control strategies towards girls than towards boys (Feldman & Klein, 2003) and some studies indicated that boys are more compliant towards fathers than towards mothers (e.g., Power et al., 1994).

We did not find an association between temperamental fearfulness and compliance or active resistance, and we also failed to find an interaction effect of relationship quality and temperamental status. These findings are in concordance with the study of Van der Mark and colleagues (2002), but do not support the findings of Kochanska and colleagues (2007). In the latter study, however, the interaction effect of temperament and relationship quality was only found when all constructs were measured at age 2, and no interaction effects were found in 3-year-old children who were the targets of the present study. Perhaps a 'developmental window' around 2 years of age could explain the lack of significant interaction effects between temperament and relationship quality in older toddlers (Kochanska et al., 2007). It is also possible that instead of fearfulness other temperamental domains such as the self-regulatory capacity or anger proneness of the child might be better predictors of respectively the level of compliance or the level of active resistance in children. Kotler and MacMahon (2004), for example, found that children with higher levels of anxiety used less confronting and more passive noncompliance strategies, whereas children with higher levels of anger and aggression showed more direct and assertive types of noncompliance. Moreover, our study was conducted in a relatively homogeneous sample of Dutch, higher socioeconomic status families. For this reason we might have encountered less variation in behaviours and weaker associations than present in more diverse populations. This could explain the relatively small effect sizes we found considering the large sample size.

Other parenting factors or child characteristics not included in this study, could of course contribute to the development of compliance. Future studies should, for example, take into account the parental style of discipline to see whether this affects the quality of the child's compliance behaviour independently or in interplay with attachment quality. However, in a recent study it has been argued that not parenting or child characteristics determine moral and prosocial behaviour but that situational characteristics are the strongest predictor of differences in prosocial behaviour (Van IJzendoorn et al., 2010). From this theoretical perspective a small contribution of relationship quality seems plausible.

In sum, this study indicates the importance of early attachment for the socialization of moral behaviour in toddlers. An important future goal is to investigate whether the differences found in active resistance at toddler age are persistent and result in higher levels of behavioural problems at a later stage.

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3

The role of maternal stress during pregnancy, maternal discipline, and child COMT Val158Met genotype in the development of compliance

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DOI: 10.1002/dev.21049

Abstract

Maternal discipline is an important predictor of child committed compliance. Maternal stress can affect both parenting and child development. In a large population-based cohort study ($N = 613$) we examined whether maternal discipline mediated the association between maternal stress during pregnancy and child compliance, and whether COMT or DRD4 polymorphisms moderated the association between maternal discipline and child compliance. Family-related and general stress were measured through maternal self-report and genetic material was collected through cord blood sampling at birth. Mother-child dyads were observed at 36 months in disciplinary tasks in which the child was not allowed to touch attractive toys. Maternal discipline and child compliance were observed in two different tasks and independently coded. The association between family stress during pregnancy and child committed compliance was mediated by maternal positive discipline. Children with more COMT Met alleles seemed more susceptible to maternal positive discipline than children with more COMT Val alleles.

Introduction

Committed compliance is an important milestone in the development of self-regulation (Kochanska & Aksan, 1995). Self-regulatory capacities of children can be either supported and guided (e.g., Bernier, Carlson, & Whipple, 2010) or hampered, depending on the quality of parenting (Karreman, Van Tuijl, Van Aken, & Dekovic, 2006). Parental stress has been found to influence the quality of parenting (Nelson, O'Brien, Blankson, Calkins, & Keane, 2009) and may be indirectly associated with compliance in the child (Karreman et al., 2006). However, the association between parenting and compliance might also be dependent on child characteristics, specifically their temperament (Kochanska, 1997) or genetic make-up (Kochanska, Phillibert, & Barry, 2009). In the current study we investigated whether the association between maternal stress during pregnancy and committed compliance is mediated by maternal discipline. We also investigated whether the association between maternal discipline and committed compliance is moderated by dopamine-related gene polymorphisms.

Self-regulated or *committed compliance* is a precursor of other self-regulatory capacities such as inhibition and emotion regulation (Karreman et al., 2006). Child compliance is considered self-regulated if the child is willing and eager to obey parental requests and child behavior is not merely controlled by parental pressure (Kochanska & Aksan, 2006). A meta-analysis of the association between parenting and self-regulation showed that maternal positive and negative discipline were the main predictors of child compliance (Karreman et al., 2006). *Positive discipline* is characterized by gentle but directive requests in which the parent considers the child's desires and needs (Karreman et al., 2006; LeCuyer-Maus & Houck, 2002). *Negative discipline* refers to power-assertive and intrusive controlling strategies, characterized by anger and harshness (Karreman et al., 2006). Parental discipline is an important predictor of self-regulation because young children rely on external regulation of their emotions and behavior, and only gradually internalize regulation strategies as offered by the parent (Calkins, Smith, Gill, & Johnson, 1998).

Quality of parenting can be negatively affected by stress (Nelson et al., 2009). Yet, minor and major stresses are quite common in human life, especially in the transitional period of becoming parents (Mulder et al., 2002). In this study the effect of different types of stress during pregnancy on maternal discipline and child compliance is investigated. Maternal stress during pregnancy can affect child development through intrauterine programming of the fetal brain (Van den Bergh, Mulder, Mennes, & Glover, 2005). Maternal stress during pregnancy can be a risk indicator of a genetic vulnerability of the mother which is inherited by the child (Schermerhorn et al., 2011). Another possibility is that maternal stress during pregnancy indirectly affects child development through *spillover* of maternal stress on parenting behavior in the postnatal period (e.g., Erel & Burman, 1995; Kanoy, Ulku-Steiner, Cox, & Burchinal, 2003). Though recent studies have mainly focused on intrauterine and genetic mechanisms, postnatal environmental factors may mediate the association between stress during pregnancy and child development (e.g., Velders et al., 2011). Most studies on *postnatal* parental stressors and parenting behavior have included family-related stressors (Erel & Burman, 1995; Krishnakumar & Buehler, 2000), whereas studies on the effects of *prenatal* stress mainly focus on general stress (e.g., Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Van den Bergh et al., 2005). In the current study we investigate the specificity of family-related stress and general stress during pregnancy in predicting maternal discipline. This approach also precludes reversed causality, that is, possible contamination of maternal stress measures by child characteristics.

Children might not be equally affected by environmental factors due to their genetic and/or physiological differences. The theories of *differential susceptibility* and *biological sensitivity to context* state that variation in susceptibility to environmental influences such as parenting has an evolutionary advantage (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). Two possible candidate polymorphisms for differential susceptibility are the COMT Val158Met polymorphism and a functional polymorphism in exon 3 of the dopamine D4 receptor gene.

The COMT gene in humans is located in chromosome 22q11 and contains a common functional polymorphism that results in a methionine (Met) to valine (Val) substitution in exon 4 at codon 158 (Lotta et al., 1995). This common polymorphism results in a significant change in enzymatic activity which particularly affects dopamine levels in the prefrontal cortex. The Met allele is associated with about one-fourth lower enzymatic activity resulting in higher extracellular dopamine activity than the Val allele which is associated with higher enzymatic activity and thus lower extracellular dopamine activity (Chen et al., 2004). The dopamine D4 receptor gene (DRD4) in humans is located near the telomere of chromosome 11p and contains various polymorphisms including variations in the number of 48-bp tandem repeats in exon 3. The three common variants in observed populations are 2R, 4R, and 7R (e.g., Wang et al., 2004). The evolutionary more recent variant DRD4-7R stands out because it codes for a receptor that is less sensitive to endogenous dopamine compared to the receptors coded for by the shorter repeats. Studies on the possibility that the DRD4 tandem repeat polymorphism and/or the COMT Val158Met polymorphism are involved in differential susceptibility to environmental factors have not found consistent results. Laucht and colleagues (2012) found that parental supervision affected alcohol use only for adolescents homozygous for the COMT Met allele, whereas Grigorenko and colleagues (2007) found that the effect of maternal rejection on reading comprehension skills was larger for carriers of the COMT Val allele than carriers of the COMT Met allele. Evidence for the DRD4 polymorphism as "susceptibility marker" is also mixed, but a recent meta-analysis confirmed the role of dopamine-related gene polymorphisms as moderators of the effects of supportive *and* insensitive parenting on child developmental outcomes, for better and for worse (Bakermans-Kranenburg & Van IJzendoorn, 2011).

In the current study we test a mediation model with mothers' self-reported stress during pregnancy as predictor, observed maternal discipline as mediator, and observed child committed compliance as outcome; and a moderation model with COMT and DRD4 as moderators of the association between maternal discipline and committed compliance. We expect that the association between stress during pregnancy and committed compliance is mediated by maternal discipline. We furthermore expect that the spillover of stress during pregnancy on maternal discipline is specific to family-related stressors and not found for general stress. We expect that not all children in our sample will be equally susceptible to their environment due to their genetic make up and that therefore the association between maternal discipline and child compliance is moderated by dopamine-related gene polymorphisms. The full model is presented in Figure 1.

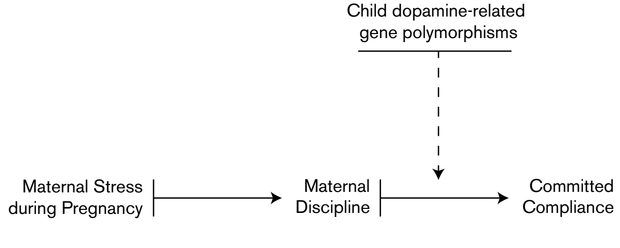

Figure 1. Design of mediation and moderation model.

Method

Setting

The current investigation is embedded within the Generation R Study, a prospective cohort study investigating growth, development, and health from fetal life onwards in Rotterdam, the Netherlands (Jaddoe et al., 2010). Detailed measurements were obtained in a subgroup of children of Dutch national origin, meaning that the children, their parents, and their grandparents were all born in the Netherlands (e.g., Luijk et al., 2010; Tharner et al., 2011). Further eligibility criteria were enrollment before a gestational age of 25 weeks and a delivery date between February 2003 and August 2005. Data were collected with questionnaires and visits to the research center for behavioral assessments. All measures were approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants.

Study population

In the current study, prenatal measurements, genetic information, questionnaire data at the child's age of 2 months, and data of the lab visit at the child's age of 36 months are presented. Data were available for 852 children and their primary caregiver participating in the 36-month visit. Because the current study focuses on mother-child dyads 136 children who attended the 36-month visit with their father or grandparent were excluded. Of the 716 remaining children data on compliance was available for 694 children. We had information on the discipline style of the mother for 675 dyads. Reasons for missing data on child compliance or maternal discipline were technical or procedural difficulties during the tasks. Information on maternal family stress during pregnancy was available for 626 mothers. Within this group, 26 mothers participated in the 36-month visit twice, with twins or siblings. One half of each twin or sibling pair was randomly selected for the analyses to avoid paired data. The final sample for the mediation analyses thus consisted of 613 mother-child dyads. Nonresponse analyses on the 81 children excluded from the analyses or with missing data on maternal discipline or maternal family stress indicated that these children did not differ from the participating children on any of the background variables. A significant difference was found for the level of maternal positive discipline during the discipline task: mothers excluded from analyses used less positive discipline strategies than mothers included in the analyses, $t(682) = -2.39$, $p < .05$, and more negative discipline strategies, $t(687) = 2.46$, $p < .05$. Also, mothers excluded from the analyses reported less family stress during pregnancy than mothers included in the analyses, $t(642) = -2.07$, $p < .05$.

Information on COMT rs4680 genotype and DRD4-7 repeat polymorphism was available for 436 of the 613 children, which comprise the population for the moderator analyses. Reasons for missing data on child genotype were lack of consent for collecting genetic material, absence of a cord blood sample due to logistical difficulties (the Netherlands has Europe's highest rate of home births, > 30%), or problems with determination of genotype. Analyses on the 177 children and mothers that could not be included in the genotype analyses indicated that they did not differ from the other dyads on most background variables, family stress during pregnancy, maternal discipline style, and child compliance. Children excluded from the analyses had less often an older sibling than children included in the analyses, $t(383.27) = -2.63$, $p < .01$, and had a lower gestational age at birth, $t(233.55) = -2.91$, $p < .01$.

Information on general stress during pregnancy was missing for 13 mothers (2%) and maternal educational level was unknown for 7 mothers (1%). Information on maternal psychological problems at 2 months was missing for 79 of the 436 mothers included in the genetic analyses (18%). In total .004% of the values in the mediation model were missing and 2.1% of the values in the moderation model. Missing data on general stress during pregnancy, educational level, and maternal psychological problems at 2 months were imputed by multiple imputations. The sample consisted of 49% girls; and 61% were firstborn. The average weight at birth was 3503 g ($SD = 549$) and the average age of the child at the 36-month visit was 37.6 months ($SD = 1.6$). The mean age of mother at intake was 31.8 ($SD = 3.8$); 66% of mothers had a high level of education (at least higher vocational training or a bachelor's degree).

Central measures

Committed compliance

Compliance was assessed at 36 months in a disciplinary context ("Don't") of 2 min in which the parent allowed the child to play with an unattractive teddy bear, but prohibited the child to touch or play with a set of attractive toys that were displayed before the child. Child behavior was coded every 20 s using a coding system based on Kochanska and Aksan (1995) and Kuczynski, Kochanska, Radke-Yarrow, and Girnius-Brown (1987). The predominant behavior of the child in the six 20 s segments was coded in five mutually exclusive categories. Committed compliance was coded if the child appeared to have embraced maternal agenda wholeheartedly, made no attempt to touch or play with the toys, and needed no prompting by the parent. Situational compliance was coded when the child needed regular prompting and/or showed difficulty in complying. Passive noncompliance was coded if the child ignored the mother's request. Resistant noncompliance was coded when a child actively resisted the mother, that is, protesting or whining. Defiant noncompliance was coded if the child reacted angrily through physical or verbal behaviors. The data were independently coded by two trained coders. Coders were unaware of other data concerning the mother-child dyad and were extensively trained and regularly supervised. Reliability of the coders was assessed directly after the training and at the end of the coding process to detect possible rater drift. The intercoder reliability (intraclass correlation coefficients, ICC) for the two coders directly after the training was .81 on average ($n = 20$) and .84 at the end of the coding process ($n = 33$), with an ICC of .87 over the total set ($n = 53$).

CATPCA (Categorical Principal Components Analysis; Meulman, Heiser, & SPSS, 2010; see also; Linting, Meulman, Groenen, & Van der Kooij, 2007) was used to investigate the correlation structure of the data. Defiant noncompliance scores were excluded from the CATPCA because only one child showed defiant noncompliance behavior. A solution with all variables on nominal scaling level was compared to a solution with all variables treated numerically (which equals the standard PCA solution) to investigate whether there was substantial nonlinearity in the relations across variables. The difference between nominal and numerical solutions was only 10% in variance accounted for, so nonlinearity did not have much influence on the solution and thus the numerical solution was selected. A one-dimensional structure explained 50% of variance. Factor scores were extracted by regression method, and were used for all further analyses. The dimension was labeled *Committed Compliance* and contrasts committed compliance with the other categories. Factor scores for Committed Compliance were log transformed to approach normality.

Maternal discipline style

The discipline style of the mother was observed at 36 months in a disciplinary context which was similar to, but independent of the task in which compliance was observed. In this task of 2 min the parent prohibited the child to touch or play with a set of attractive toys that were displayed before the child. Coding procedures were based on Kuczynski and colleagues (1987), and Van der Mark, Van IJzendoorn, and Bakermans-Kranenburg (2002). Maternal verbal and physical discipline strategies were observed and coded in different categories: Commands, Support, and Physical obstruction or interference (micro coded); and with the revised Erickson 7-point rating scale for *Supportive Presence* (macro coded; Egeland, Erickson, Clemenhagen, Hiester, & Korfmacher, 1990). Both micro- and macro coding strategies were used because they can represent two different types of parental behavior: planned or intuitive behaviors which may reflect different dimensions of the same underlying construct (Mesman, 2010). To create a more comprehensive picture of positive and negative strategies, micro- and macro codes were combined. Commanding was coded when mothers prohibited their child to touch or play with toys in an authoritarian manner. Support involved all maternal remarks that helped the child to comply, such as distracting the child from the toys and responding to what the child said. Physical obstruction or interference was coded when mothers used physical force to keep the child from touching the toys. The mother's supportiveness toward her child during the discipline task was coded with the Supportive Presence scale which refers to the amount of positive regard and emotional support the mother shows toward the child. A supportive mother is a reassuring, calm, and affectively positive secure base for the child. Support and Supportive Presence represent a maternal positive discipline style. Commands and Physical obstruction are indicators of maternal negative discipline style.

Maternal behavior was coded by five trained coders. Coders were unaware of other data concerning the mother-child dyad. Coders were extensively trained and regularly supervised. Reliability of the coders was assessed directly after the training and at the end of the coding process to detect possible rater drift. The number of times a specific behavior was coded was divided by the total number of codings to create a relative score for each behavioral category, to make the score for each category independent of the number of maternal messages. The ICC for the relative frequency of Commands was .71 directly after the training ($n = 27$) and .84 at the end of the coding process ($n = 30$), with an overall ICC of .85 ($n = 57$). The ICC for the relative frequency of Support was .80 on average directly after the training ($n = 27$) and .86 on average at the end of the coding process ($n = 30$), with an overall ICC of .85 ($n = 57$). The ICC for Physical Interference was .90 on average directly after the training ($n = 27$) and .90 at the end of the coding process ($n = 30$), overall ICC .90 ($n = 57$). The ICC for Supportive Presence was .68 on average directly after the training ($n = 27$) and .85 on average at the end of the coding process ($n = 30$), overall ICC .79 ($n = 57$). Support and Supportive Presence were positively correlated, $r(611) = .27$, $p < .01$, as were Commands and Physical discipline, $r(611) = .24$, $p < .01$. An overall maternal positive discipline score and an overall maternal negative discipline score were created by standardizing and summing the scores. Maternal positive discipline was square root transformed to normality and maternal negative discipline was log transformed to normality.

Family stress during pregnancy

Family stress during pregnancy was reported by the mothers on the subscale *General Functioning* (GF) of the McMaster Family Assessment Device (FAD, Byles, Byrne, Boyle, & Offord, 1988) at 20 weeks of pregnancy. GF is a reliable and validated self-report measure of family functioning or dysfunctioning and perceptions of how the family unit works together on essential tasks suitable for nonclinical samples (Byles et al., 1988; Kabacoff, Miller, Bishop, Epstein, & Keitner, 1990). Previous studies on the GF scale of the FAD found that this scale can be used as a single index representing the overall functioning of the family (Byles et al., 1988; Kabacoff et al., 1990; Ridenour, Daley, & Reich, 1999). Byles and colleagues (1988) found that the GF subscale is associated with marital violence or disharmony and parental separation. The GF scale consists of 12 items. One half of the items describe healthy functioning (e.g., "We can express our feelings towards each other.") and the other half describe unhealthy functioning (e.g., "We don't get on well with each other."). Mothers rated how well the statements describe their family at that moment on a 4-point Likert scale ranging from "totally disagree" to "fully agree". The internal consistency of GF was $\alpha = .90$. Item scores (reversed when necessary) were summed and divided by the total number of items. From all mothers with valid scores at least 10 item scores were available. The distribution of scores was skewed and therefore scores were transformed inversely to approach normality and mirrored for interpretation purposes.

Stress during pregnancy

General stress during pregnancy was reported by mother on the Dutch version of the long-lasting difficulties (LLD) list (Hendriks, Ormel, & Van Willige, 1990) at 20 weeks of pregnancy. This list contains 12 items on difficulties in the preceding year and mothers rate the occurrence and severity of these difficulties on a 4-point Likert scale ranging from "no" to "serious". The items concerned for example difficulties at work or school, financial and housing problems, and difficulties with friends or family. Item scores were summed and divided by the total number of items. For all mothers at least 10 item scores were available. The overall distribution was skewed and scores were square root transformed to approach normality. The internal consistency of the LLD in this sample was $\alpha = .57$. This alpha is quite low but this is expected because the list contains a broad range of difficulties that do not necessarily co-occur (Hendriks et al., 1990).

DRD4 48 bp VNTR and COMT Val158Met (rs4680)[1]

DNA was collected from cord blood samples at birth. To check for potential contamination with maternal blood, gender was determined in male participants. Gender mismatch was detected in 0.5% of cases, resulting in an expected contamination of 1% of cases. Cases with gender mismatch were not genotyped. Genotyping of polymorphism COMT was performed using Taqman allelic discrimination assay (Applied Biosystems, Foster City, CA) and Abgene QPCR ROX mix (Abgene, Hamburg, Germany). The genotyping reaction was amplified using the GeneAmp® PCR system 9600 (95 °C [15 min], then 40 cycles of 94 °C [15 s] and 60 °C [1 min]). The fluorescence was detected on the 7900HT Fast Real-Time PCR System (Applied Biosystems) and individual genotypes were determined using SDS software (version 2.3, Applied Biosystems). Genotyping was successful in 97-99% of the samples. To confirm the accuracy of the genotyping results 276 randomly selected samples were genotyped for a second time with the same method. The error rate was less than 1% for all genotypes. The allele frequency of the Met allele was 52%. Frequency distribution conformed to Hardy-Weinberg equilibrium (HWE), $\chi^2(1) = 0.44$, $p = .51$. COMT

[1] No other polymorphisms or other genetic markers were tested.

genotype was coded as 0 when the child had no Val alleles and two Met alleles, as 1 when the child had one Val allele and one Met allele, and genotype was coded as 2 when the child had two Val alleles and no Met alleles.

Genotyping of the DRD4 48 bp VNTR was amplified using primers D4-F-GCGACTACGTGGTCTACTCG and D4-R-AGGACCCTCATGGCCTTG. Reactions were performed in a 384-wells format in a total reaction volume of 10 ul containing 10 ng DNA, 1 pmol/ul of each primer, 0.4 mM dNTPs, 1 M betaine, 1x GC buffer I (Takara Bio Inc., Otsu, Japan) and 0.5 U/ul LA Taq (Takara Bio Inc.). PCR cycling consisted of initial denaturation of 1 min at 94 °C, and 34 cycles with denaturation of 30 s at 95 °C, annealing of 30 s at 58 °C and extension of 1 min at 72 °C. PCR fragments were size-separated on the Labchip GX (Caliper Life sciences, Hopkinton, MA) using a HT DNA 5K chip (Caliper Life sciences). The number of DRD4 repeats was determined using the size of the PCR fragments. To assure genotyping accuracy 225 random samples were genotyped for a second time. Three samples (1.3%) gave different genotypes. These discrepancies were specific for the repeats longer than 7. The HT DNA 5K chip was unable to accurately distinguish the 7, 8, 9, and 10 repeat. As the frequency of the 8, 9, and 10 repeat is low; all samples with a 7 repeat or longer were analyzed as one group. The allele frequency of the long repeat (7 or longer) was 20%. Frequency distribution conformed to HWE, $\chi^2(1) = 0.01$, $p = .92$. DRD4-7 R polymorphisms were entered in the analyses as two groups: no 7 or longer repeats (code 0) and one or two 7 or more repeats (code 1).

Covariates

Gender, age of mother, educational level, and maternal psychological problems

Gender of the child will be taken into account because it has been reported that the ability to inhibit responses and to comply may differ between boys and girls (e.g., Kochanska et al., 2010; Silverman, 2003). Information on gender was obtained from community midwife and hospital registries at birth. The age of the mother and her educational level were reported at the intake of the Generation R Study. Educational level was dichotomized as “high” (at least higher vocational training or a bachelor’s degree, $n = 402$) and “low/medium” ($n = 211$). Maternal psychological problems at 2 months were assessed with the Dutch version (De Beurs, 2004) of the Brief Symptom Inventory (BSI, Derogatis, 1993; Derogatis & Melisaratos, 1983). The BSI is a validated self-report questionnaire of 53 items rated on 5-point Likert scales ranging from “not at all” to “extremely”, resulting in scores on nine subscales and a global index for severity of psychological problems. The internal consistency of this index in the current study was $\alpha = .94$. Scores were transformed inversely to approach a normal distribution and mirrored for interpretation purposes.

Statistical analyses

Due to missing data on general stress during pregnancy (2%), maternal educational level (1%), and maternal psychological problems (18%) we generated five imputed data sets for the mediation analyses and 15 imputed data sets for the moderation analyses. Missing data are not uncommon in longitudinal studies, and multiple imputations are frequently used to estimate 20-40% missing data per variable (e.g., Pluess & Belsky, 2010). Missing data were imputed with the predictive mean matching method in IBM SPSS Statistics, version 19.0.1 for Windows (Meulman et al., 2010). Data were analyzed in separate data sets and subsequently pooled to obtain an overall result based on 5 or 15 imputations. Analyses conducted with the imputed data sets ($N = 613$, $N = 436$) yielded similar (significant) results compared to analyses with the complete data sets ($N = 593$, $N = 357$). Results of the imputed data sets are presented unless otherwise indicated.

The associations among covariates, family and general stress, maternal discipline style, committed compliance, DRD4-7 repeat alleles, and COMT rs4680 genotype were determined. A mediation model testing whether maternal discipline mediated the association between stress during pregnancy and child compliance was conducted according to the four criteria as described by Baron and Kenny (1986) for maternal positive discipline and maternal negative discipline separately. In the first step the association between family stress and maternal discipline style was investigated. The second step concerned the association between family stress and committed compliance. In the third step the association between maternal discipline style and committed compliance was investigated, and in step 4 a hierarchical regression analysis was conducted in which the association between family stress and committed compliance was investigated, controlling for maternal discipline style. If the four criteria were met, a Sobel test for mediation was performed as a significance test for the indirect effect of family stress on committed compliance via maternal discipline style (Baron & Kenny, 1986). The mediation model was repeated with general stress instead of family stress as the predictor to investigate the specificity of the association between family-related stressors, maternal discipline style, and child compliance.

A hierarchical regression analysis was performed to investigate possible interaction effects between maternal discipline, COMT rs4680 genotype, and DRD4 polymorphism on committed compliance. In the regression equation we included gender, maternal age, educational level, and psychological problems in the first step, followed by child genotypes, followed by maternal discipline, the interactions between child genotypes and maternal discipline, between child COMT rs4680 genotype and DRD4-7R polymorphism, and the three-way interactions between COMT, DRD4, and maternal discipline. Interaction terms between maternal discipline style and child genotype were computed after centering of the constituent variables. If interaction effects were significant, the sample was stratified by genotype to investigate the associations between maternal discipline style and committed compliance per genotype group. Furthermore, if interaction effects were significant regions of significance were estimated to further examine the differential susceptibility hypothesis (Hayes & Matthes, 2009).

Results

Distribution of main variables

Children had an average compliance score of 0.01 (range -3.31–0.84, $SD = 1.00$; transformed: $M = 0.75$, $SD = 0.19$). Mothers had an average score of 0.04 (range = -4.91–3.55, $SD = 1.54$; transformed: $M = 1.80$, $SD = 0.35$) on maternal positive discipline and an average score of -0.03 (range = -2.25–8.63, $SD = 1.46$; transformed: $M = 0.57$, $SD = 0.15$) on maternal negative discipline. The mean score for maternal family stress during pregnancy was 1.41 (range 1.00–3.50, $SD = 0.40$; transformed: $M = 1.24$, $SD = 0.18$), and the mean score for general stress was 0.14 (range 0.00–1.17, $SD = 0.18$; transformed: $M = 0.27$, $SD = 0.26$), indicating that the majority of mothers reported relatively low levels of general and family stress during pregnancy. The average global severity of maternal psychological problems was 7.70 (range 0.00–77.00, $SD = 9.58$; transformed: $M = 1.68$, $SD = 0.32$).

Bivariate associations with background variables[2]

Girls were more compliant ($M = 0.78$, $SD = 0.18$) during the discipline task than boys ($M = 0.72$, $SD = 0.20$), $p < .01$. Mothers used fewer negative discipline strategies toward girls ($M = 0.54$, $SD = 0.14$) than toward boys ($M = 0.60$, $SD = 0.15$), $p < .01$, and more positive discipline strategies toward girls ($M = 1.85$, $SD = 0.35$) than toward boys ($M = 1.75$, $SD = 0.33$), $p < .01$. Younger mothers reported more general stress during pregnancy than older mothers, $r(611) = -.08$, $p < .05$. Highly educated mothers reported less family stress during pregnancy ($M = 1.23$, $SD = 0.18$) than mothers with a lower educational level ($M = 1.27$, $SD = 0.18$), $p < .01$. Highly educated mothers also used fewer negative discipline strategies ($M = 0.56$, $SD = 0.15$) during the discipline task than mothers with a lower educational level ($M = 0.59$, $SD = 0.14$), $p < .05$, and more positive discipline strategies ($M = 1.82$, $SD = 0.35$) than mothers with a lower educational level ($M = 1.76$, $SD = 0.34$), $p < .05$. Higher levels of family stress and general stress during pregnancy were correlated with higher levels of maternal psychological problems at 2 months after birth, $r(434) = .14$, $p < .01$ and $r(426) = .25$, $p < .01$.

[2] Means and standard deviations are reported of the transformed data.

Bivariate correlations among main variables

The bivariate correlations among the main variables are presented in Table 1. Child COMT rs4680 genotype (additive: 0, 1, or 2 valine alleles) was correlated with committed compliance; children with more Val alleles were more compliant than children with more Met alleles. Family stress and general stress as reported by the mother during pregnancy were positively correlated. Higher levels of family stress also predicted less positive discipline at 36 months. Children of mothers with a higher level of family stress during pregnancy were less compliant during the discipline task at 36 months of age. Maternal positive discipline was negatively correlated with maternal negative discipline. Maternal positive discipline was correlated with a higher level of committed compliance, and maternal negative discipline was correlated with a lower level of committed compliance (observed in different settings). General stress during pregnancy was not related to parenting style or committed compliance at 36 months.

Table 1. *Correlations between child compliance and predictor variables.*

	General Stress	Family Stress	Positive Discipline	Negative Discipline	Committed compliance
COMT rs4680	-.01	-.09	.08	-.08	.11*
General Stress		.24**	.01	.01	.03
Family Stress			-.12**	.07	-.10*
Positive Discipline				-.69**	.36**
Negative Discipline					-.43**
Committed Compliance					

* $p < .05$, ** $p < .01$.

Family stress, discipline, and committed compliance: Mediation?

We tested whether the relation between family stress during pregnancy and child committed compliance at 36 months was mediated by positive or negative maternal discipline strategies. As shown in Table 1, family stress during pregnancy indeed predicted less positive maternal discipline at 36 months (step 1). The level of family stress during pregnancy also predicted committed compliance at 36 months (step 2), and maternal positive discipline was positively associated with committed compliance at 36 months (step 3). To test the fourth criterion of Baron and Kenny (1986) a hierarchical regression analysis was performed in which family stress during pregnancy was entered first and maternal positive discipline was entered second. The standardized regression weight of the association between family stress during pregnancy and committed compliance decreased from $\beta = -10$, $p < .05$ to $\beta = -.05$, $p = .17$. This suggests that the association between family stress during pregnancy and committed compliance at 36 months was mediated by maternal positive discipline. Sobel's test of the indirect effect of family stress via maternal positive discipline was significant, $z = -2.94$, $p < .01$. The mediation model is presented in Figure 2.

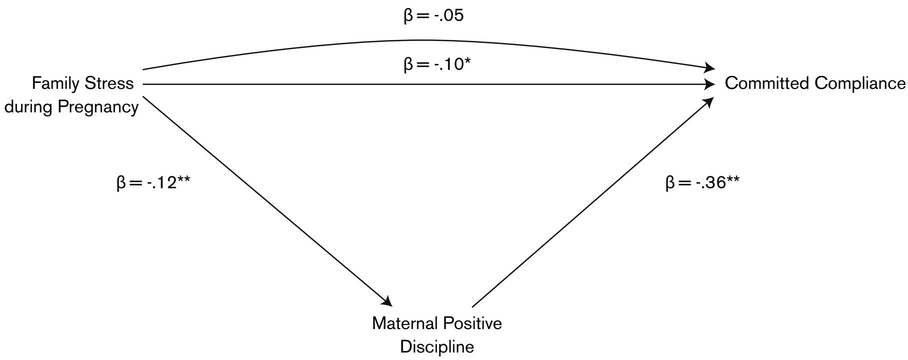

Figure 2. Maternal positive discipline mediates the association between family stress during pregnancy and child committed compliance.

The specificity of family stress as a predictor in this mediation model was supported by the fact that maternal *general* stress during pregnancy was neither associated with maternal discipline style at 36 months, nor with committed compliance at 36 months. The difference in correlations of maternal positive discipline with family stress ($r[611] = -.12$, $p < .01$) and with general stress ($r[611] = .01$, $p = .89$) was significant, $z = 1.93$, $p < .05$. The specificity of maternal positive discipline as the mediator appeared confirmed by the fact that family stress during pregnancy did not significantly predict maternal *negative* discipline at 36 months (see Table 1). However, the difference in correlations of family stress during pregnancy with maternal negative discipline ($r[611] = .07$, $p = .09$) and with maternal positive discipline ($r[611] = -.12$, $p < .01$) was not significant, $z = -0.88$, $p = .19$.

Maternal discipline and committed compliance: moderation by DRD4 or COMT?

To investigate whether DRD4 polymorphism or COMT genotype moderated the association of maternal positive and negative discipline with committed compliance a hierarchical regression analysis was performed in which we controlled for the covariates child gender, maternal age, educational level, and psychological problems. Two-way interaction effects and three-way interaction effects remained in the analysis if significant. The results of the final regression model based on the imputed datasets are presented in Table 2.

Table 2. *Predictors of child committed compliance (N = 436).*

	Committed Compliance						
	B	*SE*	β[a]	*t*	*p*	R^{2a}	$R^2change^a$
Step 1						.03	.03
Gender	.02	.02	.05	1.16	.25		
Educational level	-.01	.02	-.03	-.64	.52		
Age mother	.00	.00	.04	.98	.33		
Mat. psych. problems	.00	.03	.00	.05	.96		
Step 2						.04	.02
DRD 4	.02	.01	.09	1.97	<.05		
COMT rs4680	.02	.01	.06	1.40	.16		
Step 3							
Pos. Disc.	.05	.03	.09	1.44	.15	.20	.16
Neg. Disc.	-.43	.08	-.33	-5.53	<.01		
Step 4						.21	.01
COMT x Pos. Disc.	-.09	.04	-.11	-2.46	<.05		

Note. Betas are taken from the final models.
[a] Averages taken from the final regression models of the 15 imputed datasets.

There was a significant association between DRD4 and committed compliance, $\beta = .09$, $p < .05$, indicating that children with one or more 7-repeat alleles were more compliant than children with no 7-repeat allele. There was no significant association between COMT rs4680 genotype and committed compliance, $\beta = .06$, $p = .16$. After controlling for child genotype and maternal negative discipline, higher levels of maternal positive discipline were no longer associated with child compliance at 36 months, $\beta = .09$, $p = .15$. Higher levels of maternal negative discipline were associated with less committed compliance at 36 months, $\beta = -.33$, $p < .01$. The three-way interactions for DRD4, COMT, and maternal positive and maternal negative discipline were not significant and therefore excluded from the analysis. The two-way interaction terms for DRD4 and maternal positive discipline and DRD4 and negative discipline, and the two-way interaction term for COMT genotype and negative discipline were also not significant and excluded from the analysis. The two-way interaction effect of COMT rs4680 and positive discipline on committed compliance was however significant. COMT rs4680 genotype moderated the association between maternal positive discipline and child compliance, $\beta = -.11$, $p < .05$, R^2change = .01. Results were similar when we controlled for maternal anxiety or maternal depression instead of global severity of psychological problems.

Analyses of the association between maternal positive discipline and committed compliance per genotype indicated that the association was stronger for the Met/Met carriers ($r[106] = .51$, $p < .01$) than for the Val/Met carriers ($r[223] = .29$, $p < .01$) or the Val/Val carriers, ($r[101] = .16$, $p = .10$). The slope of the Met/Met carriers differed significantly from the slope of the Val/Met carriers, $z = 2.23$, $p < .05$, and from the slope of the Val/Val carriers, $z = 2.87$, $p < .01$. We estimated regions of significance to further test the interaction effect of COMT rs4680 genotype and maternal positive discipline on committed compliance. The lower and upper bounds of the regions of significance were 0.00 and 0.98, respectively. This indicates that the interaction effect was significant for both the lower end of maternal positive discipline and the higher end of maternal positive discipline. The unadjusted associations between maternal positive discipline and committed compliance per genotype, with the regions of significance as shaded areas, are displayed in Figure 3.

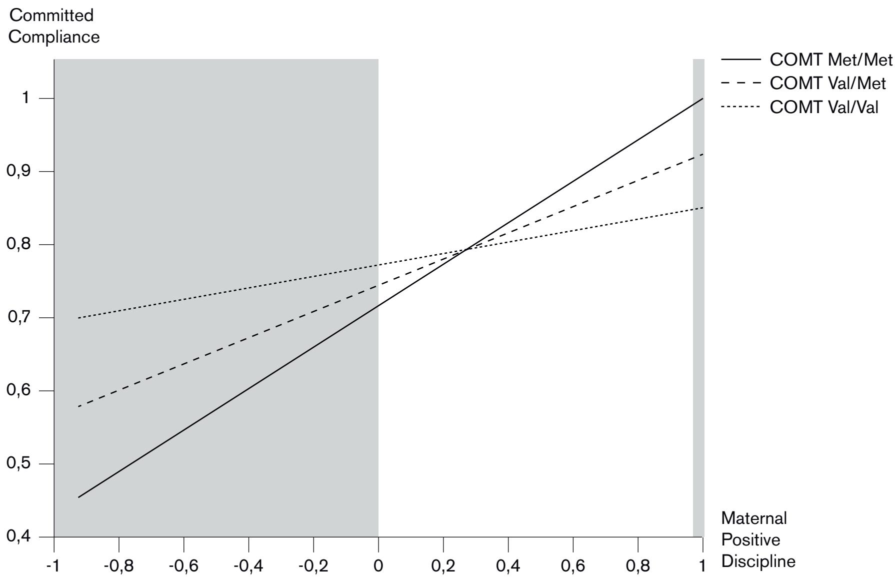

Figure 3. Interaction between COMT rs4680 and maternal positive discipline predicting child committed compliance. The shaded areas represent regions of significance.

Discussion

In our prospective cohort study, starting from fetal life, family stress during pregnancy predicted lower levels of committed compliance at 36 months of age, through lower levels of maternal *positive* discipline in toddlerhood. The positive association between maternal positive discipline and committed compliance was moderated by COMT rs4680 genotype, in that the association was stronger in children with the Met/Met genotype than for children with other COMT genotypes.

The results indicate that maternal family stress during pregnancy is associated with child self-regulation through its negative association with maternal discipline. These findings are in accordance with the spillover hypothesis (Erel & Burman, 1995) which states that parents with a positive and supportive marital relationship will be better able to sensitively respond to their children's needs, whereas parents with a stressful marital relationship may have fewer resources to provide a sensitive environment for their child. Because family stress was measured prenatally in our study and 61% of children were firstborn, this measure mostly represented stress related to the partner relationship. In 39% of cases other siblings could have influenced the measure of family stress. However, several empirical studies and meta-analyses have confirmed that not only marital discord but also other family stressors (e.g., home chaos or job-role dissatisfaction) can negatively affect parent-child interaction (Erel & Burman, 1995; Kanoy et al., 2003; Krishnakumar & Buehler, 2000; Nelson et al., 2009).

The mediation pathway through parenting complements the literature focusing on effects of prenatal stress on child development through prenatal programming effects (e.g., Bergman et al., 2007; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003; O'Donnell, O'Connor, & Glover, 2009). Although in our study we cannot rule out any intrauterine effects of family stress on the fetus, at least part of the effect on child development seems to be through the postnatal rearing environment. A recent study with a prenatal cross-fostering design in pregnancies through in vitro fertilization disentangled inherited and environmental influences on child health outcomes and also found a mediation pathway from maternal stress during pregnancy through postnatal environmental factors to child psychopathology (Rice et al., 2010). Other studies found protective effects of maternal sensitivity and attachment security in the association between maternal stress during pregnancy and child development (Bergman, Sarkar, Glover, & O'Connor, 2010; Grant, McMahon, Reilly, & Austin, 2010). Our findings emphasize the importance of the influence of parenting on the child, in addition to biological and genetic effects, for the association between maternal stress during pregnancy and child development.

Our study population represented a homogeneous, socio-economically advantaged group that experienced relatively low levels of prenatal family stress and general stress. We should therefore be cautious in generalizing our findings to less advantaged populations. On statistical grounds the influence of prenatal stress on child compliance through parenting will rather be an underestimation than an overestimation of the effect in the whole population.

The effect of stress during pregnancy on maternal discipline and committed compliance was specific for family-related stress and not found for general stress. Family stress may be more severe and therefore exert a more pronounced effect on parenting and child development. Previous studies by Bergman and colleagues (2007) and Stott (1973) also found that the effects of stress during pregnancy on parenting and child behavior are mainly accounted for by family-related stressors. However, because our measure of general stress concerned the whole preceding year the stressful events did not necessarily occur during pregnancy. This might explain why the association between family stress with maternal discipline and child compliance was stronger than for our measure of general stress. However, the content of the questionnaire did refer to long-lasting difficulties, which implies that they will not often be resolved within a short period. Because even the relatively low levels of family stress that mothers in our sample experienced during pregnancy affected maternal discipline and child compliance, this study offers important knowledge on the mechanisms underlying the spillover effect of family stress during pregnancy on parenting.

The effect of family stress on committed compliance was mediated by maternal positive discipline but not by negative discipline. Although the association between the two discipline strategies appeared to be rather strong, positive discipline and negative discipline seem not to represent the ends of one continuum. The specificity of the effect could however also be explained by the fact that our sample was relatively homogeneous, consisting of Native Dutch and middle class participants. We could not investigate the effect on more harsh types of maternal discipline, because mothers in our sample hardly showed any harsh discipline strategies. Perhaps only very severe family stress is associated with a more extreme level of maternal negative discipline style. Maternal negative discipline did appear to be a stronger predictor of child committed compliance than maternal positive discipline. We investigated the specific effect of maternal family stress *during pregnancy* on maternal discipline. Because mothers reported family stress prenatally this measure was independent of child behavior after birth and this measure could therefore not be confounded by child compliance, temperament, or other child factors.

Committed compliance and maternal discipline style were measured at the same age, thus bidirectional effects cannot be ruled out. Previous studies have stressed the importance of investigating the bidirectional nature of mother-child interaction (Combs-Ronto, Olson, Lunkenheimer, & Sameroff, 2009; Smith, Calkins, Keane, Anastopoulos, & Shelton, 2004). However, studies by Calkins (2002) and Del Vecchio and Rhoades (2010) indicate that the influence of maternal discipline on child behavior is larger than vice versa.

Unexpectedly, children with 7-repeat alleles were more compliant at 36 months than children with no 7-repeat alleles ($\beta = .09$). This seems to contrast with studies on associations between the 7-repeat allele of DRD4 and negative developmental outcomes, for example Attention Deficit Hyperactivity Disorder (for a meta-analysis see Faraone, Doyle, Mick, & Biederman, 2001). It has, however, also been found that children with a 7-repeat allele were more timid in response to new stimuli and showed low levels of excitation compared to children without 7-repeat alleles (De Luca et al., 2003). Furthermore, Auerbach, Faroy, and Ebstein (2001) found that children with the long variant of the DRD4 genotype showed less active resistance and fewer struggles in response to arm restraint. Timidity and lower levels of excitation in the disciplinary task in our study could explain our observation of little resistance and higher levels of compliance in children with 7-repeat alleles.

DRD4 did not moderate the association between maternal discipline and committed compliance ($\beta = .06$), though previous studies reported interaction effects of DRD4 and parenting on various aspects of child development. Some studies found that the children with one or more 7-repeat alleles were more susceptible to parenting (e.g., Bakermans-Kranenburg & Van IJzendoorn, 2011; Knafo, Israel, & Ebstein, 2011) others found that children without 7-repeat alleles were more affected by parenting (e.g., Gervai et al., 2007; the African-American subsample of Propper, Willoughby, Halpern, Carbone, & Cox, 2007). The difference between our findings and the findings of the above-mentioned studies might be an indicator that differential susceptibility is domain-specific instead of domain-general (Ellis et al., 2011). Because our parenting measure and our child outcome were different from these studies, we cannot confirm nor disprove the possibility of DRD4 to moderate the relation between parenting and child behavior. To our knowledge the current study is the first to investigate the moderating role of DRD4 and COMT in the association between maternal positive discipline and committed compliance. The current findings should be further investigated and replicated in future studies.

The COMT Met homozygous children were more hampered in the development of committed compliance by low levels of maternal positive discipline but they also appeared to be more positively affected by a higher level of maternal positive discipline. Though the interaction between COMT genotype and maternal discipline was only significant at the extremes, the pattern is indicative of differential susceptibility. These findings correspond to Dreher, Kohn, Kolachana, Weinberg, and Bermann (2009)' findings on differences in responses to reward related to COMT genotype. They found that Met carriers showed higher levels of activation in the orbitofrontal cortex than Val carriers when receiving a reward, which might reflect higher saliency of reward value in Met carriers. Similarly, Wichers and colleagues (2008) found that the ability to experience rewards, operationalized as the effect of minor daily event appraisals (neutral, pleasant, or very pleasant) on the level of positive affect, was higher for participants with more Met alleles. This effect was even more pronounced for pleasant events. An increased susceptibility of children with the Met/Met genotype to rewarding cues might be due to larger increases in dopamine levels in prefrontal, orbitofrontal, and limbic regions as a result of these cues (e.g., Drabant et al., 2006; Dreher et al., 2009). Effects of parental supervision on alcohol use were also found to be larger in Met/Met carriers than in Val carriers (Laucht et al., 2012).

The interaction effect of child COMT genotype with maternal positive discipline accounted for only 1% of explained variance of the total of 21% for the whole model. This is a small effect, but even moderator effects that explain only 1% of the variance should be considered important because with this magnitude of explained variance the chances are small that incorrect conclusions are drawn or that interactions are observed when none exist (Evans, 1985). COMT and DRD4-7R were the only polymorphisms that were tested for main effects on child committed compliance and moderation of the relationship between maternal discipline and child committed compliance. Future studies should replicate our findings, also in less advantaged populations and in other ethnic groups. It would be important to involve fathers' self-reported family stress together with paternal discipline style in future models to further ground the effects of family stress on child development through postnatal rearing environment. To separate the contributions of the effects of stress during pregnancy through prenatal programming from effects on postnatal rearing environment both models should be tested simultaneously in one study with observations of environmental factors.

It should be noted that the Val allele was the minor allele in our study. In European-Caucasian populations the Met allele is often the minor allele (e.g., Perroud et al., 2010; Smolka et al., 2007), though a number of studies report a higher prevalence of the Met allele (compared to the Val allele) in European descent populations (e.g, Collip et al., 2011; Van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008; Wishart et al., 2011).

Non-response analyses on the mothers and children that had to be excluded due to missing data indicated that mothers used less positive discipline and more negative discipline, and that they experienced less family stress during pregnancy. These differences imply that the excluded mothers were less able to use sensitive discipline strategies when disciplining their child which might have resulted in a restricted range of maternal behavior in the current sample. Maternal psychological problems at 2 months were not associated with maternal discipline, child COMT rs4680 genotype, or committed compliance. Because COMT rs4680 genotype has often been associated with maternal psychopathology, the absence of a relation between psychological problems and parenting or committed compliance indicates that the gene-environment interaction we found is unlikely to be due to a gene-environment correlation.

The current study provides evidence for a spillover effect of maternal family stress during pregnancy on maternal discipline during toddlerhood, which is associated with a less optimal level of self-regulation in children. The magnitude of the influence of maternal positive discipline appeared to depend on the child's susceptibility to discipline that turned out to be associated with the dopamine-related COMT genotype. These findings underline the importance of including gene-environment interactions when investigating the development of self-regulation.

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4

Parenting, corpus callosum, and executive function in preschool children

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Abstract

In this longitudinal population-based study ($N = 544$) we investigated whether early parenting and corpus callosum length predict child executive function (EF) abilities at 4 years of age. The length of the corpus callosum in infancy was measured using postnatal cranial ultrasounds at six weeks of age. At 3 years, two aspects of parenting were observed: maternal sensitivity during a teaching task and maternal discipline style during a discipline task. Parents rated EF problems at 4 years of age in five domains of inhibition, shifting, emotional control, working memory, and planning/organizing, using the Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P). Maternal sensitivity predicted less EF problems at preschool age. A significant interaction was found between corpus callosum length in infancy and maternal use of positive discipline to determine child inhibition problems: In children with a relatively shorter corpus callosum in infancy more positive discipline predicted lower levels of child inhibition problems. Our results point to the buffering potential of positive parenting for children with biological vulnerability.

Introduction

Executive function (EF) is an umbrella term for several higher-order, self-regulatory functions such as inhibitory control, working memory, planning ability, and attention shifting, which start to develop in the first five years of life (Bernier, Carlson, Deschênes, & Matte-Gagné, 2012; Garon, Bryson, & Smith, 2008; Hughes & Ensor, 2009). Early variation in the development of EF has been found to predict social functioning (Spinrad et al., 2007) and school functioning (e.g., Monette, Bigras, & Guay, 2011) at a later age. Also, problems in the development of EF have been implicated in several types of developmental disorders and psychopathologies, such as autism, Attention-Deficit Hyperactivity Disorder (Luna, Doll, Hegedus, Minshew, & Sweeney, 2007; for a review, see Pennington & Ozonoff, 1996), and depression (Maalouf et al., 2011). Prior studies on differences in EF development have mainly focused on the genetic component of EF (Friedman et al., 2008; Jester et al., 2009; Polderman et al., 2007) and its association with brain development (Ghassabian et al., 2012; Jacobs, Harvey, & Anderson, 2011; Skranes et al., 2009). Some recent studies assessed not only biological parameters but also environmental influences on EF development (e.g., Bernier et al., 2012; Carlson, 2009; Garon et al., 2008; Hughes, 2011). The current study examines whether early parenting influences child EF at preschool age independent of the impact of infant brain development as demonstrated in a previous study on the same sample (Ghassabian et al., 2012).

The complexity and diversity of EF has resulted in a multitude of definitions in empirical research (Jurado & Rosselli, 2007). Originally, EF has been described as a unitary construct but due to the complexity of the construct a multifactorial view of distinct but related EF domains seems more plausible (Garon et al., 2008; Jurado & Rosselli, 2007). EF develops over an extended period starting in infancy in which externalized monitoring is gradually replaced by internal regulation (Bernier et al., 2011), followed by a rapid development of functions during early childhood (Anderson, 2002) and further maturation of EF domains in adolescence (Crone, 2009). One focus of research in EF development has been its association with maturation or integrity of brain structures in children and adults. The prolonged developmental trajectory of EF domains during child development parallels the development of the prefrontal cortex (PFC), which makes this brain region a natural candidate to be involved in EF (Bernier et al., 2012; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000).

A meta-analysis by Alvarez and Emory (2006), however, showed that empirical support is inconsistent for the association between EF and frontal lobe functioning. Their analysis of studies on adults with brain lesions resulted in the conclusion that both frontal and non-frontal brain regions are involved in EF. Similarly, Jacobs, Harvey, and Anderson (2011) compared children with frontal pathology to children with pathology in other brain areas and to control subjects on several EF domains. All children with brain pathology showed EF deficits irrespective of the site of the damage. Studies in children with very low birth weight demonstrated that the accompanying white matter abnormalities in the corpus callosum are related to their EF problems (e.g., Skranes et al., 2009; Woodward, 2011). Similarly, in the large population-based cohort study Generation R we found that children with a shorter corpus callosum in infancy showed more EF problems at preschool age (Ghassabian et al., 2012). In summary, most recent evidence indicates that EF skills not only rely on the integrity of the prefrontal cortex but also on the quality of the white matter connections between the frontal regions and other brain regions, such as the corpus callosum, and the integrity of those connected regions (Anderson, 2002; Jacobs et al., 2011; Skranes et al., 2009; Woodward, 2011).

Because EF has an extended postnatal developmental course, EF development is particularly sensitive to environmental influences (e.g., Bernier et al., 2012; Conway & Stifter, 2012). The potential short and long term effects of early caregiving on offspring development have been established in animal and human research (e.g., Champagne, Francis, Mar, & Meaney, 2003; Sroufe, Coffino, & Carlson, 2010). Recent studies focusing on the association between parenting quality and EF development in children also emphasize the importance of early experiences in the family environment. A study by Jennings and colleagues (2008) demonstrated that maternal warmth during teaching predicted greater inhibitory capacity in toddlers. In preschoolers, maternal scaffolding (support and guidance of goal-directed activities), maternal planning, and consistent parenting were each found to predict the development of EF (Hughes & Ensor, 2009). A study on the influence of parenting on EF subdomains showed that in early childhood maternal autonomy support was the strongest predictor of child working memory and set shifting abilities 3 to 14 months later but that no parenting factor predicted child impulse control (Bernier, Carlson, & Whipple, 2010).

In a follow-up study (Bernier et al., 2012) of the role of maternal and paternal parenting and child attachment security in the development of child working memory, set shifting, inhibitory control (summarized as conflict-EF), and impulse control parenting also did not predict impulse control. Attachment security appeared to be the only contributor to conflict-EF. Studies on the association between disciplinary strategies of parents and child EF or self-regulatory abilities have shown that physically punitive discipline can be detrimental for self-regulation (Colman, Hardy, Albert, Raffaelli, & Crockett, 2006) and that positive control strategies are associated with child compliance, a self-regulatory domain, though the overall effect size of this relation in a recent meta-analysis was small (Karreman, Van Tuijl, Van Aken, & Dekovic, 2006).

The aim of the present study was to combine the socialization perspective with the neuroscience perspective and to investigate in a large population-based cohort study whether early parenting predicts child EF abilities at a later age, independent of infant brain development. In a previous report on the current sample we found that the length of the corpus callosum in infancy was associated with EF at 4 years of age (Ghassabian et al., 2012). Here we examine whether independently or in interaction with corpus callosum length maternal sensitivity and maternal discipline style at child's age of 3 years predicted child EF problems at 4 years. We included two aspects of parenting, maternal sensitivity and maternal discipline, because previous studies have found differences in associations between various parenting aspects and EF abilities in children (e.g., Bernier et al., 2010; Hughes & Ensor, 2009; Karreman et al., 2006). We investigated the influence of parenting on multiple domains of EF problems in children: inhibition, shifting, planning, emotional control, and working memory, because EF is a complex construct which is difficult to capture in a unitary score (Anderson, 2002; Garon et al., 2008; Jurado & Rosselli, 2007; Schroeder & Kelly, 2010) and because not all EF domains might be equally influenced by early parenting (e.g., Bernier et al., 2010; Hughes & Ensor, 2009; Karreman et al., 2006; Schroeder & Kelly, 2010).

Method

Setting

The current investigation is embedded within the Generation R Study, a prospective cohort investigating growth, development, and health from fetal life onwards in Rotterdam, the Netherlands (Jaddoe et al., 2008, 2012). Detailed measurements were obtained in a subgroup of children of Dutch national origin, meaning that the children, their parents, and their grandparents were all born in the Netherlands to reduce confounding and effect modification (e.g., Luijk et al., 2010; Tharner et al., 2011). Children with a delivery date between February 2003 and August 2005 were enrolled. Data were collected with questionnaires and during visits to the research centre for behavioral assessments. All measures were approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants.

Study population

In the current study postnatal cranial ultrasounds, questionnaire data, and observation data of the lab visit at 3 years are presented. A total of 904 neonates and their parents attended the lab visit for the postnatal cranial ultrasound. Because of potential differences in brain development of fetuses born to multiple and singleton pregnancies, we excluded 10 twin pairs. Eight mothers participated in the 3-year visit twice, with siblings. One child of each sibling pair was randomly selected for the analyses to avoid paired data. Of the remaining neonates ($n = 876$) we obtained 774 ultrasound images of corpus callosum length with sufficient quality. For 79% of these 774 eligible mother-child dyads observed maternal sensitivity and discipline at child age of 3 years were available. Reasons for missing observed parenting data were attrition, participation in the 3-year visit with father or grandparent, and technical or procedural difficulties during the mother-child interaction tasks. Of the remaining 613 mother-child dyads, parental report on child EF at 4 years was available for 544 children.

Non-response analyses were performed comparing these 544 mother-child dyads with the 230 mother-child dyads excluded from the analyses on predictors and background variables. Mothers excluded from the analyses were younger than mothers included in the sample, $t(367.97) = -3.02$, $p < .01$, and boys were more often excluded than girls, χ^2 $(1, 774) = 6.84$, $p < .01$. Children excluded from the analyses had a lower gestational age at birth than children included in the sample, $t(772) = -3.00$ $p < .01$. Children excluded from the analyses were 0.5 weeks older at the 6 weeks cranial ultrasound than children included in the sample, $t(383.70) = 2.31$, $p < .05$. Children excluded also had more emotional control problems around 4 years of age than children included in the sample, $t(648) = 2.90$, $p < .01$. All differences between the two groups were small (range of explained variance: 1%-2%).

Measures

Executive function problems

When the children were around 4 years of age ($M = 48.5$ months, $SD = 1.04$), the Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P) was used to measure EF problems (Gioia, Espy, & Isquith, 2003). The BRIEF-P is a parent-completed questionnaire to assess EF behaviors in a broad age range of preschoolers (2-5 years). It contains 63 items within five related but non-overlapping theoretically and empirically derived clinical scales that measure children's ability in different aspects of EF: *inhibition* (16 items), to stop his/her own behavior; *shifting* (10 items), to change focus from one mindset to another; *emotional control* (10 items), to modulate emotional responses; *working memory* (17 items), to hold information in mind for the purpose of completing a task; and *planning/organization* (10 items), to manage current and future-oriented task demands within the situational context. Parents were asked to rate how often a particular behavior was problematic in the preceding month on a 3-point scale (never, sometimes, often). A sum score (the Global Executive Composite) can be derived by adding the scores of the five domains. The clinical raw scores and the composite scores yield *T*-scores based on gender and age. Higher scores indicate more problems with EF.

The BRIEF-P measures EF in a naturalistic setting and does not have the limitations of performance-based tests and environmental effects during the administration. Correlations between the scales of the BRIEF-P and performance-based EF measures are positive and consistent though modest only (Mahone & Hoffman, 2007). The content validity and internal consistency of the BRIEF-P are adequate, and the subscales of the BRIEF-P and the Global Executive Composite show adequate to high test-retest reliability (Sherman & Brooks, 2010). The distributions of subscale *T*-scores and the Global Executive Composite *T-s*core were skewed and therefore scores were transformed with natural logarithm to approach normality.

Cranial ultrasound measurements

Postnatal cranial ultrasounds were performed in infants at the age of 6.7 weeks ($SD = 1.7$) with a commercially available multifrequency electronic transducer (3.7-9.3 MHz) with a scan angle of 146°, usable for 3-dimensional volume acquisition (Voluson 730 Expert, GE Healthcare, Waukesha, WI, USA). The details of ultrasound measurements have been described previously (Herba et al., 2010; Roza et al., 2008). The probe was positioned on the anterior fontanel and a volume box was placed at the level of the foramen of Monro in a symmetrical coronal section. A pyramid-shaped volume of the brain tissue was scanned and the diameter of brain structures were measured offline. Two raters, trained by a neonatologist with expertise in neonatal cranial ultrasound imaging (P.G.), independently measured every image. Raters also coded the quality of the ultrasound image on a 3-point rating scale, based on the ability to clearly delineate the boundaries of the structures. We excluded images with a quality rating of "very poor" by both raters.

In the best mid-sagittal view, we defined the corpus callosum length as the largest diameter from rostrum to splenium (see Figure 1). Commonly, the thickness of corpus callosum, as measured by MRI, is used in neuroimaging studies (Stewart et al., 1999). However, with ultrasound techniques variations in the thickness of corpus callosum cannot be reliably measured (Anderson et al., 2004). Therefore, we used the measurement along the entire body of the corpus callosum and obtained an average corpus callosum length using measurements from the two raters. The interrater reliability of the corpus callosum length was good (Cronbach's $\alpha = .85$, intra-class correlation coefficient [ICC] = .85; Ghassabian et al., 2012).

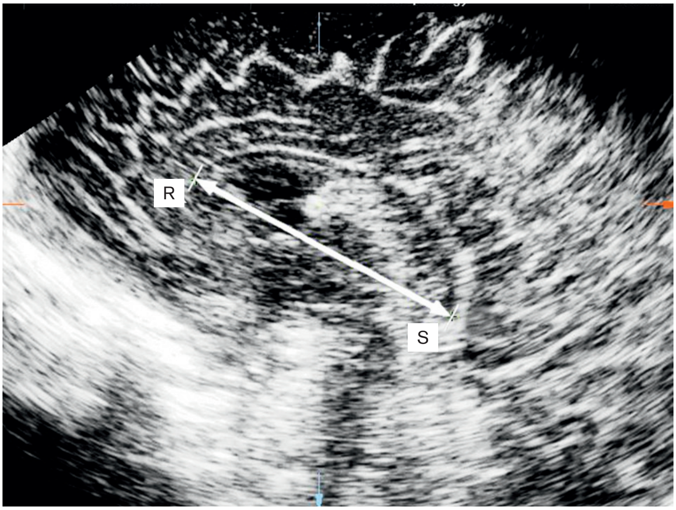

Figure 1. Corpus Callosum Length: largest diameter from rostum (R) to splenium (S).

Parenting

Sensitivity

At 3 years maternal sensitivity was observed when mother and child performed two tasks that were too difficult for the child: building a tower and an etch-a-sketch task. Mothers were instructed to help their child as usual. Maternal sensitivity was coded from DVD recordings with the revised Erickson 7-point rating scales for Supportive Presence and Intrusiveness (Egeland, Erickson, Clemenhagen, Hiester, & Korfmacher, 1990). The subscales Supportive Presence and Intrusiveness were coded for each task. An overall sensitivity score was created by reversing the Intrusiveness scales, standardizing all scores, and creating an average over both scales and both tasks. The two tasks were independently coded by 13 trained coders. Coders were unaware of other data concerning the mother-child dyad. Coders were extensively trained and regularly supervised. Reliability of the coders was assessed directly after the training and at the end of the coding process to detect possible rater drift. ICCs for the subscales were .75 on average for the tower task (range .73 - .77, $n = 53$) and .79 on average for the etch-a-sketch task (range .65 - .93, $n = 55$; Kok et al., 2012a).

Discipline style
Maternal discipline was observed at 3 years in a disciplinary context. In this task of 2 minutes the parent prohibited the child to touch or play with a set of attractive toys that were displayed before the child. Coding procedures were based on Kuczynski, Kochanska, Radke-Yarrow, and Girnius-Brown (1987) and Van der Mark, Van IJzendoorn, and Bakermans-Kranenburg (2002). Maternal verbal and physical discipline strategies were observed and coded in different categories: Commands, Support, and Physical obstruction or interference (micro coded); and with the revised Erickson 7-point rating scale for Supportive Presence (macro coded; Egeland et al., 1990). Both micro- and macro coding strategies were used because they represent two different types of parental behavior: planned and intuitive behaviors, probably reflecting two dimensions of the same underlying construct (Mesman, 2010). To create a comprehensive picture of positive and negative strategies, micro codes and macro codes were combined. Commands were coded when mothers prohibited their child to touch or play with toys in an authoritarian manner. Support involved all maternal remarks that helped the child to comply, such as distracting the child from the toys and responding to what the child said. Physical obstruction or interference was coded when mothers used physical force to keep the child from touching the toys. The mother's supportiveness toward her child during the discipline task was coded with the Supportive Presence scale, which refers to the level of positive regard and emotional support the mother shows toward the child. A supportive mother is a reassuring, calm, and affectively positive secure base for the child. Support and Supportive Presence represent a maternal positive discipline style. Commands and Physical obstruction are indicators of maternal negative discipline style.

Maternal behavior was coded by five trained coders. Coders were unaware of other data concerning the mother-child dyad. Coders were extensively trained and regularly supervised. Reliability of the coders was assessed directly after the training and at the end of the coding process to detect possible rater drift. The number of times a specific behavior was coded was divided by the total number of codings to create a relative score for each behavioral category. This resulted in scores for each category that were independent of the number of maternal messages. Intercoder reliability was adequate (ICC for Commands was .85, for Support .85, for Physical Interference .90, and for Supportive Presence .79, $n = 57$; Kok et al., 2012b). A principal components analysis on z-standardized discipline components was conducted. The first component explained 53.5% of the variance, and factor scores were extracted by regression method. Higher scores on the overall maternal discipline composite indicate a more positive discipline style and lower scores indicate a more negative discipline style. The overall maternal discipline composite was square root transformed to normality.

Covariates

Maternal depressive symptoms

Maternal depressive symptoms at 20 weeks of gestation and at child's age of 3 years were assessed by postal questionnaires with the 6-item depression scale of the Dutch version (De Beurs, 2004) of the Brief Symptom Inventory (Derogatis, 1993; Derogatis & Melisaratos, 1983), a validated self-report questionnaire of 53 items which is widely used to assess psychological distress. Sum scores were divided by the number of endorsed items with a maximum of one missing item allowed. The internal consistency of the depression scale in the current study was $\alpha = .73$ during pregnancy and $\alpha = .78$ at child's age of 3 years. Scores were transformed inversely to approach a normal distribution and reversed for interpretation purposes.

Background variables

Gestational age at birth was obtained from community midwife and hospital registries at birth. We adjusted the analyses for gestational age at birth as an indicator of the biological risk of developmental delays (MacKay, Smith, Dobbie, & Pell, 2010; Yang, Platt, & Kramer, 2010). The age of the child in weeks and the head circumference were registered at the time of the cranial ultrasound measurement. We adjusted all analyses for head circumference and age of the child at the time of ultrasound to ensure that the effects did not reflect the association with head size or with maturity. The age of the mother and her educational level were reported at the intake of the Generation R Study. Educational level was dichotomized as 'high' (at least higher vocational training or a bachelor's degree, $n = 370$) or 'low/medium' ($n = 168$). Information on maternal smoking during pregnancy was obtained by repeated self-reports in the first, second, and third trimester of pregnancy. Based on this information mothers were divided into two groups: mothers that never smoked in pregnancy ($n = 403$) versus mothers that smoked until pregnancy was known or continued smoking during pregnancy ($n = 95$).

Statistical analyses

Because of missing data on maternal educational level (1.1%), maternal smoking during pregnancy (8.5%), child age (0.4%) and head circumference at the postnatal cranial ultrasound (3.7%), and maternal depressive symptoms during pregnancy (5.3%) and at child's age of 3 years (4.8%) we generated five imputed data sets. Missing data were imputed with the predictive mean matching method in IBM SPSS Statistics, version 19.0.1 for Windows (Meulman, Heiser, & SPSS, 2010). Data were analyzed in separate data sets and subsequently pooled to obtain an overall result based on five imputations. Analyses conducted with the imputed data set ($N = 544$) yielded similar (significant) results compared to analyses with the complete data set ($N = 432$). Results of the imputed data set are presented unless otherwise indicated.

First, the bivariate associations among covariates, maternal parenting, corpus callosum length, and maternal parenting were determined. Second, linear regression analyses were performed to test whether maternal parenting at 3 years of age explained additional variance of child EF problems at 4 years of age above covariates and child brain development. In the regression equations we included covariates in the first step, followed by corpus callosum length, followed by maternal parenting, followed by interactions between corpus callosum length and maternal parenting (discipline and sensitivity). Interaction terms were computed after centering of the constituent variables. Non-significant interaction terms were removed from the model before interpreting the main effects. If interaction effects were significant, the sample was stratified by corpus callosum length based on a median split to investigate the associations between maternal parenting and child EF problems per subgroup.

Results

Sample characteristics are presented in Table 1. First, we studied gender differences on the main variables. The average corpus callosum length was larger in girls than in boys, $p < .01$. Mothers used more positive discipline behavior towards girls than towards boys, $p < .01$. Next, we studied differences on main variables by maternal educational level. Highly educated mothers demonstrated more positive discipline behavior than mothers with a lower educational level, $p < .05$, and demonstrated more sensitive behavior than mothers with a lower educational level, $p < .01$. Children of mothers with a higher educational level had a longer corpus callosum at 6 weeks of age than children of mothers with a lower educational level, $p < .05$. Mothers with a higher educational level reported lower levels of child inhibition problems at 4 years than mothers with a lower educational level, $p < .05$, lower levels of child working memory problems than mothers with a lower educational level, $p < .05$, and lower levels of child planning problems than mothers with a lower educational level, $p < .01$. Finally, mothers who smoked during pregnancy showed less sensitive behavior at 3 years of child's age than mothers who did not smoke during pregnancy, $p < .05$. Also, mothers who smoked during pregnancy reported higher levels of child working memory problems at 4 years than mothers who did not smoke during pregnancy, $p < .01$, and higher levels of child inhibition problems at 4 years, $p < .05$.

Table 1. *Sample characteristics.*

Child Characteristics		Maternal Characteristics	
Child gender, % female	52.0	Age at intake in years	32.11 (3.7)
Parity, % firstborn	63.9	Educational level, % high	68.5
Birth weight in grams	3516.56 (521.8)	Smoking during pregnancy, % yes	19.1
Gestational age in weeks	40.12 (1.6)	Positive Discipline	0.00 (1.0)
Corpus Callosum length in centimeter	4.63 (0.3)	Sensitivity	0.02 (0.7)
Inhibition Problem *T*-scores	47.67 (8.6)		
Shifting Problem *T*-scores	48.25 (8.3)		
Emotional Control Problem *T*-scores	47.98 (10.4)		
Working Memory Problem *T*-scores	47.08 (9.5)		
Planning Problem *T*-scores	45.56 (8.9)		
Global Executive Composite *T*-scores	46.60 (9.4)		

Note. Values are untransformed. Unless otherwise indicated, values are mean (*SD*).

The bivariate correlations among the main variables are presented in Table 2. A shorter corpus callosum at 6 weeks of age was correlated with higher levels of inhibition problems, emotional control problems, working memory problems, planning problems, and total EF problems at 4 years of age. Higher levels of maternal sensitivity were correlated with more positive maternal discipline. Higher levels of maternal sensitivity were associated with lower levels of inhibition problems, working memory problems, planning problems, and total EF problems one year later. More positive maternal discipline was also associated with lower levels of inhibition problems, working memory problems, and planning problems one year later. Correlations between the subdomains of EF problems were moderate to high.

Table 2. *Correlations between corpus callosum, maternal parenting, and child executive function problem T-scores.*

	Corpus Callosum	Sensitivity	Positive Discipline	Inhibition Pr.	Shifting Pr.	Emot. Contr. Pr.	Work. Mem. Pr.	Planning Pr.	Total EF Pr.
Head Circumference	.31**	.01	-.06	-.07	.06	-.05	-.12**	-.09*	-.07
Corpus Callosum		.02	-.03	-.12**	-.05	-.11*	-.10*	-.09*	-.13**
Sensitivity			.26**	-.18**	-.03	-.06	-.21**	-.17**	-.18**
Positive Discipline				-.09*	-.01	-.02	-.09*	-.09*	-.08
Inhibition Pr.					.33**	.58**	.70**	.64**	.86**
Shifting Pr.						.58**	.37**	.34**	.63**
Emot. Contr. Pr.							.47**	.48**	.78**
Work. Mem. Pr.								.74**	.85**
Planning Pr.									.80**
Total EF Pr.									

* $p < .05$, ** $p < .01$.

Pr. = problems; Emot. Contr. = Emotional Control; Work. Mem. = Working Memory

Parenting and executive function problems

We tested whether variation in the quality of parenting at 3 years contributed to differences in EF problems at 4 years of age, independent or in interaction with infant corpus callosum length. A hierarchical regression analysis was performed for the total scale of EF problems (Global Executive Composite). Interaction terms were not significant and therefore excluded from the analysis. The final regression model is presented in Table 3. Maternal depressive symptoms during pregnancy ($\beta = .10$, $p < .05$) and at 3 years of child's age ($\beta = .20$, $p < .01$) predicted higher levels of child EF problems. A shorter corpus callosum at 6 weeks of age predicted higher levels of child EF problems at 4 years of age ($\beta = -.12$, $p < .01$). After controlling for the other predictors and covariates, higher levels of maternal sensitivity at 3 years predicted lower levels of child EF problems at 4 years of age ($\beta = -.14$, $p < .01$). Maternal discipline was not independently associated with child EF problems.

Table 3. *Predictors of child executive function problem T-scores (N = 544).*

	Child Executive Function Problems				
	β^a	*T*	*p*	R^{2a}	R^2change[a]
Step 1:				.09	.09
Gestational age at birth	-.07	-1.48	.14		
Age child at ultrasound (weeks)	.03	0.78	.43		
Head circumference 6w	-.02	-0.39	.70		
Maternal age at intake	-.03	-0.75	.45		
Maternal educational level	-.01	-0.18	.86		
Maternal smoking during pregnancy	.05	1.13	.26		
Maternal depression during pregnancy	.10*	2.30	<.05		
Maternal depression at child's age 36m	.20**	4.62	<.01		
Step 2:				.10	.01
Corpus Callosum Length 6w	-.12**	-2.72	<.01		
Step 3:				.13	.02
Maternal Positive Discipline 36m	-.03	-0.70	.48		
Maternal Sensitivity 36m	-.14**	-3.33	<.01		

* $p < .05$, ** $p < .01$.

[a] averages taken from the final regression models of the 5 imputed datasets.
Note. Betas are taken from the final models.

Executive function subdomains

To specify which specific EF domains accounted for the association with maternal parenting, the hierarchical regression analysis was repeated for the subscales of EF. Again, interaction terms remained in the analyses only if significant. Final regression models are presented in Table 4.

Table 4 shows that a shorter corpus callosum at 6 weeks of age predicted higher levels of inhibition problems at 4 years of age ($\beta = -.11$, $p < .01$). Maternal sensitivity at 3 years of age predicted lower levels of inhibition problems at 4 years of age ($\beta = -.14$, $p < .01$) but maternal discipline was not associated with the level of inhibition problems. A significant interaction was found between corpus callosum length at 6 weeks of age and maternal positive discipline at 3 years of child's age on the child's level of inhibition problems ($\beta = .09$, $p < .05$, R^2change = .01). The moderating effect of corpus callosum length was examined by comparing the association between discipline and inhibition problems in children with a relatively long corpus callosum ($n = 272$) versus children with a relatively short corpus callosum at 6 weeks postnatal ($n = 272$). The association between discipline and inhibition problems was stronger for the children with a short corpus callosum at 6 weeks postnatal ($r[270] = -.19$, $p < .01$) than for children with a long corpus callosum ($r[270] = .04$, $p = .48$). The bivariate associations between maternal discipline and child inhibition problems per group are displayed in Figure 2.

Table 4. *Predictors of child executive function problems subdomain T-scores (N = 544).*

	Inhibition Problems		Shifting Problems		Emotional Control Problems		Working Memory Problems		Planning Problems	
	β^a	R^{2a}	β^a	R^{2a}	β^a	R^{2a}	β^a	R^{2a}	β^a	R^{2a}
Step 1:		.08		.07		.06		.08		.05
Gestational age at birth	-.06		-.09		-.05		-.03		-.03	
Age child at ultrasound (w)	.04		.00		.05		.02		.04	
Head circumference (6w)	-.02		.12*		-.01		-.09		-.07	
Maternal age at intake	-.03		.02		-.03		-.04		-.01	
Maternal educational level	-.03		.03		.08		-.03		-.07	
Maternal smoking (during pregnancy)	.07		.00		.01		.10*		-.01	
Maternal depression (during pregnancy)	.07		.05		.10*		.09*		.11*	
Maternal depression (3y)	.18**		.22**		.18**		.15**		.09*	
Step 2:		.09		.07		.08		.09		.06
Corpus Callosum Length (6w)	-.11**		-.09*		-.12**		-.06		-.07	
Step 3:		.11		.07		.08		.12		.08
Maternal Discipline (3y)	-.04		.01		.00		-.03		-.04	
Maternal Sensitivity (3y)	-.14**		-.02		-.05		-.17**		-.13**	
Step 4:		.12		--		--		--		--
Corpus Callosum * Maternal Discipline	.09*									

* $p < .05$, ** $p < .01$.

[a] averages taken from the final regression models of the 5 imputed datasets.
Note. Betas are taken from the final models.

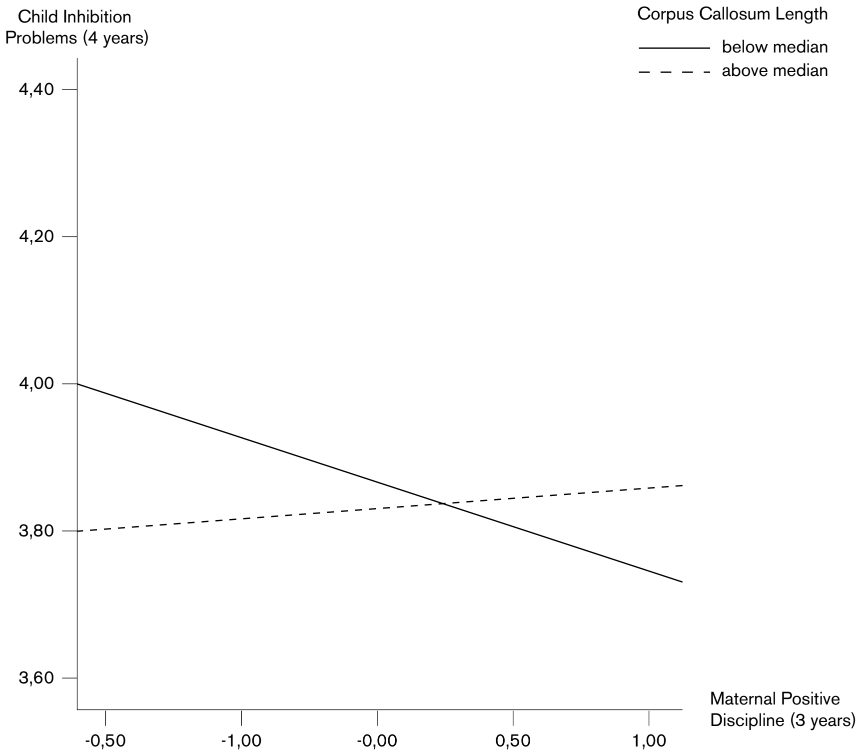

Figure 2. Interaction between corpus callosum length and maternal discipline predicting child inhibition problem T-scores.

As shown in Table 4 a shorter corpus callosum in infancy was associated with higher levels of shifting problems and emotional control problems at 4 years of age ($\beta = -.09$, $p < .05$; $\beta = -.12$, $p < .01$), but not related to working memory problems or planning problems. Maternal sensitivity and maternal discipline were not associated with shifting problems or emotional control problems. However, maternal sensitivity at 3 years was associated with lower levels of working memory problems ($\beta = -.17$, $p < .01$) and lower levels of planning problems one year later ($\beta = -.13$, $p < .01$).

Discussion

In this study we examined whether maternal sensitivity and maternal positive discipline were related to child EF problems one year later, independently or in interaction with corpus callosum length in infancy. In addition to the association of corpus callosum length in infancy with EF development (Ghassabian et al., 2012), we found that higher levels of maternal sensitivity at 3 years were associated with lower levels of EF problems at 4 years. Further analyses indicated that high levels of maternal sensitivity were associated with lower inhibition problem scores, working memory problem scores, and planning problem scores in preschoolers, but not lower emotional control problem scores or shifting problem scores. A significant interaction was found between the length of the corpus callosum in infancy and maternal discipline in association with child inhibition problem scores at preschool age. The beneficial effect of maternal positive discipline on child inhibition problem scores was stronger for children with a relatively short corpus callosum in infancy than for children with a relatively long corpus callosum.

The fact that maternal sensitivity was associated with lower levels of child EF problems one year later underlines the importance of parenting in the development of EF. The association of maternal sensitivity with child EF was independent of a marker of early brain maturation, maternal psychopathology, and background variables related to EF development. The exact mechanisms behind the influence of parenting on child EF remain unknown. A common explanation is that positive parenting can foster the development of regulatory skills by modeling appropriate behavior and by providing the child with a safe and encouraging environment in which it can practice self-regulation (e.g., Bernier et al., 2010; Perez & Gauvain, 2010). An alternative mechanism is that positive parenting may directly impact on child brain development and thus influence child EF. The notion that early brain development is under constant influence of the environment, in particular early caregiving experiences, has become widely accepted (Belsky & De Haan, 2011; Cicchetti, 2002; Glaser, 2000). Most studies have, however, focused on the influence of extreme rearing conditions, such as child abuse and neglect. Experience of neglect, child physical abuse, and child sexual abuse were all found to be associated with a reduced corpus callosum size (for a review, see Belsky & De Haan, 2011). It seems plausible that normal variation in parenting quality can also affect the development of the brain (Belsky & de Haan, 2011; Glaser, 2000). A randomized controlled trial in which maternal sensitivity towards preterm infants was enhanced found promising short-term benefits for the infants' brain development that might result in better cognitive development at a later age (Milgrom et al., 2010). An alternative explanation for the association between maternal sensitivity and child EF is that children with lower levels of EF problems might elicit a more positive response in their parents and thus increase maternal sensitivity (Bernier et al., 2010). In our research design bidirectional influences cannot be ruled out.

The relation between maternal sensitivity and child EF was specific for child working memory, inhibition, and planning. We did not find an association between maternal sensitivity and shifting problems or emotional control problems. Working memory skills and inhibition skills are usually referred to as basic EF skills that develop earlier in life than more complex EF skills such as set shifting (Garon et al., 2008). This may be an explanation for our finding that shifting abilities were less influenced by maternal sensitivity than the EF subdomains that were already more mature at 4 years of age. The fact that we did not find an association between maternal sensitivity and child emotional control problems a year later was unexpected. Previous studies suggest that in an environment of sensitive and responsive care the child gradually learns how to regulate his behavior and emotions, resulting in higher levels of behavioral and emotional control (e.g., Fox & Calkins, 2003; Kochanska & Aksan, 1995; Morris, Silk, Steinberg, Myers, & Robinson, 2007). Overall our findings seem to imply that shifting and emotional control abilities follow a different developmental pattern than inhibition, planning, and working memory abilities.

An interaction effect between maternal discipline and infant corpus callosum length to determine child inhibition problems at the age of 4 years was found. In children with a relatively short corpus callosum at 6 weeks postnatal more maternal positive discipline predicted lower levels of child inhibition problems. The length of the corpus callosum is thought to be associated with the number of axons and the degree of myelination (Anderson, Laurent, Woodward, & Inder, 2006), and the integrity of this structure predicts the efficiency of interhemispheric connectivity (Keshavan et al., 2002). Corpus callosum abnormalities are indicative of less connectivity between the hemispheres and are often found in children born preterm (Woodward et al., 2011). Though in our sample most children were born a term (only 3.3% under 37 weeks) a relatively short corpus callosum might be an indicator of suboptimal white matter development and higher risk of EF problems. The fact that the level of maternal positive discipline was associated with child inhibition problems in the children with a small corpus callosum indicates that positive parenting might act as a buffer in children at risk. Similarly, a study comparing the influence of maternal sensitive responsiveness on child psychopathology in children with low birth weight versus normal weight demonstrated that sensitive responsiveness had a protective effect in the development of internalizing problems and ADHD symptoms in very low birth weight children (Laucht, Esser, & Schmidt, 2001).

Despite our study's strength such as the use of an observational paradigm in measuring different aspects of parenting, the longitudinal nature of our data, and the large number of participants, its results must be interpreted within the context of a number of methodological limitations. Firstly, we measured corpus callosum length using cranial ultrasound which does not provide detailed images of specific substructures in the brain. Although cranial ultrasound in neonates has limited value in reflecting variations in the brain structures as compared to MRI (Anderson et al., 2004), it is a reliable, non-invasive, and cost-effective technique to image very young children and can be used in follow-up studies of healthy infants (Riccabona, 2005). In a prospective study including neonates ultrasound measures are therefore the preferred choice. Secondly, whereas the corpus callosum area may be a better indicator of its size, we measured the corpus callosum across the entire length because the corpus callosum area cannot be measured reliably by cranial ultrasound. However, studies have reported strong correlations between the corpus callosum length and thinness (Anderson et al., 2006). Thirdly, we used parental report of child EF problems which might have introduced bias (Seifer, 2003). However, given that preschoolers have difficulty staying on task for longer periods of time and that parents are able to provide a picture of the everyday functioning of children on EF domains (Sherman & Brooks, 2010), maternal report is appropriate to assess EF problems. Also, observational measures were used to assess maternal sensitivity and maternal discipline which reduces the risk of bias in the association between parenting and EF problems. Fourthly, in the current study design we cannot rule out bidirectional effects between parenting and EF problems or the possibility that there is an underlying cause for both parenting and EF problems that might explain the association we found.

It is important to emphasize that the variation in corpus callosum length in the infants in our study was within the normal range. A relatively short corpus callosum length should not be interpreted as an indication of white matter or brain development abnormality. Furthermore, we do not know whether the reduction in length of the corpus callosum is due to a smaller number of axons or due to reduced degree of myelination and whether there might be a neuronal problem underlying the short length. Future research in high risk populations of children with white matter abnormalities is needed to investigate whether maternal sensitivity can contribute to EF development in this group of children and whether positive maternal discipline can act as a buffer for the development of inhibition problems. Moreover, although the buffering potential of positive discipline was congruent with some findings of earlier studies, the interaction effect accounted for only a small part of the variance in inhibition problems. We therefore have to be cautious in interpreting this interaction and the results should be considered hypothesis generating. This finding needs to be replicated in future research, including high-risk populations. Also, future research should focus on the mechanisms behind the influence of parenting on EF. It would be interesting to follow the children in the current study with new measures of brain development and EF to investigate whether the association between parenting and child brain development increases over time and alters the course of EF problems. We intend to measure final callosal size by structural magnetic resonance imaging in these children in the future. Furthermore, future studies should investigate the influence of both fathers' and mothers' parenting on child EF development as the role of the father in research on child development is often neglected.

The current study provides evidence for the importance of maternal sensitive parenting in the development of EF in preschoolers. The use of positive discipline strategies by mothers was associated with lower levels of inhibition problems in children with reduced corpus callosum length in infancy, which points to the buffering potential of positive parenting in children with biological risk.

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5

Maternal sensitivity and internalizing problems: Evidence from two longitudinal studies in early childhood

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Abstract

The goal of this study is to clarify the relation between maternal sensitivity and internalizing problems during the preschool period. For this purpose, a longitudinal, bidirectional model was tested in two large prospective, population-based cohorts, the Generation R Study and the National Institute of Child Health and Human Development Study of Early Child Care and Youth Development (NICHD SECCYD), including over 1800 mother-child dyads in total. Maternal sensitivity was repeatedly observed in mother-child interaction tasks and information on child internalizing problems was obtained from maternal reports. Modest but consistent associations between maternal sensitivity and internalizing problems were found in both cohorts, confirming the importance of sensitive parenting for positive development in the preschool years. Pathways from maternal sensitivity to child internalizing problems were consistently observed but child-to-mother pathways were only found in the NICHD SECCYD sample.

Introduction

It is broadly acknowledged that internalizing problems can develop already during the preschool years [1], that these problems are relatively stable over time [2, 3], and that they can have a profound effect on young children and their families [4]. There is mixed evidence on the influence of early parenting on internalizing problems in early childhood and the possible bidirectional nature of the relationship between parenting and internalizing problems has not been extensively studied in longitudinal designs [5]. The current study aims to clarify the relation between maternal sensitivity and internalizing problems in the preschool period by investigating and replicating a longitudinal, bidirectional model in two large prospective, population-based cohort studies, the Generation R Study and the NICHD SECCYD, including over 1800 mother-child dyads in total.

The dearth of studies on the origins of internalizing problems in the preschool period may be reminiscent of the historical notion that prepubertal children lack the cognitive and emotional abilities to experience depression [1] and the perception that the manifestation of internalizing problems in the preschool period is markedly different from the presentation at later ages [3]. Population-based studies and clinical studies focusing on the role of parenting in the development of internalizing problems in children and adolescents have found mixed results. In toddlerhood over-involved and protective parenting was associated with higher levels of internalizing problems [4]. However, in an earlier study on the NICHD SECCYD sample, a composite of maternal sensitivity over seven years was not found to contribute to maternally reported internalizing problem trajectories from preschool to school years [6]. A study on the association between parenting and internalizing problems in a heterogeneous sample of European Americans and African Americans indicated that warm and responsive parenting was associated with less internalizing problems only in African American families [7]. In middle to late childhood some studies find no evidence for an association between high quality of mother-child interaction and lower levels of internalizing problems [8, 9]. Other studies indicate that low levels of parental warmth and high levels of harsh punishment contribute to depressive symptoms in children [10, 11]. In adolescence, parental positive discipline was negatively associated with initial levels of internalizing problems but did not predict trajectories over time [12]. Overall, more and stronger evidence is found for an association between parenting quality and externalizing problems in children than between parenting quality and internalizing problems [8, 9, 12].

Mixed findings on the association between maternal sensitivity and child internalizing problems might be the result of methodological issues. Firstly, some studies include relatively small or convenience samples [4, 7, 12] which makes it difficult to generalize and compare results. Secondly, some studies rely partly or solely on parental reports [9-12] which can result in artificially inflated correlations and can introduce reporter bias. Finally, though some studies have measured predictors and outcome across time [4, 6, 7] most studies have not used repeated measures of parenting and repeated measures of child internalizing problems in their analyses. An exception is the study by Haltigan, Roisman, and Fraley [13] in which transient and enduring effects models of early caregiving experiences on child behavioral problem trajectories were distinguished. However, in this study the main focus was on total behavioral problem trajectories and not specifically on internalizing problems. Because in most studies predictors and outcomes were not measured across time, the pattern and direction of the association between parenting and internalizing problems is not yet clarified. Even though the unidirectional view of parent-child socialization has been replaced by a bidirectional model of parent-child interactions in the last decades empirical studies focusing on both sides of the coin are still relatively rare [5]. Recent evidence indicates that emotional and behavioral problems in children can influence the behavior of parents. Increases in disruptive behavior in children can evoke more negative maternal parenting [14] and depressed mood in girls predicted lower parental warmth over time [10].

We addressed these issues by conducting a study on the association between observed maternal sensitivity and mother-reported child internalizing problems with repeated measures of both variables in two independent large population-based samples of the Generation R Study and the NICHD SECCYD. We applied structural equation modeling of enduring effects similar to Fraley, Roisman, and Haltigan [15] and Haltigan and colleagues [13] but in this study we emphasized the implications of bidirectional associations between sensitivity and internalizing problems over time. We hypothesized that maternal sensitivity and child internalizing problems are significantly though modestly associated across time. The use of repeated, standardized observational assessments of parenting and of a well-known and accepted mother-report instrument of child internalizing problems in two well-powered cohorts can extend the knowledge on the nature of the association between maternal sensitivity and child internalizing problems.

Method

Setting

This investigation was based on two studies, the Generation R Study, a prospective cohort study investigating growth, development, and health from fetal life onwards in Rotterdam, the Netherlands [16], and the NICHD SECCYD, a prospective study carried out at 10 sites in the United States following children from birth to 17.5 years of age [17]. As the variables measured with these samples were not the same, we will analyze the data sets separately, and compare results.

Detailed measurements were obtained in a subgroup of the Generation R Study of children of Dutch national origin, that is, the children, their parents, and their grandparents were all born in the Netherlands. Further eligibility criteria were enrollment before a gestational age of 25 weeks and a delivery date between February 2003 and August 2005. The NICHD SECCYD is an ethnically diverse sample. To match the Dutch Generation R sample, we restricted the NICHD SECCYD sample to Caucasian non-Hispanic participants, as done by Luijk and colleagues [18]. Data in both samples were collected during visits to the research centre or home visits for observational assessments and with questionnaires. All measures were approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam and the Internal Review Boards of the NICHD SECCYD participating universities, respectively. Written informed consent was obtained from all adult participants.

Study samples

In Generation R information on child internalizing problems was obtained from mother-reports on postal questionnaires at 1.5, 3, and at 6 years of age. Maternal sensitivity was observed and coded during lab and home visits at 1, 3, and 4 years of age. Mother-child dyads were included in the analyses when at least one measure of maternal sensitivity and at least one measure of child internalizing problems was available. 1137 mothers reported on their child's internalizing problems at least once. For 913 of these mothers at least one observation of maternal sensitivity was available. Two dyads were excluded because the data available concerned 3 years only, making it impossible to investigate pathways. Twenty-five mothers participated in Generation R with twins. One sibling of each twin pair was randomly selected for the analyses. The final sample therefore consisted of 886 mother-child dyads. Non-response analyses were performed. Children included in the analyses were more often firstborn than excluded children, χ^2 (1, 1137) = 8.92, $p < .05$. Dyads included in the analyses did not differ from the excluded dyads on child gender, maternal educational level, child internalizing problems, and maternal sensitivity.

In the NICHD SECCYD Study mothers reported on their child's internalizing problems in postal questionnaires at 2, 3, 4.5, and 5.4 years. Maternal sensitivity was observed in the home or in the laboratory at 0.5, 1.3, 2, 3, and 4.5 years. Similar to the Generation R selection, mother-child dyads were included in the analyses when at least one measure of maternal sensitivity and at least one measure of child internalizing problems was available. A total of 1022 mothers reported on their child's internalizing problems at least once. For 935 of these mothers at least one observation of maternal sensitivity was available. Non-response analyses were performed. Mothers included in the analyses were older than mothers excluded, $t(1020) = -3.66$, $p < .01$, and had a higher educational level than mothers excluded, χ^2 (1, 1022) = 6.00, $p < .05$. Dyads included in the analyses did not differ from the excluded dyads on child gender, parity, child internalizing problems, and maternal sensitivity.

Regarding the final samples, in Generation R ($N = 886$) information on maternal sensitivity was incomplete for 135 mothers (15%) at 1 year, for 102 mothers (12%) at 3 years, and for 266 mothers (30%) at 4 years. Information on child internalizing problems was missing for 61 children at 1.5 years (7%), 89 children at 3 years (10%), and 207 children at 6 years of age (23%). In the NICHD SECCYD ($N = 935$) information on maternal sensitivity at 0.5, 1.3, 2, 3, and 4.5 years of age was missing for respectively 20, 16, 44, 41, and 139 mothers (2%, 2%, 5%, 4%, and 15%). Information on child internalizing problems was missing for 28 children at 2 years (3%), 28 children at 3 years (3%), 124 children at 4.5 years (13%), and for 129 children at 5.4 years (14%).

Characteristics of the mothers and children in the two samples are displayed in Table 1. In the Generation R Study gender was evenly distributed and 62.5% of children were firstborn. The majority of mothers had a high educational level (65.7%, at least higher vocational training or a bachelor's degree). In NICHD SECCYD gender was evenly distributed and 44.8% of children were firstborn. In addition, 42.7% of mothers had a high educational level, operationalized as having at least a bachelor's degree at the study onset.

Central measures

Child internalizing problems

In both the Generation R and the NICHD SECCYD Study, the Child Behavior Checklist (CBCL) was used to repeatedly measure child internalizing problems. However, different versions were used. In the Generation R Study the CBCL/1½-5 [19] was repeatedly used. Mothers filled out this questionnaire when the children were on average 1.5 years of age, 3 years of age, and 6 years of age. We decided to use the CBCL for ages 1½-5 for the last measurement because 74% of the children were younger than 6 years at assessment (90th percentile 6.1 years). The CBCL/1½-5 contains 99 items, which are scored on a three-point scale; 0 = not true, 1 = somewhat true or sometimes true, and 2 = very or often true, based on the two proceeding months. The Internalizing Symptoms subscale consists of four syndrome scales: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn. In our analyses, we used the scores on these four syndrome scales as indicators of Internalizing Problems. The psychometric properties of the CBCL/1½-5 are well established [20]. The internal consistency of the CBCL internalizing syndrome scales in the Generation R sample ranged from $\alpha = .61$ to $\alpha = .75$.

Table 1. *Sample characteristics for Generation R and NICHD SECCYD.*

	Generation R	NICHD SECCYD
Child characteristics		
Child gender (% female)	49.3	48.7
Birth weight (g)	3502.2 (553)	3530.1 (511)
Gestational age (weeks)	40.0 (1.8)	39.3 (1.5)
Apgar score (% < 7)	4.6	---
Parity (% firstborn)	62.5	44.8
Maternal characteristics		
Age at intake	31.9 (3.7)	29.1 (5.4)
Educational level (% high)	65.7	42.7

Note. Unless otherwise indicated, values are mean (*SD*).

In the NICHD SECCYD, child internalizing problems were repeatedly measured with the CBCL 2-3 [21] at 2 and 3 years of age, and with the CBCL 4-18 [22] at 4.5 years and 5.4 years of age. The CBCL 2-3 contains 99 items, which are scored on a three-point scale; 0 = not true, 1 = somewhat true or sometimes true, and 2 = very or often true, based on the two proceeding months. The Internalizing Symptoms subscale of the CBCL 2-3 consists of two syndrome scales: Anxious/Depressed and Withdrawn. In the analyses, scores on these two syndrome scales were used as indicators of Internalizing Problems. The CBCL 4-18 contains 118 items and is similarly scored. The Internalizing Symptoms subscale of the CBCL 4-18 consists of the same two syndrome scales plus a scale on Somatic Complaints. In the analyses, the scores on the three syndrome scales were used as indicators of Internalizing Problems. The internal consistency of the CBCL internalizing syndrome scales in the NICHD SECCYD sample ranged from $\alpha = .66$ to $\alpha = .76$.

Maternal sensitivity

In the Generation R Study maternal sensitivity was measured when the children were 1, 3, and 4 years of age. In the lab visit at 1 year of age, DVD recordings were made of a 5-minute free play session and a psychophysiological assessment, which were coded using the Ainsworth's 9-point rating scales for *Sensitivity* and *Cooperation* [23]. The intercoder reliability (intraclass correlation coefficient [ICC], single measure, absolute agreement) ranged from .65 to .71. Sensitivity and Cooperation were used as indicators of maternal sensitivity at 1 year of age. In a lab visit at 3 years of age and a home visit at 4 years of age, mother and child were asked to perform two 3- to 4-minute tasks that were too difficult for the child: building a tower and an etch-a-sketch task. Mothers were instructed to help their child as usual. DVD recordings of these tasks were used to code maternal sensitivity using the revised Erickson 7-point rating scales for *Supportive Presence* and *Intrusiveness* [24]. The intercoder reliability (ICC) ranged from .75 to .79 for the 3 year measurement and from .79 to .85 for the 4 year measurement [25, 26]. Maternal Supportive Presence scores and Intrusiveness scores were used as indicators of maternal sensitivity at 3 and 4 years of age.

In the NICHD SECCYD maternal sensitivity was measured at child age 0.5, 1.3, 2, 3, and 4.5 years in semi-structured 15-minute observations in the home (0.5 and 1.3 years) or in lab visits (2, 3, and 4.5 years). Details on the tasks and procedures can be found in prior publications [27, 28]. Maternal sensitivity at 0.5 to 2 years was coded from videotapes on 4-point scales of *sensitivity to non-distress, positive regard,* and *intrusiveness* during play, ranging from 1 (not at all characteristic of the interaction) to 4 (highly characteristic of the interaction). Intercoder reliability (ICC) ranged from .83 to .87. The three subscales were used as indicators of maternal sensitivity at 0.5 to 2 years of age. Maternal sensitivity at 3 and 4.5 years was coded from videotapes on 7-point scales of *supportive presence, respect for autonomy,* and *hostility,* ranging from 1 (not at all characteristic of the interaction) to 7 (highly characteristic of the interaction). ICCs ranged from .84 to .88. The three subscales were used as indicators of maternal sensitivity at 3 and 4.5 years of age.

Statistical analyses

We used Structural Equation Modeling with EQS 6.1 for Windows [29] to test whether sensitivity of the mother is related to the child's internalizing problem behavior across time. Structural equation models in this study were comparable to the "enduring effects model" as presented in Fraley and colleagues [15] and Haltigan and colleagues [13]. For both the Generation R and the NICHD SECCYD data, we first estimated measurement models for sensitivity and internalizing problem behavior separately, followed by estimating a combined model by adding cross-paths between different constructs across time. Error terms corresponding to the same or similar measurement scales across time were allowed to correlate.

We moved a few extreme scores (99th percentile and higher) of problem behavior in Generation R close to the 99th percentile of the variables. The original data ordering was maintained (this procedure resembles winsorizing, [30]). The NICHD SECCYD data did not contain extreme values. As in both data sets the input variables were skewed, and multivariate kurtosis values were high (normalized estimate of Yuan, Lambert, & Fouladi's coefficient equaled 26.1 for the Generation R data and 42.4 for the NICHD SECCYD data), we report and interpret robust parameter estimates. Missing values were imputed using the maximum likelihood (ML) imputation procedure in EQS (see, for instance, Allison [31]).

We report the following estimates of model fit: (a) χ^2 (*df*), (b) the ratio between χ^2 and degrees of freedom, where a ratio smaller than 2.0 indicates a good model fit [30], (c) the non-normed fit index (NNFI) and the comparative fit index (CFI), with values exceeding .90 indicating reasonable model fit, and values above .95 indicating good model fit, and (d) the root mean square error of approximation (RMSEA), with values lower than .05 indicating good model fit [32, 33].

Results

Inspection of observed data

We inspected the correlation matrices of the raw variables (see Appendix A, Tables A1 and A2) and the latent variables within both study samples (see Appendix B, Tables B1 and B2) before performing the structural equation models. As expected, bivariate correlations within the two constructs were modest to high in both samples which indicates the relatively stable nature of maternal sensitivity and child internalizing problems. Cross-over correlations between maternal sensitivity and child internalizing problems were rare and of modest size.

Model testing

Measurement models

We tested the measurement models for maternal sensitivity and child internalizing problems in both samples. For each measurement model we specified pathways between adjacent time-points and all other pathways across time. Per latent variable, the loading on one indicator was set to 1.0, the others were freely estimated. We allowed the errors of indicators measured with the same subscales to correlate across time. In the measurement model for maternal sensitivity in the Generation R dataset the error-variance of the indicator 'sensitivity at 1 year' and the corresponding error covariance were constrained at zero. In the measurement model for maternal sensitivity in the NICHD SECCYD dataset the error-variance of the indicator 'sensitivity to non-distress at 0.5 years' and the corresponding error covariance were constrained at zero by EQS. We found a reasonable to good fit for all four measurement models (see Table 2).

Table 2. *Measurement models for Generation R and NICHD SECCYD.*

		Chi-square	CFI	NNFI	RMSEA
Generation R	Sensitivity	9.46, *df* = 5; χ^2/df = 1.89	1.00	0.98	0.04
	Internalizing	48.52, *df* = 39; χ^2/df = 1.24	0.98	0.97	0.03
NICHD SECCYD	Sensitivity	224.40, *df* = 71; χ^2/df = 3.16	0.95	0.92	0.05
	Internalizing	11.48, *df* = 16; χ^2/df = 0.72	1.00	1.00	0.00

Predictive models

The results of the analyses based on the theoretical models are presented in Figures 1 and 2. In the predictive models for both samples we specified all crossing pathways between maternal sensitivity and child internalizing problems in both directions across time. Structural equation modeling showed a good fit for both samples: for the Generation R sample, $\chi^2(108) = 133.01$; $\chi^2/df = 1.23$; NNFI = 0.97; CFI = 0.98; RMSEA = 0.03, and for the NICHD SECCYD sample, $\chi^2(220) = 380.00$; $\chi^2/df = 1.73$; NNFI = 0.95; CFI = 0.97; RMSEA = 0.03.

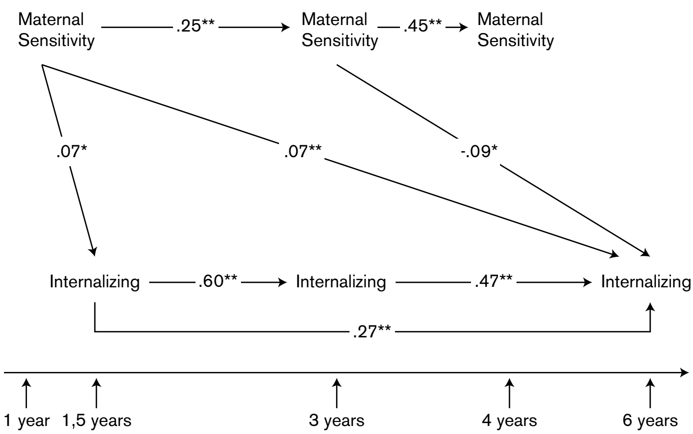

Figure 1. Standardized coefficient estimates of final Structural Equation Model for the Generation R Study (*N*=886). Only significant paths are presented in this figure. For the sake of clarity indicators and error covariances are not presented.

In the Generation R sample both maternal sensitivity and child internalizing problems showed stability over time (see Figure 1). Only three of eight possible pathways between maternal sensitivity and child internalizing problems or vice versa were significant. Higher levels of maternal sensitivity at 1 year predicted lower levels of child internalizing problems at 1.5 years but higher levels of child internalizing problems at 6 years. However, the standardized coefficient estimate of the total effect of maternal sensitivity at 1 year on child internalizing problems at 6 years, including both the direct path and the indirect pathways via maternal sensitivity at 3 years and via internalizing problems at 1.5 and 3 years, was non-significant (β = .01). More maternal sensitivity at 3 years predicted fewer child internalizing problems at 6 years.

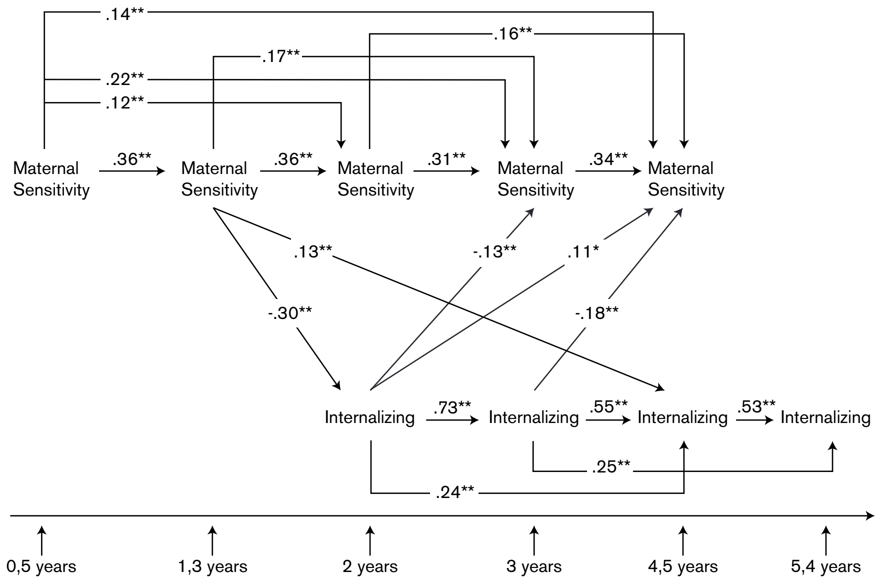

Figure 2. Standardized coefficient estimates of final Structural Equation Model for the NICHD SECCYD (*N*=935). Only significant paths are presented in this figure. For the sake of clarity indicators and error covariances are not presented.

In the NICHD SECCYD sample a very similar level of stability was found for maternal sensitivity and child internalizing problems (see Figure 2). Only 5 of the 17 possible pathways between maternal sensitivity and child internalizing problems or vice versa were significant. Lower maternal sensitivity at 1.3 years predicted more internalizing problems at 2 years but fewer internalizing problems at 4.5 years. The standardized coefficient estimate of the total effect of maternal sensitivity at 1.3 years on child internalizing problems at 4.5 years, including both the direct path and the indirect pathway via internalizing problems at 2 and 3 years of age, was non-significant (β = -.01). Child internalizing problems at 2 years predicted lower levels of maternal sensitivity at 3 years but higher levels of maternal sensitivity at 4.5 years. However, the total effect of child internalizing problems at 2 years on maternal sensitivity at 4.5 years, including both the direct path and the indirect pathways via maternal sensitivity at 3 years and via internalizing problems at 3 years of age, was negative (β = -.07, $p < .05$). Child internalizing problems at 3 years predicted less maternal sensitivity at 4.5 years. All other cross pathways were non-significant and are therefore not displayed in Figure 2.

Discussion

In this study we aimed to clarify the nature and direction of the association between maternal sensitivity and internalizing problems during the preschool years. When taking into account all associations within the two constructs at all time points to control for stability, in both samples we found modest but consistent evidence for an association between sensitivity and internalizing problems across time. Initial levels of sensitivity and internalizing problems were the strongest predictors for subsequent sensitivity and subsequent internalizing problems. Because we controlled for the stability of maternal sensitivity and child internalizing problems over time, the associations between maternal sensitivity and child internalizing problems or vice versa represent longitudinal pathways and not concurrent associations. Pathways between adjacent time points of maternal sensitivity and child internalizing problems were negative, indicating that lower levels of maternal sensitivity predicted higher levels of internalizing problems and higher levels of internalizing problems predicted lower levels of maternal sensitivity in the short term. Positive associations between maternal sensitivity and child internalizing problems were found over a longer period of time. In the interpretation of these positive associations one should be aware that these pathways do not represent bivariate associations. The positive pathways from maternal sensitivity to child internalizing problems or the other way around are corrected for all other associations within the models, including the negative associations between adjacent time points. The direct positive pathways combined with the indirect negative pathways yielded non-significant or negative (but not positive) overall associations between maternal sensitivity and child internalizing problems and vice versa in both samples. Our models seem consistent with the modest associations that have been reported in earlier studies [4, 10, 11]. The advantage of investigating these associations in two well-powered samples is the possibility to clearly demonstrate the pathways from maternal sensitivity to child internalizing problems and the other way around even if they show rather small effect sizes.

We investigated the bidirectional nature of the association between maternal sensitivity and child internalizing problems. Both pathways from maternal behavior to child behavior and pathways from child behavior to maternal behavior were found, but the child-to-mother pathways could not be replicated. The influence of parenting on child internalizing problems is more consistent and replicable than the influence of the child's internalizing problems on the parent's behavior. This finding is in accordance with studies indicating that the influence of parenting on child development is larger and more robust than vice versa [34, 35]. However, our finding also supports the idea that mother-child interaction is bidirectional in nature and that preschoolers are already active agents in this interaction [5].

Of course, alternative explanations should be considered for the fact that we did not find evidence for a strong association between maternal sensitivity and child internalizing problems. Characteristics of the mothers, such as history of psychopathology, can influence the validity of the perception of her child [36, 37]. However, our samples were population-based, including mainly healthy mother-child dyads, so psychopathology was rare in our sample of mothers. Moreover, maternal sensitivity can directly influence the validity of the perception of internalizing problems. In prior studies it has been found that the security of the attachment relationship between mothers and children can be related to maternal ratings of child and mother-child relationship characteristics. For example, mothers of securely attached children rated their child as less securely attached and more fearful of strangers compared to laboratory assessments, while mothers of insecurely attached children rated their child more securely attached and less fearful of strangers [38]. Similarly, sensitive mothers who are more attuned to their child's thoughts, feelings, and interests might be more inclined to report internalizing problems in their children compared to less sensitive mothers. However, this bias should have resulted in quite strong positive associations between maternal sensitivity and child internalizing problems.

Another argument against the validity of maternal reports is that the nature of internalizing problems makes them less visible to the outside world [39-41]. However, considering the challenge of obtaining valid self-reports in preschoolers, and considering the fact that children might be more likely to confide in a parent than in a teacher their internalizing problems [42] and that parental reports are more predictive of future diagnoses than teacher reports [43], maternal reports appear to be the most suitable way of measuring internalizing problems in preschoolers.

As only modest associations between maternal sensitivity and internalizing problems were found, perhaps other aspects of parenting may be more predictive of preschool internalizing problems. For example, more extreme parenting experiences such as physical neglect in the preschool period have been found related to internalizing problems [44]. Also, a combination of specific parenting practices might influence the developmental course of internalizing problems. For example, high levels of psychological control when combined with high maternal affection have been found to predict increases in internalizing problems [45]. Lastly, the two study samples consisted of a homogeneous, population-based group of Caucasian, non-Hispanic mother-child dyads. Therefore, we do not know whether these results are easily generalizable to more high-risk or clinical populations, or populations with a different ethnic and cultural background.

In sum, this study contributes to the literature by clarifying the nature of the relation between maternal sensitivity and internalizing problems in the preschool period. Modest negative associations between maternal sensitivity and internalizing problems exist, with the most robust influences of parental sensitivity on child internalizing problems.

Summary

In this study the longitudinal and bidirectional nature of the associations between maternal sensitivity and child internalizing problems in the preschool years were studied. Maternal sensitivity was observed and coded in mother-child interaction tasks and child internalizing problems were reported repeatedly using the Child Behavior Checklist, completed by the child's mother. Structural equation modeling of enduring effects were applied to the large population-based sample of the Generation R Study ($N = 886$) and the NICHD SECCYD ($N = 935$) to see whether similar patterns of associations between maternal sensitivity and child internalizing problems were found.

In both samples modest but consistent negative associations between maternal sensitivity and internalizing problems were found over the preschool years. The pathways from maternal sensitivity to child internalizing problems were apparent in both cohorts. Child-to-mother pathways were only found in the NICHD SECCYD sample. Our findings emphasize the importance of sensitive parenting for positive development in preschoolers. Although this study also supports the bidirectional nature of mother-child interactions, the results are clearly in accordance with studies indicating that the influence of parenting on child development is larger and more robust than vice versa.

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Appendix A

Table A1. *Generation R: Bivariate correlations between raw variables (N = 886).*

	Age (y)		1	2	3	4	5	6	7	8
						Maternal Sensitivity				
1	1	Sens.		.00	.01	-.02	.00	.01	.01	-.04
2		Coop.	.88[b]		.05	.05	.02	-.02	.03	-.04
3	3	Sup. Pr.	.17[b]	.19[b]		.00	.00	.00	.02	.00
4		Non-Intrus.	.13[b]	.18[b]	.41[b]		.01	.00	-.03	-.05
5	4	Sup. Pr.	.12[b]	.13[b]	.30[b]	.21[b]		.00	.02	.00
6		Intrus.	-.11[a]	-.13[b]	-.20[b]	-.32[b]	-.51[b]		-.02	.04
						Child Internalizing Problems				
7	1.5	Emot. R	-.04	-.01	.02	-.03	.03	-.04		-.01
8		Anx-D.	-.08[a]	-.08[a]	-.01	-.04	.01	.03	.44[b]	
9		Somat.	-.01	.00	.10[b]	.03	-.04	.03	.28[b]	.31[b]
10		Withd.	-.04	-.05	.01	-.01	.01	-.01	.29[b]	.26[b]
11	3	Emot. R	-.01	-.03	-.03	-.03	-.06	.00	.40[b]	.23[b]
12		Anx-D.	-.03	-.03	.02	.04	-.01	.00	.29[b]	.34[b]
13		Somat.	-.07	-.07	-.01	-.02	-.06	.06	.20[b]	.20[b]
14		Withd.	.02	.03	-.01	-.02	.01	-.03	.23[b]	.20[b]
15	6	Emot. R	-.02	-.03	-.02	-.08	.03	.05	.32[b]	.17[b]
16		Anx-D.	.06	.05	-.04	-.04	-.01	.06	.37[b]	.21[b]
17		Somat.	.01	.01	-.03	-.06	-.07	.13[b]	.19[b]	.15[b]
18		Withd.	-.01	-.01	-.04	-.10[a]	.01	.04	.26[b]	.16[b]

[a] $p < .05$; [b] $p < .01$

Note. Below diagonal: bivariate correlations. Above diagonal: standardized residuals derived from total model for Generation R data. Sens. = Sensitivity; Coop. = Cooperation; Sup.Pr. = Supportive Presence; Non-Intrus. = Non-Intrusiveness; Intrus. = Intrusiveness; Emot. R. = Emotionally Reactive; Anx-D = Anxious/Depressed; Somat. = Somatic Complaints; Withd. = Withdrawn; y = years

9	10	11	12	13	14	15	16	17	18	*M(SD)*
Maternal Sensitivity										
.03	-.01	.01	-.02	-.07	.03	-.04	.05	-.01	-.03	0.00 (0.85)
.03	-.02	.00	-.01	-.06	.06	-.04	.04	.00	-.02	0.00(0.86)
.10	.00	-.03	.01	-.02	-.01	.03	.02	.00	-.01	0.01 (0.80)
.02	-.02	-.03	.03	-.02	-.03	-.04	.01	-.04	-.08	0.00 (0.82)
-.05	.01	-.04	.01	-.05	.04	.05	.02	-.06	.02	0.01 (0.79)
.03	.00	.00	-.01	.06	-.05	.02	.03	.12	.01	-0.01 (0.81)
Child Internalizing Problems										
-.02	-.02	.00	.01	.00	.00	.01	.05	.03	.01	1.34 (1.54)
.06	.01	-.03	-.01	.03	.01	-.08	-.03	.02	-.04	0.81 (0.95)
	.01	.01	.01	.01	-.03	-.05	-.01	.00	-.03	1.25 (1.26)
.18[b]		-.01	.02	-.04	.00	.01	.01	.06	.01	0.56 (0.79)
.18[b]	.16[b]		.00	.01	-.01	-.01	.00	-.01	.03	1.30 (1.45)
.17[b]	.18[b]	.47[b]		.01	.01	-.08	-.04	.07	-.04	0.62 (0.98)
.25[b]	.08[a]	.34[b]	.32[b]		-.01	.03	.01	.03	.04	1.32 (1.33)
.10[b]	.28[b]	.37[b]	.35[b]	.24[b]		.06	.04	.06	.04	0.68 (0.93)
.10[b]	.18[b]	.46[b]	.23[b]	.23[b]	.29[b]		.00	-.01	.05	1.58 (1.90)
.16[b]	.19[b]	.34[b]	.33[b]	.24[b]	.28[b]	.62[b]		.02	.00	1.15 (1.46)
.18[b]	.15[b]	.17[b]	.24[b]	.36[b]	.19[b]	.32[b]	.37[b]		-.04	1.22 (1.46)
.10[a]	.29[b]	.29[b]	.21[b]	.20[b]	.43[b]	.54[b]	.51[b]	.23[b]		1.03 (1.16)

Table A2. *NICHD SECCYD: Bivariate correlations between raw variables (N = 935).*

			1	2	3	4	5	6	7	8	9	10	11
	Age (y)						Maternal Sensitivity						
1	0.5	Sens.		-.01	.01	-.01	-.06	.04	-.01	-.06	.06	.01	-.03
2		Intrus.	-.65[b]		.07	.01	.04	.00	-.01	.04	-.03	-.01	-.02
3		Pos.R.	.55[b]	-.28[b]		.11	-.01	.06	.05	-.02	.07	.14	.05
4	1.3	Sens.	.29[b]	-.19[b]	.26[b]		-.03	.03	-.01	-.03	.04	.04	-.05
5		Intrus.	-.26[b]	.27[b]	-.12[b]	-.51[b]		.04	.06	-.01	.02	.02	-.01
6		Pos.R.	.21[b]	-.11[b]	.28[b]	.44[b]	-.24[b]		.05	-.01	.05	.15	.04
7	2	Sens.	.22[b]	-.16[b]	.17[b]	.23[b]	-.15[b]	.22[b]		.01	.02	.00	-.01
8		Intrus.	-.18[b]	.20[b]	-.09[b]	-.20[b]	.27[b]	-.10[b]	-.48[b]		.09	.02	-.11
9		Pos.R.	.20[b]	-.12[b]	.23[b]	.24[b]	-.11[b]	.30[b]	.56[b]	-.22[b]		.10	.03
10	3	Sup.Pr.	.30[b]	-.19[b]	.30[b]	.31[b]	-.16[b]	.30[b]	.34[b]	-.17[b]	.31[b]		.01
11		Resp.A	.26[b]	-.20[b]	.20[b]	.22[b]	-.19[b]	.18[b]	.33[b]	-.30[b]	.25[b]	.64[b]	
12		Host.	-.24[b]	.17[b]	-.22[b]	-.19[b]	.12[b]	-.18[b]	-.27[b]	.24[b]	-.19[b]	-.47[b]	-.50[b]
13	4.5	Sup.Pr.	.27[b]	-.20[b]	.27[b]	.22[b]	-.09[a]	.20[b]	.30[b]	-.14[b]	.25[b]	.38[b]	.32[b]
14		Resp.A	.24[b]	-.16[b]	.18[b]	.18[b]	-.16[b]	.20[b]	.29[b]	-.21[b]	.21[b]	.33[b]	.37[b]
15		Host.	-.22[b]	.19[b]	-.14[b]	-.15[b]	.14[b]	-.13[b]	-.21[b]	.21[b]	-.11[b]	-.23[b]	-.28[b]
							Child Internalizing Problems						
16	2	Anx-D	-.11[b]	.11[b]	-.07[a]	-.20[b]	.13[b]	-.10[b]	-.15[b]	.12[b]	-.10[b]	-.16[b]	-.16[b]
17		Withd.	-.11[b]	.11[b]	-.07[a]	-.20[b]	.13[b]	-.12[b]	-.15[b]	.12[b]	-.13[b]	-.16[b]	-.15[b]
18	3	Anx-D	-.06	.10[b]	-.03	-.11[b]	.12[b]	-.06	-.10[b]	.10[b]	-.05	-.13[b]	-.12[b]
19		Withd.	-.11[b]	.09[b]	-.10[b]	-.10[b]	.10[b]	-.06	-.13[b]	.13[b]	-.09[b]	-.15[b]	-.14[b]
20	4.5	Anx-D	.01	-.03	.02	.02	-.01	.00	-.03	.07[a]	-.02	-.02	-.03
21		Withd.	.01	-.04	.00	.01	.01	.01	.04	-.03	.00	-.03	.00
22		Somat.	-.01	-.01	-.02	-.03	.06	-.03	-.01	.07	-.02	-.04	-.06
23	5.4	Anx-D	.04	-.04	-.01	-.01	.02	-.01	-.01	.08[a]	.02	.00	.01
24		Withd.	.00	.00	-.06	-.01	.03	.02	.00	.04	-.06	-.05	-.01
25		Somat.	-.02	.01	-.05	.05	.03	.00	-.02	.05	-.04	-.01	.01

[a] $p < .05$; [b] $p < .01$

Note. Below diagonal: bivariate correlations. Above diagonal: standardized residuals derived from total model for NICHD data. Sens = Sensitivity; Intrus. = Intrusiveness; Pos. R. = Positive Regard; Sup. Pr. = Supportive Presence; Resp A. = Respect for Autonomy; Host. = Hostility; Anx-D. = Anxious/Depressed; Withd = Withdrawn; Somat. = Somatic Complaints; y = years

12	13	14	15	16	17	18	19	20	21	22	23	24	25	M (SD)
Maternal Sensitivity														
-.03	.01	-.02	-.01	.00	.00	.03	-.04	.01	.00	-.02	.02	-.02	-.04	3.06 (0.70)
.03	-.04	-.01	.06	.04	.04	.04	.05	-.03	-.03	-.01	-.03	.02	.02	1.50 (0.71)
-.11	.13	.04	-.03	-.03	-.02	.01	-.06	.01	-.01	-.03	-.02	-.07	-.05	2.91 (0.65)
.01	.02	-.03	.02	.01	.00	.01	.01	.01	.00	-.04	.00	-.01	.04	3.15 (0.64)
-.01	.03	-.03	.02	-.01	.00	.03	.02	-.01	.01	.07	.01	.03	.04	1.33 (0.61)
-.08	.09	.07	-.03	.02	-.01	.01	.00	.00	.00	-.04	-.01	.02	.01	2.87 (0.65)
-.02	.02	.00	.03	-.05	-.06	-.02	-.06	-.05	.02	-.03	-.02	-.01	-.03	3.11 (0.69)
.10	.01	-.06	.08	.06	.07	.05	.09	.09	-.01	.08	.09	.05	.06	1.38 (0.63)
-.04	.08	.03	.04	-.04	-.08	.00	-.05	-.03	-.01	-.03	.01	-.06	-.05	2.89 (0.67)
.01	.02	.02	.03	.00	-.02	-.02	-.04	.00	-.02	-.03	.00	-.05	-.01	5.48 (1.20)
-.01	.01	.00	-.02	.00	-.01	-.01	-.04	-.02	.01	-.05	.01	.00	.01	5.44 (1.03)
	-.01	.04	-.02	.02	.03	.04	.08	.02	.01	.07	.06	.00	.03	1.30 (0.69)
-.25[b]		.00	.01	-.04	-.05	-.05	-.05	-.01	-.03	-.02	-.01	-.01	.02	5.35 (1.18)
-.21[b]	.69[b]		-.02	.04	.01	.02	.01	.03	.03	-.06	.00	.02	.01	5.39 (1.01)
.22[b]	-.57[b]	-.59[b]		.02	.06	-.01	.01	.02	.01	.05	.05	-.03	.00	1.33 (0.77)
Child Internalizing Problems														
.12[b]	-.13[b]	-.04	.09[a]		.00	.00	.00	.00	.02	.01	.00	.01	-.02	4.27 (2.75)
.12[b]	-.13[b]	-.07[a]	.13[b]	.55[b]		.01	.00	-.02	.00	.01	.00	.00	-.02	3.41 (2.51)
.13[b]	-.18[b]	-.10[b]	.09[a]	.59[b]	.41[b]		.00	.00	.02	-.01	.00	.01	-.05	4.53 (2.84)
.16[b]	-.17[b]	-.11[b]	.11[b]	.41[b]	.59[b]	.61[b]		-.01	.00	-.02	.00	.01	.02	3.84 (2.67)
.04	-.06	-.02	.06	.38[b]	.31[b]	.49[b]	.40[b]		-.01	.02	.00	-.01	.01	2.02 (2.38)
.02	-.06	-.01	.04	.32[b]	.31[b]	.40[b]	.41[b]	.56[b]		-.03	-.01	-.01	-.01	1.63 (1.61)
.08[a]	-.04	-.08[a]	.07	.20[b]	.18[b]	.22[b]	.21[b]	.39[b]	.28[b]		.03	-.03	.01	0.69 (1.17)
.07	-.06	-.07	.10[b]	.31[b]	.27[b]	.41[b]	.38[b]	.60[b]	.40[b]	.29[b]		-.01	.00	2.29 (2.47)
.02	-.06	-.03	.02	.25[b]	.24[b]	.34[b]	.37[b]	.39[b]	.54[b]	.19[b]	.60[b]		.01	1.32 (1.58)
.03	-.01	-.03	.03	.15[b]	.14[b]	.18[b]	.24[b]	.29[b]	.22[b]	.40[b]	.43[b]	.36[b]		0.86 (1.35)

Appendix B

Table B1. *Correlations between latent variables Generation R Study.*

		Sensitivity			Internalizing		
		1y	3y	4y	1.5y	3y	6y
Sensitivity	1y						
	3y	.30[b]					
	4y	.16[b]	.58[b]				
Internalizing	1.5y	-.06[b]	-.01[b]	.03			
	3y	-.02	-.03	-.04	.68[b]		
	6y	.01	-.10	-.06	.54[b]	.70[b]	

[a] $p < .05$; [b] $p < .01$

Note. $\chi^2/df = 3.76$; NNFI = 0.84; CFI = 0.88; RMSEA = 0.06; y = years

Table B2. *Correlations between latent variables NICHD Study.*

		Sensitivity					Internalizing			
		0.5y	1.3y	2y	3y	4.5y	2y	3y	4.5y	5.4y
Sensitivity	0.5y									
	1.3y	.37[b]								
	2y	.27[b]	.36[b]							
	3y	.38[b]	.44[b]	.49[b]						
	4.5y	.33[b]	.34[b]	.41[b]	.53[b]					
Internalizing	2y	-.15[b]	-.31[b]	-.23[b]	-.28[b]	-.19[b]				
	3y	-.11[b]	-.17[b]	-.18[b]	-.24[b]	-.23[b]	.87[b]			
	4.5y	.01	.00	-.04	-.06	-.07[a]	.60[b]	.72[b]		
	5.4y	.02	-.04	-.04	-.03	-.10[a]	.45[b]	.59[b]	.78[b]	

[a] $p < .05$; [b] $p < .01$

Note. $\chi^2/df = 3.76$; NNFI = 0.84; CFI = 0.88; RMSEA = 0.06; y = years

6

Variations in maternal 5-HTTLPR affect observed parenting

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Abstract

Little is known about the genetic determinants of sensitive parenting. We examined whether the serotonin transporter polymorphism (5-HTTLPR) is an independent predictor of observed maternal sensitivity, and whether observed child social fearfulness moderates the effect of 5-HTTLPR on maternal sensitivity. The population-based sample consisted of 767 mother-child dyads. Maternal sensitivity was repeatedly observed and coded with the Ainsworth's rating scales for Sensitivity and Cooperation and the revised Erickson rating scales for Supportive Presence and Intrusiveness over a three year period. At 3 years, child social fearfulness was observed using the Stranger Approach episode of the Laboratory Temperament Assessment Battery. Maternal 5-HTTLPR significantly predicted sensitivity; mothers carrying the *S*-allele were more sensitive towards their children ($p = .004$). Also, we found some evidence that child social fearfulness moderated the effect of 5-HTTLPR on sensitivity ($p = .059$). Mothers carrying the *S*-allele were more sensitive than mothers without *S*-alleles when parenting children with the lowest fear scores. However, no difference in sensitivity between mothers with different genotypes was observed if they parented more fearful children. Our study showed that variations in maternal 5-HTTLPR genotype appear to be involved in the etiology of parenting behavior.

Introduction

Parental support, guidance and structure are important for children to achieve developmental milestones, and they contribute to long term health (Sroufe et al., 2005a). Sensitive parenting, defined as the ability to accurately perceive children's signals and to respond to them in an adequate and prompt way (Ainsworth et al., 1978), is an important predictor of children's attachment security (Bakermans-Kranenburg, Van IJzendoorn, & Juffer, 2003). Secure attachment is, in turn, related to growth of self-reliance, social competence, and emotional regulation (Sroufe et al., 2005b). Furthermore, sensitive parenting has shown to be predictive of children's social problem solving (Raikes & Thompson, 2008), executive functioning (Bernier, Carlson, & Whipple, 2010), and relationships with siblings and peers (McFarlane et al., 2010; Volling & Belsky, 1992).

Against the background of the critical role of sensitive parenting in children's healthy development, research has investigated the determinants of sensitive parenting. According to Belsky's (1984) widely cited process model of parenting there are three main groups of determinants of parenting. The model presumes that parenting is influenced by parental characteristics including psychopathology, for example depression, anxiety disorder, and ADHD (Chronis-Tuscano et al., 2008; Dix et al., 2004; Newman et al., 2007; Nicol-Harper, Harvey, & Stein, 2007) and personality traits, such as neuroticism and agreeableness (Bornstein, Hahn, & Haynes, 2011; Clark, Kochanska, & Ready, 2000). Another important group of determinants is constituted by child characteristics. For example, sensitive parenting may be challenged by child negativity or difficult temperament of the child (Mills-Koonce et al., 2007; Van den Boom, 1994; Vaughn, Bost, & Van IJzendoorn, 2008). The third group of determinants identified in the process model are contextual sources of stress and support in which the parent-child relationship is embedded, including social support (Kivijarvi et al., 2004), and work-related stress (Repetti & Wood, 1997).

Although a wide variety of determinants of parenting have been investigated, molecular genetic determinants have been studied to a far lesser extent (Swain et al., 2007). However, substantial genetic influences may be involved in parenting (Collins et al., 2000; Neiderhiser et al., 2004; Plomin et al., 1994). In terms of Belsky's process model (1984), genetic factors may impact on parenting by their effects on parental and child characteristics. Furthermore, they may interact with various other determinants of parenting. The first studies on the molecular genetic basis of parenting using the candidate genes approach targeting dopamine-, oxytocin-, and serotonin-related genes yielded promising results (Bakermans-Kranenburg & Van IJzendoorn, 2008; Van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008).

Three earlier studies focusing on a repeat polymorphism of the dopamine gene, the DRD4 7-repeat, consistently reported no direct effect of the DRD4 7-repeat on sensitive parenting (Fortuna et al., 2011; Kaitz et al., 2010; Van IJzendoorn et al., 2008) However, all investigators did report an effect of the DRD4 7-repeat in interaction with various stressors on sensitive parenting. Van IJzendoorn and colleagues (2008) reported this gene-environment interaction (GxE) for the combination of the DRD4 7-repeat and the COMT polymorphism, another polymorphism involved in the dopamine system. All three studies assessed very different stressors which were all previously related to sensitive parenting (i.e. infant difficult temperament and infant risk at birth, infant difficult temperament, and stressful life events). As the DRD4 7-repeat moderated the effect of all stressors, this may suggest that this polymorphism moderates the effect of stress in general, rather than the effect of specific stressors on maternal sensitivity. In line with these findings, Lee and colleagues (2010) reported that another polymorphism of the dopamine system, DAT1, interacted with the child's disruptive behavior to predict maternal negative parenting. However, in contrast to the previous studies, they also found a main effect of the DAT1 polymorphism on negative maternal parenting (e.g., critical and negative statements) while no main effect on positive parenting (e.g., praise, positive affect) was detected. Next to polymorphisms involved in the dopamine system, one study also investigated the effect of an oxytocin polymorphism on observed parenting for which a main effect was reported as well (Bakermans-Kranenburg & Van IJzendoorn, 2008).

In the current study we focus on the serotonin transporter polymorphism (5-HTTLPR). This polymorphism has been investigated by two previous studies (Bakermans-Kranenburg & Van IJzendoorn, 2008; Mileva-Seitz et al., 2011). Both studies reported a main effect of 5-HTTLPR on maternal sensitivity. The serotonin transporter gene encodes the serotonin transporter, a key receptor for regulating serotonin levels in the synaptic cleft. In humans, the 5-HTTLPR repeat polymorphism in the promoter-region of the gene has two alleles; the short (*S*) allele and the long

(*L*) allele. The alleles account for differences in transcription efficiency of the serotonin transporter gene; the short allele of the 5-HTTLPR is found to be less active than the long allele, resulting in decreased transcription of the serotonin transporter gene (Murphy & Lesch, 2008). Decreased transcription of the gene reduces serotonin transporter levels and consequently increases the levels of serotonin in the synaptic cleft. In humans, the *S*-allele of 5-HTTLPR is associated with an increased risk of depressive disorders in the presence of environmental stress (Karg et al., 2011), with higher levels of trait anxiety (Schinka, Busch, & Robichaux-Keene, 2004; Sen, Burmeister, & Ghosh, 2004), and with selective attention to negative, threat-related stimuli (Pergamin-Hight et al., 2012). Consistent with these findings, the *S*-allele has also been associated with relatively increased amygdala activation to negative stimuli, a key structure mediating emotional arousal (Munafo, Brown, & Hariri, 2008). In contrast, there is also evidence that the *S*-allele is related to better cognitive functioning including improved decision making and cognitive flexibility (Borg et al., 2009; Homberg & Lesch, 2011), and to social cognition (Canli & Lesch, 2007) which are fundamental components of parenting (Atkinson et al., 2009; Barrett & Fleming, 2011).

While the two previous studies focusing on 5-HTTLPR found a direct effect of the polymorphism on sensitive parenting (Bakermans-Kranenburg & Van IJzendoorn, 2008; Mileva-Seitz et al., 2011), they reported opposite effects: In a sample of mothers with toddlers at high risk for behavioral problems, mothers carrying the short allele of 5-HTTLPR had lower levels of observed sensitive parenting towards their toddlers (Bakermans-Kranenburg & Van IJzendoorn, 2008). In contrast, a general population-based study reported that mothers carrying the short allele had higher levels of observed sensitive parenting (Mileva-Seitz et al., 2011). Mileva-Seitz and colleagues (2011) also tested the hypothesis that early care quality (as experienced by the mother) moderated the relation between 5-HTTLPR and sensitive parenting. They found no evidence for an interaction effect on maternal sensitivity, but they did find a significant interaction effect for mother's orienting away from the baby during free play: early care quality moderated the association between 5-HTTLPR and orienting away from the baby, which was to a certain extent negatively associated with maternal sensitivity. Mothers with no *S* alleles oriented away more frequently from their babies if they reported more negative early care quality.

It is well recognized that for complex traits, such as maternal sensitivity, many genetic associations are not consistently replicated. Much attention has been paid to the attribution of population stratification (i.e. allele frequencies and disease risks differ between subpopulations leading to false-positive associations), misclassification of genotype and outcome, and to underlying gene-environment interaction to this inconsistency (Colhoun, McKeigue, & Davey Smith, 2003; Hirschhorn et al., 2002; Ioannidis et al., 2001). Other important reasons that also contribute to a high chance for initial false-positive findings are publication bias, variation of power between studies, and failure to ascribe findings of positive association to chance (Colhoun et al., 2003; Wacholder et al., 2004).

In the current study we aimed to further examine the association between 5-HTTLPR and observed sensitive parenting while taking notice of the rectifiable problems attributing to inconsistent and false-positive findings: First, the current study is performed within an ethnically homogeneous cohort, thereby minimalizing the risk of population stratification. Second, we used a four times larger sample (*n* = 767 mother-child dyads) than in previous studies to increase the power to detect any effect of 5-HTTLPR. Precision of the findings was further improved by assessing observed maternal sensitivity repeatedly, at 14 months, at 3 years, and at 4 years. Furthermore, we assessed whether observed child social fearfulness moderated the effect of 5-HTTLPR on maternal sensitivity. Previous research has demonstrated that child characteristics such as shyness and approach withdrawal are associated with maternal intrusiveness and less maternal warmth (Bates & Pettit, 2007; Brunk & Henggeler, 1984). This association was especially observed in anxious mothers, most likely due to shared genetic factors (Moore, Whaley, & Sigman, 2004). It has also been proposed that shy children are cognitively more challenged in new situations, eliciting maternal overinvolvement (Bates & Pettit, 2007). Because social fear is implicated in maternal sensitivity and in the same neurobiological systems as 5-HTTLPR, social fearfulness is a good candidate environmental factor (Moffitt, Caspi, & Rutter, 2005). Because it is well-recognized that maternal sensitivity includes reciprocal interactions between mother and child (Shin et al., 2008), we also examined whether any associations with maternal 5-HTTLPR and sensitivity were independent of the child's 5-HTTLPR genotype. Last, to test the specificity of any association between 5-HTTLPR and maternal sensitivity, we repeated all analyses with two other polymorphisms available in this cohort and previously examined in relation to sensitivity: the Val158Met polymorphism in the Catechol-O-Methyltransferase gene (COMT) and rs53576, a polymorphism in the oxytocin-receptor gene (OXTR).

We hypothesized that in this large homogeneous cohort with repeated measurements of observed sensitive parenting genetic main effects of 5-HTTLPR can be detected.

Method

Setting

The study was embedded within the Generation R Study, a population-based prospective cohort from fetal life onwards in Rotterdam, the Netherlands, which has been described in detail elsewhere (Jaddoe et al., 2012).

In a randomly assigned subgroup of Dutch pregnant women and their children, detailed assessments were conducted including observations of maternal sensitivity and child temperament. This subgroup is ethnically homogeneous to exclude confounding or effect modification by ethnicity. All children were born between February 2003 and August 2005 and form a prenatally enrolled birth-cohort. The study was conducted in accordance with the guideline proposed in the World Medical Association Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam (numbers: prenatal, MEC 198.782/2001/31 and postnatal, MEC 217.595/2002/202). Written informed consent was obtained from all participants.

Study population

Mothers were considered eligible for the current study if they had singleton pregnancies and gave full consent for postnatal follow-up ($n = 1079$). Of these, data on 5-HTTLPR genotype was available for $n = 919$ mothers. Within this group, information on observed maternal sensitivity was available for $n = 780$ (85%) mothers. Data of 13 mother-child dyads were randomly excluded because they participated with multiple children (e.g., older or younger siblings). Thus, the cohort for analysis compromised $n = 767$ mothers. Of these mothers, the majority ($n = 584$, 76%) participated in 2 or 3 assessments of sensitivity.

To study the main effect, information on all 767 mother-child dyads were included in the analyses. As for the GxE effect, data on 604 mother-child dyads with assessments of child fearful temperament was available.

Non-response

Non-response (i.e. mothers without any data on maternal sensitivity, $n = 139$) did not differ on the distributions of 5-HTTLPR genotypes, parity, or level of family stress compared to mothers included in the study. Non-respondents were however lower educated than mothers included in the study (43.6% vs 34.4%, $\chi^2 = 4.22$, $p = .04$). The children of non-respondents did not differ on social fearfulness compared to children of mothers included in the study.

5-HTTLPR genotyping

Maternal DNA was derived from blood samples at enrolment and child DNA was derived from cord blood samples at birth. The 43-base pair insertion/deletion in the promoter region of the 5-HTT gene was genotyped using Taqman allelic discrimination. Primer sequences were taken from Hu and colleagues (2006). Reactions were performed in a 384-wells format in a total volume of 5 ul containing 2 ng DNA, 120 nM FAM-probe, 80 nM VIC-probe, PCR primers (100 nM each), dimethyl sulfoxide (DMSO) (4% by volume), and 1 x genotyping master mix (Applied Biosystems Inc.).

PCR cycling consisted of initial denaturation for 10 minutes at 95° C, and 40 cycles with denaturation of 15 seconds at 96° C and annealing and extension for 90 seconds at 62.5° C. Signals were read with the Taqman 7900HT (Applied Biosystems Inc.) and analyzed using the sequence detection system 2.3 software (Applied Biosystems Inc.). To evaluate genotyping accuracy of 5-HTTLPR, 225 random child samples were genotyped a second time. No discrepancies were found. Two additional maternal polymorphisms were genotyped using Taqman allelic discrimination: the Val158Met polymorphism, a functional variant in the Catechol-O-methyltransferase gene (COMT), and a polymorphism in the oxytocin receptor gene OXTR, rs53576).

Maternal sensitivity

During the lab visit at the child's age of 14 months, maternal sensitivity was observed during 5 minutes free play ($SD = 2.0$). Maternal sensitivity was coded from DVD recordings with the Ainsworth's 9-point rating scales for Sensitivity and Cooperation (Ainsworth, Bell, & Stayton, 1974). The intraclass correlation (ICC) for intercoder agreement was .79 for sensitivity and .69 for cooperation (n = 24). Sensitivity and Cooperation correlated strongly ($r = .84$). An overall 14-month sensitivity score was created by standardizing the two scores and computing the average.

During the lab visit at the child's age of 3 years and the home visit at age 4 years, maternal sensitivity was observed during two tasks that were too difficult for the child, considering his or her age: building a tower and etch-a-sketch. Mothers were instructed to help their child as usual. Maternal sensitivity was coded from DVD recordings with the revised Erickson 7-point rating scales for Supportive Presence and Intrusiveness (Egeland et al., 1990). An overall sensitivity score was created by reversing the Intrusiveness scale, standardizing the scores, and computing the average across both scales and both tasks. The two tasks were independently coded by 13 and 10 extensively trained coders, respectively. At 3 years, average ICCs for the subscales were .75 for the tower task ($n = 53$) and .79 for the etch-a-sketch task ($n = 55$). At 4 years, average ICCs for the subscales were .85 for the tower task ($n = 40$) and .79 for the etch-a-sketch task ($n = 40$).

Overall, coders were trained in approximately 7 sessions and regularly supervised during the coding process; interreliability between coders was not only assessed directly after the training, but also monitored during the coding process to avoid rater drift. Coders were unaware which of their DVDs would be assigned to a second coder. Based on the guidelines as described by Cicchetti and colleagues (2006) the ICCs for our sensitivity assessments, ranging from 0.69 to 0.85, are good to excellent.

Child social fearfulness

Child social fearfulness was measured using the Stranger Approach (SA) episode of the Laboratory Temperament Assessment Battery Preschool Version (Lab-TAB) during the lab visit at 3 years of age (Goldsmith et al., 1999). The Lab-TAB is a widely used, standardized instrument for observational assessment of early temperament. During the SA episode the child has to deal with social fear when a novel, slightly threatening stranger approaches. The episode was modeled after real-life events: The child was left alone in a room. After 10 seconds a stranger entered the room and asked the child standard questions in a neutral tone of voice.

Episodes were coded from DVD recordings according to the coding system described in the Lab-TAB manual. Coders were extensively trained and reliability was established before data were coded. Coders were blind to all other measures. Each episode was divided into nine epochs. Eight parameters were scored in each epoch: Intensity of fear expressions, distress vocalizations, activity decrease, approach, avoidance, gaze aversion, verbal hesitancy, and nervous fidgeting. For each parameter, average scores were calculated by dividing the child's overall score for that parameter across the 9 epochs. The mean intercoder agreement ICC for these average scores was .84 ($n = 25$). Then each average score was divided by the maximum attainable score for that parameter per epoch. This was done to standardize parameters along the same scale to range between 0 and 1. Finally, an overall 'fearfulness' score was created by taking the mean of the standardized average scores of the different parameters. This fearfulness score ranged from 0 to 1 with higher scores indicating a more social fearfulness.

Social fear was also assessed by questionnaire. When the child was three years old, parents reported on the following questions: 'my child is afraid of other children', 'my child is afraid of adults other than his/her parents', 'my child is afraid of places crowded with people, like a shopping mall or playground'. Parents responded on a 3-point-Likert scale (0 'not at all', 1 'sometimes', 2 'often'). The sum-scores of both parents were summed and the average was taken.

Other covariates

Maternal age, educational level, marital status, and parity were assessed using questionnaires at enrolment. Educational level (highest education finished) was dichotomized into 'lower education' (until secondary school) and 'higher education'. At 20 weeks of pregnancy, family stress was assessed by a subscale, General Functioning, of the Family Assessment Device (FAD), which is a validated self-report measure of health or psychopathology of the family (Byles et al., 1988). A score > 2.17 (cut-off) denotes unhealthy family functioning. Family stress was defined on the basis of the General Functioning cut-off score as either 'family stress present' or 'no family stress'.

Amount of non-parental care was assessed using a questionnaire at the child's age of one year. Mothers were asked 'for how many hours per week is your child been taken care of by 1) a babysitter, 2) an au-pair, 3) a host-parent, 4) neighbors or family members, 5) daycare, or 6) some-one else ?'. The total hours of non-parental care per week was computed by summing the answers to the different items.

Lifetime depressive and anxiety disorders of mother were assessed using the Composite International Diagnostic Interview (CIDI) Version 2.1. The CIDI is a structured interview based on DSM-IV criteria. A home interview was conducted at 30 weeks during pregnancy by research assistants trained in an official training centre for the CIDI. Good interrater reliability and validity have been reported (Andrews & Peters, 1998).

Statistical analyses

An additive model was used in the analyses with the 5-HTTLPR genotype, with *LL*=0, *LS*=1, and *SS*=2. Using this model an r-fold increased effect was assumed for *LS*, and a 2r-increased effect for *SS*. The 5-HTTLPR genotype was also analyzed by a general genetic model with the *LL* genotype as the reference group. Using this model 5-HTTLPR was analyzed per genotype.

Data were analyzed in three steps. We first assessed the main effect of maternal 5-HTTLPR on maternal sensitivity. To analyze the associations between the repeatedly measured sensitivity scores and 5HTTLPR we used unbalanced repeated-measurements regression analysis assuming random effects for intercept and slope. These regression models enable studies of repeatedly measured outcomes taking into account the correlation between measurements, and allowing for incomplete outcome data (Twisk, 2003). The covariance parameters were estimated using Restricted Maximum Likelihood (REML). We used unstructured covariance structures. These structures estimate every covariance individually and therefore offer the best fit. As simple models are preferred over more complex models including fractional polynomials (Royston & Sauerbrei, 2005) and a scatter plot of the raw data did not give evidence of non-linearity, a linear model was fit. The model fitted can be written as:

$$\text{Maternal sensitivity} = \beta_0 + \beta_1{*}\text{5-HTTLPR} + \beta_2{*}\text{age} + \beta_x{*}\text{covariates.}$$

In this model, 'β_0' reflects the intercept and 'β_1*5-HTTLPR' tests the difference in intercept between mothers with different alleles of 5-HTTLPR. The term 'β_2*age' reflects the linear slope of the model with age defined as the child's age in months at the sensitivity assessment. It was also tested whether 5-HTTLPR interacts with age, i.e. whether the development of maternal sensitivity over time differs between mothers with different alleles of 5-HTTLPR. However, as this term was not significant ($p = 0.54$) it was not further included in the models.

To test whether any effect of 5-HTTLPR on maternal sensitivity was driven by a specific time-point, we examined the per time-point associations between 5-HTTLPR and maternal sensitivity using multivariate linear regression analyses. Second, we tested whether the interaction between child social fearfulness and maternal 5-HTTLPR predicted maternal sensitivity. To this end, the fearfulness score was standardized. Again, unbalanced repeated-measurement regression analysis was used to test the repeated associations and multivariate linear regression analyses were performed to examine the per time-point associations. Third, we reran all analyses in the mothers, now adjusting for the child's genotype. This enabled us to test whether the results found for the maternal genotype were independent of the child's genotype. At the same time, it allowed us to test whether there was also an effect of the child's genotype on sensitivity.

Bivariate correlations between the determinants, outcome, and possible confounding covariates were assessed using Pearson's correlations for continuous variables and Spearman's rho for categorical variables. Based on the bivariate correlations, all analyses were additionally adjusted for family stress, maternal educational level, and parity, as these covariates were significantly correlated with 5-HTTLPR and maternal sensitivity (e.g., parity) or with maternal sensitivity alone (e.g., family stress and maternal educational level) (see Supplementary material, Table S1). Adjusting for covariates significantly associated with a quantitative outcome may improve the efficiency without biasing the associations between the predictors and the outcome (Schisterman, Cole, & Platt, 2009). Maternal lifetime depressive disorder, maternal lifetime anxious disorder, maternal age at intake, and gender of the child were also tested as possible covariates but were not significantly correlated with either the predictors or the outcome and were therefore not included in the analyses. To exclude gene-environment correlations, we assessed whether maternal or child 5-HTTLPR were associated with child social fearfulness. To test the specificity of our findings for 5-HTTLPR, the analyses testing the main effect of 5-HTTLPR and the interaction effect with social fearfulness were repeated using COMT and OXTR.

We used Multiple Imputation in SPSS 17 to impute the missing data on covariates (family stress 6.9%, educational level 0.8%, parity 0.1%, lifetime diagnoses of depression or anxiety disorder 12% each). All test statistics and regression coefficients were averaged over 5 imputed datasets. We used an alpha of .05 to indicate statistical significance. All repeated measurements analyses were carried out using the Statistical Analysis System version 9.2 (SAS, Institute Inc. Gary NC, USA), including the PROC MIXED procedure for unbalanced repeated measurements. All per time-point analyses and correlations were carried out using the Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS, Inc. Chicago, Illinois).

Results

Descriptive statistics of the mothers and children are presented in Table 1. Maternal and child 5-HTTLPR genotype distribution were both in Hardy Weinberg equilibrium ($p = .6$ and $p = .6$, respectively). Approximately 15% of the mothers met the criteria for a lifetime depressive disorder. Likewise, 14% of the mothers met the criteria for a lifetime anxious disorder.

Correlations between predictor variables, maternal sensitivity, and covariates are presented in Supplementary material, Table S1. Maternal 5-HTTLPR genotype was not correlated with either a lifetime depressive disorder ($\rho = -.03$) or a lifetime anxiety disorder ($\rho = -.02$). The correlations between the measurements of maternal sensitivity at different time points were low to modest (14 months and 3 years $r = .16$, 14 months and 4 years $r = .07$, 3 years and 4 years $r = .32$).

The repeated measurement analyses showed that, overall, with each additional *S*-allele of the mother she was more sensitive towards her child ($B = 0.11$ (95% C.I. = 0.03, 0.18), $p = .005$) taking into account family stress, educational level and parity (see Table 2). Using a general genetic model we found that mothers carrying the *SL* and *SS* genotypes were more sensitive towards their children than mothers with the *LL* genotype.

The results of the individual per time-point analyses are summarized in Table 2. Maternal 5-HTTLPR was associated with maternal sensitivity at 14 months and with maternal sensitivity at 4 years. These associations remained significant after adjusting for family stress, maternal educational level, and parity. Although 5-HTTLPR did not predict maternal sensitivity at 3 years, the association was in the same direction as the associations observed at 14 months and 4 years, and was not significantly different from those associations.

Table 1. *Sample descriptives (N=767).*

	Mean*	(*SD*)*
Mothers		
5-HTTLPR (%)		
LL (*n*=257)	33.5	
LS (*n*=371)	48.4	
SS (*n*=139)	18.1	
Sensitivity at 14 months, mean (range)[a]	0.0	(-4.16, 2.58)
Sensitivity at 3 years, mean (range)[b]	0.0	(-2.75, 2.86)
Sensitivity at 4 years, mean (range)[c]	0.0	(-2.56, 2.42)
Lifetime depressive disorder (%)	14.8	
Lifetime anxiety disorder (%)	14.4	
Family stress (%)	4.5	
Educational level (% lower)	34.6	
Parity (% nulli)	63.5	
Age at intake	31.8	(3.74)
Non-parental care, hours per week	16.0	(9.85)
Children		
5-HTTLPR (%)[d]		
LL (*n*=205)	26.7	
LS (*n*=295)	38.5	
SS (*n*=124)	16.2	
Child's social fearfulness, mean (range)[e]	0.0	(-2.72, 3.67)
Child's gender (% boys)	50.1	
Age at 14mo visit, months, median (95% range)	14.5	(13.4, 17.1)
Age at 3 years visit, months, median (95% range)	37.3	(35.5, 41.4)
Age at 4 years visit, months, median (95% range)	51.1	(49.8, 55.1)

* Unless otherwise indicated
[a] *n* = 537, [b] *n* = 574, [c] *n* = 524, [d] *n* = 624, [e] *n* = 624

Table 2. *Associations between 5HTTLPR and maternal sensitivity.*

	Maternal sensitivity (per *SD*)			
	Unadjusted Model		Adjusted Model	
	B (95% C.I.)	*p*	*B* (95% C.I.)	*p*
Repeated measurements analyses				
5-HTTLPR	0.11 (0.04, 0.19)	.004	0.11 (0.03, 0.18)	.005
5-HTTLPR (general model)				
LL	0.00 (ref)	-	0.00 (ref)	-
LS	0.17 (0.04, 0.29)	.008	0.18 (0.06, 0.29)	.01
SS	0.21 (0.05, 0.37)	.009	0.19 (0.04, 0.35)	.004
Per time-point analyses				
Sensitivity at 14 months (n=537)				
5-HTTLPR	0.13 (0.01, 0.25)	.04	0.12 (0.00, 0.24)	.049
Sensitivity at 3 years (n=574)				
5-HTTLPR	0.08 (-0.04, 0.19)	.2	0.06 (-0.05, 0.18)	.3
Sensitivity at 4 years (n=524)				
5-HTTLPR	0.16 (0.04, 0.28)	.008	0.17 (0.05, 0.28)	.006

Note. The adjusted model was adjusted for family stress, maternal educational level, and parity. Unless otherwise specified, additive models were used.

The repeated measurements analysis showed a trend for an interaction between 5-HTTLPR and child temperament in predicting maternal sensitivity; $B = -0.09$ (95% C.I. = -0.18, 0.00), $p = .059$ (see Table 3). Figure 1 shows that mothers carrying the *SS* or *SL* genotype were more sensitive than mothers carrying the *LL* genotype when parenting children with the lowest fear scores. In contrast, no difference in sensitivity between mothers with different genotypes was observed if they parented more socially fearful children. The per time-point analyses showed that the effects of an interaction between 5-HTTLPR and child temperament on sensitivity were essentially the same at 3 and 4 years (see Table 3). To test the robustness of these findings we also tested the effect of the interaction between 5-HTTLPR and social fear on sensitivity with social fear reported by both parents. The correlation between the observed and reported measurement of social fear was low ($r = .08$, $p = 0.07$, $n = 552$), but the effect of the interaction was similar ($B = -0.19$ [95% C.I. = -0.42, 0.57], $p = .13$), data not shown.

Table 3. *The moderating effects of social fearfulness on the association between 5-HTTLPR and maternal sensitivity.*

	Maternal sensitivity (per *SD*)			
	Unadjusted Model		Adjusted Model	
	B (95% C.I.)	*p*		
Repeated measurements analyses				
Social Fearfulness x 5-HTTLPR	-0.08 (-0.18, 0.02)	.099	-0.09 (-0.18, 0.00)	.059
Per time-point analyses				
Sensitivity at 36 months (n=532)				
Social Fearfulness x 5-HTTLPR	-0.08 (-0.20, 0.04)	.2	-0.09 (-0.20, 0.03)	.1
Sensitivity at 48 months (n=453)				
Social fearful x 5-HTTLPR	-0.07 (-0.19, 0.06)	.3	-0.08 (-0.20, 0.04)	.2

Note. The adjusted model was adjusted for family stress, maternal educational level, and parity. Furthermore, all models included the main effects of social fearfulness and 5-HTTLPR. Unless otherwise specified, additive models were used.

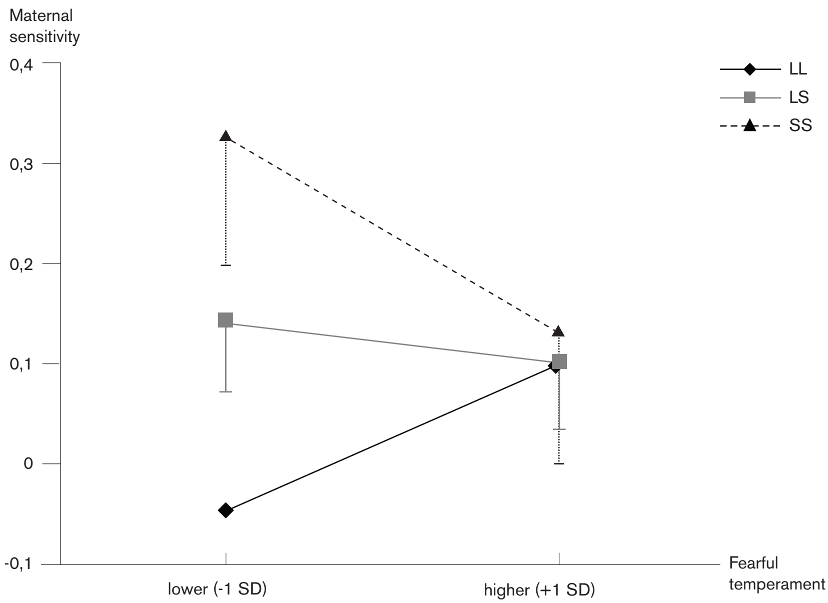

Figure 1. Mean maternal sensitivity per *SD* (with 95% C.I.'s) based on 5-HTTLPR genotype and child social fearfulness (per *SD*). Figure based on an additive genetic model (*LL* = reference), adjusted for family stress, maternal educational level, and parity.

To test whether our results were due to an independent effect of the maternal 5-HTTLPR genotype and could not be explained by the child's 5-HTTLPR genotype, we reran all analyses in mothers also including the child's 5-HTTLPR genotype. The results are illustrated in Figure 2, which shows the effect of the child's 5-HTTLPR genotype on maternal sensitivity adjusted for maternal genotype. Within the strata of maternal genotype, child 5-HTTLPR genotype did not affect maternal sensitivity (B = -0.01 [95% C.I. = -0.10, 0.08], p = .9), while the effect of maternal genotype on sensitivity remained essentially the same (B = 0.12 [95% C.I. = 0.03, 0.21], p = .01). Also, when tested separately, the child's genotype did not predict maternal sensitivity (B = 0.05 [95% C.I. = -0.03, 0.13], p = .2). Likewise, in strata of maternal genotype, there was no interaction between child 5-HTTLPR genotype and social fearfulness in the prediction of maternal sensitivity (data not shown).

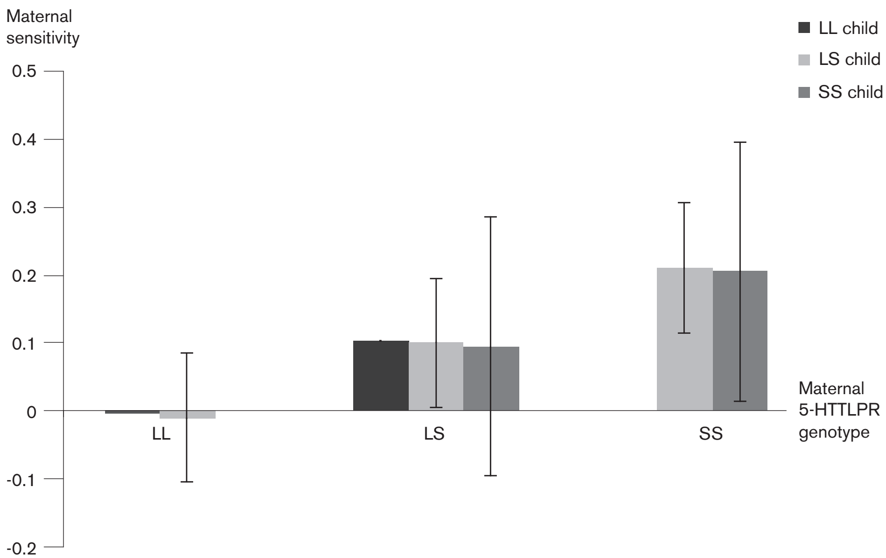

Figure 2. The effect of child 5-HTTLPR genotype on maternal sensitivity. In the different strata of maternal genotype, no effect of the child's 5-HTTLPR genotype on maternal sensitivity was observed. Figure based on an additive genetic model adjusted for family stress, maternal educational level, and parity.

To exclude the possibility that the reported GxE result was due to gene-environment correlation (Rutter, Moffitt, & Caspi, 2006), we assessed whether maternal or child 5-HTTLPR genotype was correlated with child social fearfulness. No significant correlations between maternal or child 5-HTTLPR genotype and child social fearfulness were observed (see Supplementary Table S1).

To test the specificity of the findings for 5-HTTLPR, the analyses were repeated using COMT and OXTR. No main effects or interaction effects with social fear on maternal sensitivity were found (see Supplementary Table S2).

Discussion

The present study investigated the effect of 5-HTTLPR on maternal sensitivity in a large population-based sample of mother-child dyads, using repeated measurements of sensitivity at different ages of the child. Mothers carrying *S*-alleles showed more sensitive behavior towards their children than mothers carrying *L*-alleles. Furthermore, we found some evidence that child social fearfulness may moderate the effect of 5-HTTLPR on maternal sensitivity. Mothers carrying the *SS* or *LS* genotype were more sensitive than mothers carrying the *LL* genotype when parenting children with the lowest fear scores. In contrast, no difference in sensitivity between mothers with different genotypes was observed when they parented more fearful children.

The findings of a direct effect of 5-HTTLPR on maternal sensitivity are in line with the observations of Mileva-Seitz and colleagues (2011) who also found that the *S*-allele was associated with more sensitive parenting. The 5-HTTLPR polymorphism may exert its influence on parenting through its associations with maternal characteristics because the 5-HTTLPR polymorphism is associated with various aspects of cognitive functioning. Both rodent and human studies have suggested that *S*-allele carriers show improved cognitive functioning on a variety of tasks including cognitive flexibility, reversal learning, attention, and inhibition (Brigman et al., 2010; Homberg & Lesch, 2011; Jedema et al., 2010). Especially cognitive flexibility and attention are important components of parenting behavior as sensitive parenting depends on the ability to accurately perceive children's signals and to respond to them in an adequate and prompt way (Ainsworth et al., 1978). For example, it has been shown that maternal attention deficit/hyperactivity disorder (ADHD) negatively impacts on maternal parenting practices (Chronis-Tuscano et al., 2008; Murray & Johnston, 2006). Also, poor working memory is predictive of observed reactive parenting (Deater-Deckard et al., 2010).

Besides an effect on parenting via maternal characteristics the 5-HTTLPR polymorphism may also exert a direct influence on parenting through underlying neural and hormonal influences. Both oxytocin and vasopressin appear to be of major importance for understanding differences in parenting behavior across species (Galbally et al., 2011; Swain et al., 2007). The two hormones are secreted by the hypothalamic paraventricular nucleus (PVN) which is innervated by serotonergic fibers (Skuse & Gallagher, 2011). Furthermore, serotonin receptors are present in the PVN. Studies have indicated that through its receptors, serotonin influences the release of oxytocin and vasopressin (Jorgensen et al., 2003). Therefore, through its associations with the oxytocin and vasopressin systems, 5-HTTLPR may influence maternal sensitive parenting.

When we discuss our GxE finding, it should be noted that the finding was only marginally significant ($p = .059$) and must therefore be interpreted with caution. While the sample size in the current study was larger than previous reports on molecular genetics in relation to observed parenting, power was still small (e.g., < 20%) to detect a significant GxE in a fairly homogeneous sample (Duncan & Keller, 2011). We found that mothers with the *SS* or *LS* genotypes were more sensitive than mothers with the *LL* genotype when parenting low fearful children. In contrast, when parenting more fearful children, no differences in sensitive parenting between mothers with different genotypes was observed. The present observations of social fearfulness were obtained in a relatively healthy, general population sample of mother-child dyads. We cannot rule out the possibility that if the fear scores had included more extremes of social fearfulness (e.g., clinical levels of social fear) we might have observed a different picture. GxE effects depend on the distribution of the environmental exposure in the sample (Aiken & West, 1991; Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007).

Also, if risk exposure differs among samples and there is an underlying GxE, findings for candidate genes may be inconsistent (Caspi et al., 2003). This offers a possible explanation for the divergent findings reported by Bakermans-Kranenburg & Van IJzendoorn (2008) who found that the *S*-allele was related to less sensitive parenting. Their study involved a sample of mothers with children with externalizing behavioral problems. In the absence of a reference group of children without behavioral problems, an underlying GxE (i.e. the 5-HTTLPR genotype in interaction with the stress of parenting a problematic child) could even have resulted in this seemingly reversed effect. On the other hand, children at high risk for externalizing behaviors may well be a different parenting challenge than children who are socially fearful.

In the current study we aimed to rule out artifact sources of GxE findings. First, no correlations were observed between the maternal or child's 5-HTTLPR and social fearfulness of the child. If the psychosocial environmental variable (here: social fearfulness of the child) is not genetically independent of the outcome variable (here: sensitive parenting), then any GxE would reflect Gene Environment correlation (rGE): Children inherit the genes of the mother associated with sensitive parenting which then predispose them to social fearfulness (passive rGE), or these inherited genetic variants may evoke certain parenting behaviors (evocative rGE) (Rutter & Silberg, 2002). Second, in the current study child social fearfulness was observed rather than reported by the mother. This is important as the 5-HTTLPR genotype has been associated with anxious and neurotic personality traits (Karg et al., 2011), and there is some evidence that maternal personality traits influence their reports of the child's temperamental traits (Hayden et al., 2010; Kiel & Buss, 2006). In theory, mothers, predisposed by their genetic make-up, could ascribe their children certain temperamental characteristics (rGE). In the present study child fearfulness was observed, excluding maternal reporting bias.

Moreover, we showed that, in strata of maternal genotype, no effect of child genotype on sensitive parenting was observed. In other words, the effect of 5-HTTLPR genotype on maternal sensitivity was driven by the maternal genotype, thereby confirming the independent effect of the maternal genotype on maternal sensitivity.

Both the direct, indirect genetic effects, and GxE effects may be seen as an extension of Belsky's model. However, not only structural genetic variants account for the transmission of parenting effects. For example, animal research has shown that early maternal parenting alters the DNA structure of the offspring (i.e. DNA methylation) which may persist into adulthood. This altered DNA structure of the offspring subsequently affects the offspring's parenting as adults (Kappeler & Meaney, 2010; Meaney, 2001). Therefore, future research on the determinants of parenting would not only benefit from including genetic factors, but also from epigenetic research.

Our study has strengths and limitations, and these are worth mentioning as well. First, our results may be somewhat biased due to the overrepresentation of higher educated mothers. Second, the Generation R Focus Study is a relatively homogenous population-based cohort that mainly consists of low risk families. While the homogeneity of the sample is advocated for validly testing genetic effects, results may be less generalizable to samples including high-risk families. Furthermore, we did not differentiate between L and Lg although Lg is considered a low expressing genotypic variant of the 5-HTTLPR polymorphism (Hu et al., 2006). However, in Caucasian samples the percentages of Lg have been found to be rather low (Zalsman et al., 2006). Also, our GxE finding was only marginally significant. Clearly, independent replication of this finding is needed. Last, no more than 10% (varying from $n = 24$ to $n = 55$) of the sensitivity assessments were re-evaluated for rater agreement.

In conclusion, we showed that the maternal 5-HTTLPR polymorphism most likely is associated with maternal sensitive parenting. Furthermore, we showed that the association between maternal 5-HTTLPR and maternal sensitivity may differ depending on fearful temperamental traits of the child. These findings contribute to growing knowledge that parental behavior is a multifactorial concept. As noted by Swain and colleagues (2007), parenting can be viewed as an interaction among genes, past parenting, current experience, psychological state, neurobiological systems, and environmental constraints. Acknowledging and providing further insights into the multifactorial processes underlying parenting will provide a better understanding of parenting. In particular, investigation of possible mediators of the association between 5-HTTLPR and maternal sensitivity, such as cognitive flexibility and attention, may provide valuable insights into underlying biological pathways and provide further evidence for an association between 5-HTTLPR and parenting. Moreover, as for many complex traits it remains challenging to find and recognize true genetic associations. Therefore, replication of the currents association between 5-HTTLPR and sensitive parenting remains warranted. In the future, all efforts to provide insight into processes underlying parenting may lead to early identification of mother-child dyads who are candidates for early (parenting) interventions.

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Supplementary material

Table S1. *Correlations among the variables.*

	Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Maternal 5-HTTLPR	-													
2	Child's 5-HTTLPR	.51***	-												
3	Sensitivity at 14mo	.08*	-.02	-											
4	Sensitivity at 3 year	.05	.07	.16**	-										
5	Sensitivity at 4 year	.11**	.07	.07	.32***	-									
6	Social fearfulness	-.03	-.01	.04	.01	-.01	-								
7	Lifetime depressive disorder	-.03	.05	-.03	.02	-.05	-.01	-							
8	Lifetime anxiety disorder	-.02	-.03	-.04	-.01	-.04	-.01	.24***	-						
9	Family stress	.02	.04	-.09**	-.04	-.06	-.00	.05	.04	-					
10	Educational level (ref=higher)	-.03	-.03	-.06	-.18***	-.20***	.02	.05	.02	-.01	-				
11	Parity (ref=0)	.04*	-.01	.02	.07**	.04	.05	.00	.00	.00	.02	-			
12	Age at intake	.03	-.07*	.05	.03	.00	.02	.04	.02	.00	-.20***	.40***	-		
13	Non-parental care	.03	.04	-.00	.06	.03	.01	-.10*	.00	-.04	-.30**	-.03	.18**	-	
14	Child's gender (ref=girl)	.03	.04	-.07	-.05	.00	.08**	-.01	.04	-.01	.05	.00	-.08**	.05	-

*$p < 0.1$, **$p < 0.05$, ***$p < 0.01$

Table S2. *Associations between COMT, OXTR and maternal sensitivity.*

	Maternal sensitivity (per *SD*)			
	Unadjusted Model		Adjusted Model	
	B (95% C.I.)	*p*	*B* (95% C.I.)	*p*
COMT	0.02 (-0.06, 0.10)	.6	0.03 (-0.05, 0.11)	.5
COMT (general model)				
ValVal	0.00 (ref)	-	0.00 (ref)	
ValMet	0.04 (-0.09, 0.17)	.6	0.04 (-0.08, 0.17)	.5
MetMet	0.04 (-0.12, 0.20)	.6	0.06 (-0.10, 0.21)	.5
Social Fearfulness x COMT	0.01 (-0.11, 0.12)	0.99	0.00 (-0.10, 0.11)	.9
OXTR	0.001 (-0.09, 0.09)	0.97	-0.01 (-0.10, 0.09)	.8
OXTR (general model)				
GG	0.00 (ref)	-	0.00 (ref)	-
GA	0.07 (-0.06, 0.19)	.3	0.06 (-0.06, 0.18)	.3
AA	-0.08 (-0.28, 0.13)	.5	-0.10 (-0.30, 0.10)	.3
Social Fearfulness x OXTR*				
Social Fearfulness x GA	0.07 (-0.08, 0.21)	.4	0.07 (-0.08, 0.22)	.4
Social Fearfulness x AA	0.01 (-0.20, 0.21)	.9	0.01 (-0.20, 0.21)	.9

Note. The adjusted model was adjusted for family stress, maternal educational level, and parity. Furthermore, all models included the main effects of social fearfulness and 5-HTTLPR.
Unless otherwise specified, additive m odels were used.
*For the interaction between social fearfulness and OXTR a general genetic model was used as the association between OXTR and sensitivity was not linear.

7

Discussion

Discussion

In the current series of studies, we investigated the role of parenting and biology in the development of self-regulation in the preschool period.

We found that attachment insecurity in infancy was related to higher levels of toddler active resistance during Clean-Up but not related to the level of noncompliance. No evidence was found for a moderating role of fearful temperament in the association between attachment security and child compliance behaviors. Child self-regulated, committed compliance in a prohibition context was associated with maternal negative discipline. Children of mothers who used more negative disciplines strategies showed less committed compliance. A small main effect of DRD4 genotype on committed compliance was found; children carrying the 7-repeat allele were more compliant than those not carrying the 7-repeat allele. The association between maternal positive discipline and child committed compliance was moderated by the child's COMT rs4680 genotype, indicating that the association was stronger in children with the Met/Met genotype than for children with other COMT genotypes.

Maternal family-related stress during pregnancy predicted lower levels of committed compliance at 3 years of age through lower levels of maternal positive discipline. Moreover, if mothers were more sensitive, children had lower levels of inhibition problems, working memory problems, and planning problems one year later. The influence of sensitive parenting on these domains of executive function development was independent of the length of the corpus callosum in infancy, which is an indicator of early brain maturation and the efficiency of interhemispheric connectivity (Keshavan et al., 2002). In children with a relatively short corpus callosum in infancy, higher levels of maternal positive discipline predicted lower levels of inhibition problems.

The longitudinal relation between sensitive parenting and internalizing problems in preschoolers was studied in two independent and large population-based samples. Maternal sensitivity was found to be modestly but consistently related to internalizing problems across time. Differences in levels of maternal sensitivity appeared partly genetically determined; mothers carrying the *s*-allele of 5-HTTLPR were more sensitive than *l*-allele carriers. Some evidence was found that the level of social fearfulness in children might moderate the effect of 5-HTTLPR on sensitivity; mothers carrying the *s*-allele were more sensitive than mothers without *s*-alleles to children with low levels of social fear.

The findings presented in this thesis provide a comprehensive overview of the role of parenting and the interplay between parenting and biology in the development of self-regulation. In our studies we replicate and extend previous findings in a large population-based cohort study with observations of parenting and child behavior and biological measures.

Parental determinants of self-regulation

Early childhood socialization is an important factor in the development of self-regulation, because infants rely on their parents for regulation of behavior and emotions (Kopp, 1982) and because the extended development of self-regulation in the preschool years makes the development of regulatory abilities particularly sensitive to environmental influences (Conway & Stifter, 2012). Earlier studies have provided mixed findings with regard to the importance of positive parenting for self-regulation (e.g., Calkins, Smith, Gill, & Johnson, 1998; Karreman, Van Tuijl, Van Aken, & Dekovic, 2006). We found evidence that a variety of parental determinants are involved in aspects of self-regulation in the preschool age. First, both difficulties in emotion regulation, associated with internalizing problems (e.g., Bayer, Sanson, & Hemphill, 2006), and difficulties in behavior regulation, such as active resistance and executive function problems (e.g., Bernier, Carlson, & Whipple, 2010; Kochanska et al., 2010), were predicted by less positive parenting or an insecure attachment relationship. Second, the role of parenting was not only restricted to aspects of self-regulation with a relational component, such as compliance and active resistance (Kim & Kochanska, 2012), but also apparent for an aspect of self-regulation that is considered nonsocial, namely executive function. Third, aspects of parenting that are control-focused, such as maternal positive and negative discipline, as well as aspects of parenting or relationship quality with mainly an affective component, such as maternal sensitivity and attachment security (Karreman et al., 2006), were found to contribute to self-regulation.

Interplay of parental and biological determinants of self-regulation

In the past years evidence has accumulated confirming the hypothesis that some children are more susceptible than others to both positive and negative environmental influences based on temperamental, physiological, or genetic differences (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). Our findings partly converge with earlier studies testing this hypothesis. No evidence was found for an interaction effect of attachment security and fearful temperament in determining compliance and active resistance during Clean-Up. This does not support earlier studies demonstrating the moderating role of fearful or difficult temperament in the association between the quality of the parent-child relationship and self-regulation (Kim & Kochanska, 2012; Kochanska, Aksan, & Joy, 2007). Our findings may indicate that the interaction between child temperament and parenting is restricted to a relatively limited developmental window around two years of age (Kochanska et al., 2007).

We did find evidence that child genotype moderates the association between maternal positive discipline and child committed compliance; children with the Met/Met variant of the COMT rs4680 genotype appeared more hampered by lower levels of maternal positive discipline but also appeared to benefit more from high levels of maternal positive discipline. To our knowledge, our study was the first to explore the role of the dopamine-related common polymorphism COMT in the association between parenting and committed compliance. Others have found evidence that variations in 5-HTTLPR moderate the association between insecure attachment and self-regulation (Kochanska, Philibert, & Barry, 2009) and that variations in the DRD4 gene may be involved in the susceptibility of children for positive parenting (Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008). In our study, variations in the dopamine D4 receptor gene did not moderate the association between maternal discipline and child committed compliance. In general it has been suggested that the basis of differential susceptibility to the environment might be found in allelic variation in the dopamine and serotonin circuitries as these are related to sensitivity to reward and punishment (Ellis et al., 2011). It seems plausible that systems of reward and punishment would also be involved in the development of self-regulation and the ability of parenting strategies to modulate this development. Research in this field has just begun, and future research is needed to clarify the role of dopaminergic and serotonergic system variations in the association between parenting and self-regulation.

The association between a shorter corpus callosum in infancy and child inhibitory problems appeared moderated by the level of maternal positive discipline; children with a relatively short corpus callosum experiencing high levels of maternal positive discipline showed less inhibitory problems than children with a shorter corpus callosum experiencing low levels of maternal discipline. This finding is congruent with earlier studies indicating that positive parenting might act as a buffer in children with biological vulnerability (Laucht, Esser, & Schmidt, 2007; Poehlmann et al., 2011).

In general, our findings suggest that a simple model of parental influence on self-regulation may not be sufficient to explain the relatively large individual differences in self-regulation across children. The modest effect sizes of our studies do not allow for firm conclusions on the exact roles of parenting and biological factors in self-regulation. The discrepancies between our findings and earlier studies may suggest that the susceptibility of individuals to the environment is domain specific instead of domain general (Belsky & Pluess, 2009), which could imply diverging results of studies using different environmental exposures and different outcome measures. Research in this field would profit especially from experimental studies on the differential susceptibility hypothesis (Van IJzendoorn, & Bakermans-Kranenburg, 2011; Van IJzendoorn et al., 2011a). Intervention studies to enhance sensitive parenting or attachment security have found evidence for differences in effectiveness in reducing externalizing problems or enhancing attachment security based on variations in temperamental reactivity or genotype of the child (Bakermans-Kranenburg et al., 2008; Klein Velderman, Bakermans-Kranenburg, Juffer, & Van IJzendoorn, 2006).

Despite the excitement and enthusiasm about gene-environment research in the past decade, critics worry that the combination of multiple testing and publication bias against null results has resulted in an inflation of false positives in gene-environment literature (Duncan & Keller, 2011). Independent and well-powered replications (Duncan & Keller, 2011) and thoroughly conducted meta-analyses (Ioannidis, 2003) might improve the quality of gene-environment research in the future.

Mechanisms behind the association between parenting and self-regulation

Attachment security, maternal sensitivity, and positive discipline were associated with less active resistance during Clean-Up, more committed compliance to prohibitions, and lower levels of internalizing problems, inhibition problems, working memory problems, and planning problems. Several mechanisms may explain the relation between positive parenting and the development of self-regulation. First, because infants have not yet developed the ability to regulate their emotions and behavior, they have to rely on their caregiver as a source of external regulation (Kopp, 1982). It has been postulated that this process of *dyadic regulation* eventually resulting in self-regulation, is established in a secure attachment relationship or with a sensitive and responsive caregiver (Sroufe, 1996). Specific aspects of positive parenting appear essential in this shift from external regulation to self-regulation. Consistent parenting that provides structure in the child's early life, makes the environment predictable, and allows the child to recognize regular routines, which foster the development of emotion regulation (Bronson, 2000). From a social learning perspective, sensitive and responsive parents can model regulation of emotions and behavior for the child and thus stimulate the growth of self-regulation (Bandura, 1971). Also, positive parenting can provide the child with opportunities to practice self-regulation by challenging the child. This process of providing support and guidance in planning and organizing so that children can perform tasks beyond their current level of ability has been conceptualized as *scaffolding* (Wood, Bruner, & Ross, 1976). The theoretical framework of scaffolding is reminiscent of the work by Lev Vygotsky, emphasizing the importance of competent social partners in the development of cognitive functions (Vygotsky, 1962, 1978). According to Vygotsky, children learn by giving them experiences that are challenging, but within their *zone of proximal development*; the range of developmental achievements they can attain with guidance by social partners. In this series of studies we did not include direct measures of the quality of maternal scaffolding, but this concept appears to be closely related to other aspects of positive parenting that are incorporated in our studies. It has been suggested that a mutually responsive and secure relationship between mother and child is associated with the frequency of scaffolding and the effectiveness of scaffolding (Carlson, 2009). Moreover, for scaffolding to be effective, it should be appropriately timed and contingent to the child's behavior (Bibok, Carpendale, & Müller, 2009), which is characteristic of sensitive parenting (Ainsworth, Blehar, Waters, & Wall, 1978).

A second potential mechanism behind the relation between parenting and self-regulation is that positive parenting might have a direct impact on brain development (Belsky & De Haan, 2011) or gene expression (Van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011b). Although research on the influence of parenting on child neurobiology is still in its infancy, more and more evidence is accumulating that early caregiving experiences alter the structure and functioning of the brain (for an overview, see Belsky & De Haan, 2011). Most research on the influence of parenting on brain development has focused on extremely negative parenting such as neglect and abuse, however there is some evidence that variation in parenting in the normal range can also influence brain function or structure (Belsky & De Haan, 2011). For example, a sensitivity training for parents of preterm children was found to result in short-term improvements in children's cerebral white matter (Milgrom et al., 2010).

A similar but different mechanism might be that the influence of early caregiving on the child's development is the result of epigenetic changes in the child (Van IJzendoorn et al., 2011b). Epigenetic changes are alterations in the expression or function of genes due to biochemical modifications such as methylation of DNA. Variations in maternal care in rodents have been found to alter methylation patterns that impact the function of the stress system in offspring (Szyf, Weaver, Champagne, Diorio, & Meaney, 2005) and next generations (Meaney, 2001). Interestingly, these alterations in methylation patterns were the consequence of variations in maternal care within the normal range (Meaney, 2001). In humans, there is still very little evidence for the impact of parental care on development through epigenetic processes. It is especially unclear whether normal variations in parental care influence methylation patterns. Considering more extreme rearing experiences, epigenetic differences in the stress system have been found in postmortem examinations of adult suicide victims with and without experiences of childhood abuse (McGowan et al., 2009).

A third explanation that needs to be considered is the possibility that the relation between positive parenting and child self-regulation is due to a confounding factor that underlies both parental behavior and child behavior. Although we were able to control for a number of possible confounding factors in our analyses, such as child gender, socio-economic status and maternal psychological symptoms, other factors such as personality characteristics and particular genetic factors were not assessed. An indication that it is possible that genetic factors underlie the association between parenting and self-regulation might be found in our results that the level of maternal sensitivity was predicted by maternal 5-HTTLPR and that child committed compliance was predicted by the child's DRD4 genotype. Because genetic variation appears to predict part of the variation in maternal and child behavior, a shared genetic variant in both mother and child can constitute an alternative explanation for the relation between positive parenting and preschool self-regulation.

Bidirectional effects

In the past decades, the importance of considering the bidirectional nature of parent-child interactions over the course of development has been emphasized in a growing number of studies (for an overview, see Pardini, 2008). At the same time, behavioral genetic research has stimulated the study of evocative gene-environment correlations, defined as genetically influenced child characteristics that might shape the parenting environment of the child (Rutter, Moffitt, & Caspi, 2006). However, empirical studies that examined bidirectional influences between parents and children remain rare. The inherently correlational nature of many studies on parenting and child development makes it difficult to confer the direction of effects and possible causation (Rutter, 2007). In our studies we found associations between attachment security and active resistance two years later, and associations between maternal sensitivity and child executive function abilities one year later. Maternal discipline and child committed compliance were concurrently associated. Although the longitudinal nature of some of these associations makes reverse causation less probable (Rutter, 2007), evocative gene-environmental correlations or person-environment correlations cannot be precluded. Moreover, because no baseline measures of child self-regulation were included in our studies, we could not assess whether there was within-individual change in self-regulation as a result of parenting.

In our study on the association between maternal sensitivity and child internalizing problems across the preschool years we attempted to overcome these methodological problems by investigating the contribution of bidirectional pathways between maternal behavior and child behavior across time. Modest but consistent associations were found between maternal sensitivity and child internalizing problems at a later age. The mother-to-child pathways were more consistent and replicable than the child-to-mother pathways. These findings converge with the hypothesis that the influence of parenting on child behavior is larger than vice versa (Lansford et al., 2011), although they also support the bidirectional nature of mother-child interaction (Pardini, 2008). More research is needed to further disentangle parental contributions to child behavior and child contributions to parental behavior, and to study possible underlying genetic factors that can influence both. Longitudinal adoption studies are among the interesting designs to answer these questions. For example, a study by O'Connor, Deater-Deckard, Fulker, Rutter, and Plomin (1998) demonstrated that children with a genetic risk for antisocial behavior were more likely to receive negative parenting from their (not biologically related) adoptive parents. Moreover, prenatal cross-fostering designs including children born through in vitro fertilization who are genetically unrelated to their rearing parents have the potential to disentangle genetic and environmental influences on child development (e.g., Harold et al., 2011; Rice et al., 2010).

Self-regulation: a social construct?

Although self-regulation is generally considered an internal motivation of controlling one's behavior and emotions, one could argue that the associations between positive parenting and self-regulation suggest that behavioral and emotional regulation are relational or social constructs. Child compliance, for instance, is inherently linked to the person posing the rules and the quality of the relationship with this person. Indeed, we found that the quality of the attachment relationship between mother and child predicted the level of active resistance to parental requests. A study on the relational nature of self-regulated compliance has found large similarities in the quality of compliance of a child toward requests of mother, father, or another caregiver (Feldman & Klein, 2003). However, the similarities in self-regulated compliance between caregivers might be explained by similarities in the quality of the relationship of the child with these different caregivers (Feldman & Klein, 2003).

The question whether self-regulation should be considered internally controlled or controlled by environmental and social factors has been elaborated from a motivational framework by Ryan, Kuhl, and Deci (1997). In this theoretical framework, a more complex portrayal of regulation is described on a continuum varying in the locus of control, source of motivation, and level of internalization. External regulation and internalized self-regulation are the ends of this continuum but several intermediate types of regulation are described. Ryan and colleagues (1993) suggest that supportive and autonomy-granting parenting behavior fosters the development of internalized self-regulation.

Although most theories on the development of self-regulation sketch a shift from external or co-regulation to a more mature and internalized type of regulation (e.g., Bronson, 2000; Kopp, 1982), it has also been argued that external regulators might remain important long after internalization has been established (Diamond & Aspinwall, 2003). Over the life course, individuals often rely on external regulation of emotion by the provision of comfort and support or distraction by others. Perhaps the boundaries between internal and external regulation of emotions and behavior should be considered more or less fluid (Diamond & Aspinwall, 2003). Although children appear to develop internally motivated regulation over time, this does not preclude the possibility that external agents help regulate behavior and emotions in certain situations. Some aspects of behavior and emotion regulation might be more dyadic in nature, such as compliance, than other types of regulation that are considered to be individual, cognitive attributes, such as executive function (Kim & Kochanska, 2012). Future studies on the regulation of behavior and emotions should consider the possible role of social agents for regulation without discarding the importance of individual characteristics (Diamond & Aspinwall, 2003).

Measurements

In the current series of studies different measurement methods were used, including observational measures, parental reports, and biological measures. In behavioral research a frequent threat to the validity of conclusions is *common method bias*, variance attributable to the measurement method instead of the constructs the measures represent (Podsakoff, MacKenzie, Lee, & Podsakoff, 2003). To avoid this bias, predictor and criterion variables in all studies were derived from different sources of information or from independent raters. Observational measures in structured situations were used to assess maternal parenting and attachment security. Advantages of observations over parental reports of parent-child interaction are that observations are not influenced by parental characteristics such as mood (Aspland & Gardner, 2003) or the ability of parents to reflect on their behavior (Hoff, Laursen, & Tardif, 2002). Furthermore, it is thought that self-reported parenting is a reflection of the parent's beliefs and aspirations about parenting but not necessarily a good indication of the actual parenting behavior (Hoff et al., 2002). Meta-analyses on the association between parenting and child development have demonstrated that the effect sizes for the relation between observed parenting and child outcomes are larger than for the relation between self-reported parenting and child development (e.g., McLeod, Wood, & Weisz, 2007; Rothbaum & Weisz, 1994).

Although observational measures are generally considered the preferred method to measure parenting, for self-regulation in preschoolers there is debate about the value of different measurement methods. Reasons for this debate are the complex nature of the concept self-regulation, which makes it difficult to measure (Gioia & Isquith, 2004), and the fact that preschoolers are limited in their behavioral repertoire compared to older children and adolescents (Espy, Kaufmann, Glisky, & McDiarmid, 2001). The validity of self-regulation tasks has been questioned for several reasons. The traditional measures of self-regulation are dependent on lower-order cognitive skills such as language and attention, which makes it difficult to determine the exact cause of deficits (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002). Furthermore, the structured nature of some neuropsychological tasks might obscure deficits in self-regulation in daily life (Gioia & Isquith, 2004). Studies comparing parental reports of self-regulatory functions and results on neuropsychological tests have found surprisingly low correlations suggesting that these two methods measure different aspects of self-regulation (e.g., Anderson et al., 2002; Mahone & Hoffman, 2007). In our studies both observational measures of committed compliance and active resistance, and parental reports of child executive function and internalizing problems were used.

Limitations

Despite the strengths of our studies, such as the longitudinal nature of the data, the large number of participants, and the variety of sources of information, the results must be interpreted within the context of their limitations. First, the studies were conducted within the Generation R Focus Cohort, a relatively homogeneous sample of Dutch families. A large proportion of these families was of higher socioeconomic status. The homogeneity of this sample makes it difficult to generalize our findings to less advantaged and ethnically diverse populations. The associations we found between positive parenting and self-regulation might not be representative for other populations. For example, earlier studies have demonstrated that the negative associations between maternal physical discipline and child externalizing problems found in European-descent families are not necessarily similar in families with a different ethnic background (e.g., Deater-Deckard, Dodge, Bates, & Pettit, 1996). However, the association between maternal sensitive parenting and positive child outcomes appears to be similar in different ethnic groups (Mesman, Van IJzendoorn, & Bakermans-Kranenburg, 2011). Still, the developmental outcomes of variations in early self-regulation might not be the same in all cultures. It has for example been found that emotion regulation strategies such as physical comfort seeking and self-soothing behavior predict lower levels of externalizing problems in Caucasian children but higher levels of externalizing problems in African American children (Supplee, Skuban, Shaw, & Prout, 2009). Research in more diverse populations is needed to further test the effects of parental and biological determinants for the development of self-regulation, and the importance of early self-regulation for later development across ethnic and socio-economic groups.

A second limitation is that the observations of parenting and child self-regulation were based on relatively short tasks of two to eight minutes per construct which might have affected the reliability and validity of these measures. Due to the size of the sample used in this series of studies it was logistically not feasible to observe the mothers and children for a longer period of time. To assure that we would be able to measure the target behavior in this short period of time, the tasks were highly structured and designed to elicit mother-child interaction or self-regulatory behavior. To increase the ecological validity of the observations, the measures of parenting and child self-regulation were conducted at the end of a 1.5 hour lab visit, so mother and child had had time to adjust to the unfamiliar setting.

A third limitation is that we focused only on the influence of parenting by mothers on self-regulation, although in the last decades the independent or buffering role of the father in the development of children has been widely confirmed (e.g., Martin, Ryan, & Brooks-Gunn, 2010; Pleck, 2010). Because the level of involvement of fathers has increased over the years, it has become more important to focus on the influence of fathers (Lamb, 2010) and the influence of the whole family system on child development (Cox & Paley, 1997). Mothers and fathers might differ in their parenting behavior and roles; fathers for example spend a larger proportion of time with their child in playful interaction while mothers specialize in caregiving and comforting (Lamb, 2010). As a result of these differences, mothers and fathers might play different roles in the socialization process of their child (Grossmann et al., 2002). Future studies should investigate the specific role of paternal parenting and its interplay with maternal parenting in the development of self-regulation, as done by Lucassen and colleagues.

Implications for practice and research

Self-regulation has been found to be essential for a wide variety of developmental domains. Committed compliance in young children is associated with higher levels of empathy in childhood and adolescence (Feldman, 2007). More advanced self-regulation predicts higher quality of social functioning (Spinrad et al., 2007) and school functioning (e.g., Monette, Bigras, & Guay, 2011), and self-regulation deficits have been implicated in a variety of developmental disorders and psychopathologies, such as autism and ADHD (e.g., Pennington & Ozonoff, 1996).

Our studies demonstrate the role of various aspects of positive parenting and mother-child relationship quality in preschool children's regulation of emotions and behaviors. Our findings underline the importance of the recent shift in research on self-regulation from mainly focusing on the neuropsychological perspective to also considering the role of social interactions and parenting (Lewis & Carpendale, 2009). A combination of both perspectives is more fruitful in our understanding of early self-regulation (Carlson, 2009). Although we found some preliminary evidence that self-regulation depends on the interplay of biological and parental determinants, our studies can only provide a glimpse on the complex mechanisms that might be involved.

Future research should try to shed more light on the mechanisms behind the relation between positive parenting and child self-regulation. Clarification of these mechanisms provides essential knowledge to develop appropriate interventions that can enhance regulatory abilities of children. These interventions can be directly focused on enhancing self-regulatory skills of children in the preschool years or in school (for an overview, see Blair & Diamond, 2003). However, the importance of positive parenting for the development of self-regulation suggests that one of the few evidence-based interventions available to enhance maternal sensitivity and maternal positive discipline, Video-feedback Intervention to promote Positive Parenting and Sensitive Discipline (VIPP-SD), could be used to indirectly improve self-regulation (Juffer, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Van Zeijl et al., 2006). More research is needed to investigate the effectiveness of these different intervention foci and methods for stimulating the development of self-regulation in children. Given the broad range of developmental outcomes of self-regulation, further research on its etiology and the ways we can promote self-regulatory ability is an important task for the future.

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Appendices

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Samenvatting (Summary in Dutch)

Het leren reguleren van gevoelens en gedrag is een belangrijk onderdeel van de ontwikkeling van kinderen. *Zelfregulatie* is een overkoepelende term voor de verzameling functies die nodig zijn om zelfstandig sturing te geven aan gedrag en om te gaan met gevoelens. Al in de babyjaren begint de ontwikkeling van zelfregulatie. De grootste vooruitgang vindt plaats in de vroege kindertijd, maar de verfijning van zelfregulatie loopt door tot in de adolescentie. Onderzoek naar de ontwikkeling van zelfregulatie bij jonge kinderen heeft zich gericht op verschillende aspecten van zelfregulatie. Een vorm van vroege zelfregulatie is *zelfgereguleerde gehoorzaamheid*, waarbij kinderen zich de regels die zijn gesteld (door bijvoorbeeld de ouders) eigen hebben gemaakt en zich vanuit een interne motivatie houden aan deze regels. In de peuterjaren begint de ontwikkeling van de *executieve functies*, een verzamelnaam voor controlefuncties, zoals het onderdrukken van impulsen, het plannen van gedrag en het richten van de aandacht. Het reguleren van gevoelens is eveneens een belangrijk aspect van zelfregulatie. Als kinderen niet in staat zijn gevoelens van angst of verdriet te boven te komen, kunnen zij *internaliserende problemen* ontwikkelen, zoals depressieve klachten of lichamelijke klachten zonder medische oorzaak.

Zelfregulatie is van belang voor een groot scala aan ontwikkelinguitkomsten op latere leeftijd. Kinderen met een goed ontwikkelde zelfregulatie zijn beter in het leggen en onderhouden van sociale contacten en presteren beter op school. Problemen op het gebied van zelfregulatie zijn gerelateerd aan psychiatrische stoornissen zoals aandachtsstoornissen en autisme. Echter, ook in normaal ontwikkelende kinderen zijn de onderlinge verschillen in zelfregulatiecapaciteiten vrij groot.

Voorspellers van zelfregulatie

Een belangrijke stroming in het onderzoek naar de ontwikkeling van zelfregulatie richt zich op de rol van biologische kindfactoren, zoals de genetische bagage en de hersenontwikkeling. Uit deze studies is gebleken dat zelfregulatie een erfelijke component heeft en dat kinderen met afwijkingen in de groei van de hersenen meer moeite hebben met zelfregulatie. De omgeving van het kind, bijvoorbeeld de kwaliteit van de opvoeding en van de relatie tussen ouder en kind, kan ook een belangrijke rol spelen in de ontwikkeling van zelfregulatie. Eerder onderzoek kon geen eenduidig antwoord geven op de vraag welke opvoedingsfactoren de ontwikkeling van verschillende aspecten van zelfregulatie beïnvloeden. Een recente onderzoekslijn richt zich op het samenspel van biologische factoren en omgevingsfactoren om de individuele verschillen in zelfregulatie te verklaren. Ons onderzoek sluit aan bij deze nieuwe benadering in het onderzoek naar zelfregulatie. Het doel van dit proefschrift is een bijdrage leveren aan het beantwoorden van de vraag welke rol opvoedingsfactoren en biologische factoren spelen in de ontwikkeling van zelfregulatie bij peuters en kleuters.

Dit proefschrift

De onderzoeken die zijn beschreven in dit proefschrift zijn uitgevoerd binnen de Generation R studie, een grootschalig prospectief cohortonderzoek in Rotterdam. In het Generation R geboortecohort worden kinderen en hun ouders vanaf de zwangerschap gevolgd om de groei, ontwikkeling en gezondheid van de kinderen in kaart te brengen. In een subgroep binnen dit cohort, bestaande uit bijna 1000 gezinnen van Nederlandse nationaliteit, zijn gedetailleerde metingen verricht waarop dit proefschrift is gebaseerd. Een groot deel van de informatie die is gebruikt in dit onderzoek is verkregen uit observaties van het gedrag van de moeders en hun kinderen tijdens labbezoeken. In deze labbezoeken hebben we moeder en kind samen een aantal taken laten uitvoeren, zoals het bouwen van een moeilijke toren en het opruimen van speelgoed. De taken zijn gefilmd en het filmmateriaal is later teruggekeken om het gedrag van de moeders en de kinderen systematisch in kaart te brengen. Bij de kinderen is bijvoorbeeld geobserveerd of zij in staat waren speelgoed een tijdje niet aan te raken of te beginnen met opruimen als hun moeder dit vroeg. Bij de moeders hebben we onder andere gecodeerd of zij adequaat reageerden op de signalen van hun kind en voldoende steun gaven tijdens de taken die voor het kind lastig waren. Andere observaties waren gericht op de stijl van disciplineren die de moeder toepaste en de kwaliteit van de relatie tussen moeder en kind. Daarnaast hebben wij gebruik gemaakt van ouderrapportages en biologische metingen van hersenontwikkeling en genetische bagage van moeder en kind.

Opvoeding en zelfregulatie

In de babytijd zijn kinderen nog niet in staat om hun eigen gedrag en emoties te reguleren en zijn hiervoor afhankelijk van hun ouders. De kwaliteit van de opvoeding en van de relatie tussen moeder en kind speelt dus misschien een belangrijke rol in de ontwikkeling van zelfregulatie bij jonge kinderen. De conclusies van eerdere onderzoeken naar de rol van opvoeding in de ontwikkeling van zelfregulatie lopen uiteen.

Wij hebben de rol van meerdere opvoedingsfactoren onderzocht: de kwaliteit van de gehechtheidrelatie tussen moeder en kind, de sensitiviteit van de moeder en haar stijl van disciplineren. In een veilige gehechtheidrelatie kan een kind erop vertrouwen dat de moeder beschikbaar is als een veilige basis in stressvolle situaties. Uit onze resultaten (Hoofdstuk 2) bleek dat een veilige gehechtheidrelatie tussen moeder en kind op de leeftijd van 14 maanden niet de mate van gehoorzaamheid van het kind in een opruimtaak op 3-jarige leeftijd voorspelde, maar wel een afname in actief verzet tegen het opruimen. Actief verzet werd gekarakteriseerd door tegenspreken van de moeder, hevige boosheid of verdriet bij het kind. De 3-jarige kinderen vertoonden dit gedrag minder vaak als zij een veilige gehechtheidrelatie hadden met hun moeder toen ze 14 maanden oud waren. De stijl van disciplineren die de moeder toepaste, was gerelateerd aan de kwaliteit van de gehoorzaamheid van het kind in een taak waarbij het kind gedurende een korte tijd van speelgoed moest afblijven (Hoofdstuk 3). Als moeders meer negatief disciplineerden, bijvoorbeeld gebieden en fysiek ingrijpen in plaats van verzoeken en ondersteunen, lieten de kinderen minder zelfgereguleerde gehoorzaamheid zien. Daarnaast bleek dat kinderen van sensitieve moeders, die tijdig en op de juiste manier de signalen van hun kind interpreteren en beantwoorden, minder executieve functieproblemen (Hoofdstuk 4) en minder internaliserende problemen (Hoofdstuk 5) hadden. Uit deze resultaten kunnen wij concluderen dat meerdere opvoedingaspecten een rol spelen in de ontwikkeling van zelfregulatie. Zowel de kwaliteit van de moeder-kindrelatie als de sensitiviteit van de moeder en de strategieën die de moeder gebruikt om haar kind te disciplineren, bepalen de kwaliteit van zelfregulatie van het kind. De kwaliteit van de opvoeding bleek niet alleen belangrijk voor de relationele aspecten van zelfregulatie, zoals zelfgereguleerde gehoorzaamheid en actief verzet, maar ook voor controlefuncties zoals executief functioneren.

Er zijn verschillende factoren die bepalen hoe sensitief een moeder zich gedraagt naar haar kind. Ten eerste kunnen ouderkenmerken een rol spelen, zoals de persoonlijkheid van de ouder en eventuele psychiatrische problemen. Ten tweede kunnen kindkenmerken de kwaliteit van de opvoeding beïnvloeden, zoals een moeilijk temperament. Ten derde kunnen ook omgevingsinvloeden, zoals stress en het sociale netwerk van het gezin, beïnvloeden hoe sensitief de moeder is. In de afgelopen jaren is daarnaast onderzocht in hoeverre genetische verschillen de variatie in sensitiviteit kunnen verklaren. Binnen ons onderzoek hebben wij gekeken of een variatie in het serotonine transporter gen (5-HTTLPR) bij moeders hun sensitiviteit voorspelde

(Hoofdstuk 6). Het serotonine transporter gen is betrokken bij het verwerken van emotionele prikkels, bij cognitieve flexibiliteit en bij sociale cognitie. Twee eerdere studies naar de relatie tussen 5-HTTLPR en sensitiviteit vonden tegenstrijdige resultaten. Er zijn drie varianten van 5-HTTLPR: moeders kunnen twee korte allelen, twee lange allelen, of zowel één kort allel als één lang allel hebben. Uit ons onderzoek bleek dat moeders met de korte variant van 5-HTTLPR sensitiever waren naar hun kind dan moeders die deze variant niet hadden.

Samenspel van biologie en opvoeding

Recent onderzoek richt zich naast de invloed van de opvoeding op de ontwikkeling van kinderen ook op biologische factoren en het complexe samenspel tussen opvoeding en biologie. Onder biologische factoren worden bijvoorbeeld het aangeboren temperament van het kind, de genetische bagage en de hersenontwikkeling verstaan. De invloed die omgevingsfactoren hebben op de ontwikkeling van kinderen kan versterkt of verzwakt worden door biologische verschillen tussen kinderen. Er zijn onderzoeken die laten zien dat sommige kinderen meer gevoelig zijn voor omgevingsinvloeden dan andere kinderen, op basis van verschillen in temperament, biologische kwetsbaarheid, zoals vroeggeboorte of een laag geboortegewicht, of genetische bagage. Dit wordt ook wel *differentiële ontvankelijkheid* genoemd: afhankelijk van de omgeving (negatief dan wel positief) zorgen deze verschillen voor een risico voor een niet-optimale ontwikkeling of juist voor meer mogelijkheden voor een optimale ontwikkeling.

In ons onderzoek hebben wij ons gericht op het samenspel tussen biologische factoren en opvoeding in de ontwikkeling van zelfregulatie. Onze resultaten zijn deels in overeenstemming met eerdere bevindingen. Eerdere studies naar de rol van opvoeding in het voorspellen van zelfgereguleerde gehoorzaamheid lieten zien dat deze relatie afhankelijk was van hoe angstig een kind is. Bij angstige kinderen werkte positief disciplineren het beste, omdat deze vorm van disciplineren spanning opwekt bij de kinderen, waardoor regels sneller worden eigen gemaakt. Bij minder angstige kinderen bleek dat een positieve ouder-kindrelatie de motivatie van deze kinderen om te gehoorzamen vergrootte. In ons onderzoek bleek de mate van angst echter geen rol te spelen in de samenhang tussen een veilige gehechtheidrelatie en een afname in actief verzet tegen opruimen (Hoofdstuk 2).

In een vervolgstudie, beschreven in Hoofdstuk 3, hebben we onderzocht of er sprake is van differentiële ontvankelijkheid voor disciplinering op basis van genetische verschillen in twee genen in het dopaminesysteem van kinderen: het COMT gen en het dopamine D4 receptor gen (DRD4). Deze genen zijn betrokken bij processen van beloning, straf en motivatie. Er zijn drie varianten van het COMT gen: kinderen kunnen twee Methionine allelen, twee Valine allelen, of zowel één Valine allel als één Methionine allel hebben. Kinderen met meer Methionine allelen lieten meer zelfgereguleerde gehoorzaamheid zien als hun moeder meer positieve disciplineringsstrategieën hanteerde, zoals ondersteuning bieden en het kind afleiden van het speelgoed. Kinderen met meer Methionine allelen bleken minder zelfgereguleerde gehoorzaamheid te laten zien als hun moeder minder positieve disciplineringstrategieën gebruikte. Voor kinderen met meer Valine allelen speelde positief disciplineren een veel kleinere rol of zelfs geen rol in de ontwikkeling van zelfgereguleerde gehoorzaamheid. Genetische variatie in het COMT gen lijkt dus de gevoeligheid van kinderen voor omgevingsinvloeden te beïnvloeden. Alhoewel er nog niet eerder onderzoek was gedaan naar de interactie tussen het COMT gen en opvoeding in het voorspellen van zelfregulatie, sluiten onze resultaten wel aan bij eerdere studies naar de interactie tussen genen in het dopaminesysteem en opvoeding in het voorspellen van kinduitkomsten. Variaties in het DRD4 gen beïnvloedden de ontvankelijkheid voor disciplineren niet.

Een aanwijzing dat positief disciplineren ook bescherming kan bieden als er sprake is van een biologische kwetsbaarheid bleek uit onze studie naar executief functioneren bij jonge kinderen. In dit onderzoek, beschreven in Hoofdstuk 4, hebben we gekeken naar de invloeden van opvoeding en vroege hersenontwikkeling op executief functioneren. De hersenontwikkeling van de kinderen was in kaart gebracht toen zij 6 weken oud waren, door middel van een echo via de fontanel (opening tussen de schedelbeenderen). We hebben specifiek gekeken naar de lengte van het *corpus callosum*, dit is een hersenstructuur die de verbinding vormt tussen de linkerhersenhelft en de rechterhersenhelft. Een korter corpus callosum kan ertoe leiden dat de communicatie tussen de twee hersenhelften niet optimaal verloopt en komt vaak voor bij kinderen die te vroeg geboren zijn. Een eerder onderzoek onder dezelfde groep kinderen toonde al aan dat kinderen met een korter corpus callosum in de babytijd meer problemen hadden met executief functioneren op 4-jarige leeftijd. Uit onze studie bleek dat de relatie tussen de lengte van het corpusc callosum in de babytijd en de ontwikkeling van zelfregulatie afhankelijk was van de manier van disciplineren. Kinderen met een korter corpus callosum op de leeftijd van 6 weken vertoonden later minder inhibitieproblemen als hun moeder positiever disciplineerde. Dit wijst er op dat positief disciplineren een buffer kan zijn tegen de negatieve gevolgen van een niet optimale corpus callosumontwikkeling.

De bevindingen in dit proefschrift over het samenspel tussen biologie en opvoeding in het voorspellen van zelfregulatie moeten met enige voorzichtigheid worden geïnterpreteerd. Onderzoek op dit gebied staat nog in de kinderschoenen. Onze resultaten lijken wel te impliceren dat enkel en alleen variatie in opvoeding niet voldoende is om de verschillen in zelfregulatiecapaciteiten tussen kinderen te verklaren. Meer onderzoek is nodig om verdere duidelijkheid te scheppen over hoe biologie en opvoeding samenwerken in de ontwikkeling van zelfregulatie.

Wederzijdse beïnvloeding ouder en kind

Naast de invloed van opvoeding op het gedrag van het kind, kan ook het gedrag van het kind de opvoeding beïnvloeden. Vooral kindgedrag dat als negatief ervaren wordt door de ouder, zoals agressiviteit of impulsiviteit, kan negatief oudergedrag uitlokken of positief oudergedrag verminderen. Dit blijkt ook uit gedragsgenetisch onderzoek: genetische kenmerken van het kind kunnen invloed hebben op de latere omgeving en opvoeding van het kind. Hoewel in de laatste decennia het belang van wederzijdse beïnvloeding alom wordt onderkend, zijn er nog weinig empirische studies die daadwerkelijke rekening houden met dit gegeven. In ons onderzoek naar de associatie tussen sensitiviteit van de moeder en internaliserende problemen bij het kind, hebben we geprobeerd de richting van de verbanden helder te krijgen (Hoofdstuk 5). In onze studie en in een tweede grote cohortstudie, de *NICHD Study of Early Child Care and Youth Development (SECCYD)* hebben we op meerdere momenten in de vroege kindertijd de sensitiviteit van de moeder geobserveerd en de moeders bevraagd over de mate van internaliserende problemen bij hun kind. In beide cohorten werden kleine, maar wel consistente associaties gevonden tussen sensitiviteit op jongere leeftijd en internaliserende problemen op latere leeftijd; als moeders meer sensitief zijn, ervaren hun kinderen minder internaliserende problemen. De paden van moedergedrag (sensitiviteit) naar kindgedrag (internaliserende problemen) werden consistenter teruggevonden dan de paden van kindgedrag naar moedergedrag. In dit geval lijkt het dus dat de invloed van moederlijke sensitiviteit op internaliserende problemen bij het kind groter is dan de invloed van internaliserende problemen op sensitiviteit van de moeder.

Conclusie

Uit dit proefschrift blijkt dat opvoeding een belangrijke rol speelt in de ontwikkeling van zelfregulatie. In een warme en veilige gehechtheidrelatie, met een sensitieve en positief disciplinerende moeder zijn jonge kinderen beter in staat hun emoties en gedrag zelfstandig te reguleren. Naast de rol van opvoeding spelen biologische factoren ook een rol in de ontwikkeling van zelfregulatie. Enerzijds suggereert het huidige onderzoek dat de genetische bagage van moeders de mate van sensitiviteit kan beïnvloeden. Anderzijds blijkt dat de invloed van de opvoeding op de ontwikkeling van zelfregulatie deels afhankelijk is van de genetische bagage van kinderen en de vroege hersenontwikkeling. Het is van groot belang dat toekomstig onderzoek naar zelfregulatie zich richt op zowel de biologische basis van zelfregulatie als de invloed van opvoeding, waarbij een valide en betrouwbare meting van de kwaliteit van de opvoeding en het kindgedrag wordt verkregen door middel van systematische observaties. Daarnaast is meer onderzoek nodig naar de mechanismen achter de invloed van opvoeding op de ontwikkeling van zelfregulatie. Verduidelijking van deze mechanismen zou het mogelijk maken specifieke interventies te ontwikkelen om zelfregulatiecapaciteiten bij jonge kinderen te vergroten. De invloed van zelfregulatie op een groot aantal ontwikkelingsdomeinen op latere leeftijd onderstreept het belang van dergelijke interventies.

Dankwoord (Acknowledgements)

Hora Est! Maar niet voordat ik een aantal belangrijke mensen heb genoemd dat heeft bijgedragen aan het tot stand komen van dit proefschrift. BEDANKT aan alle kinderen en ouders die deelnemen aan Generation R. Zonder jullie inzet en enthousiasme door de jaren heen zou dit project niet mogelijk zijn geweest. BEDANKT aan alle studenten die samen met mij de honderden filmfragmenten hebben gecodeerd. Jullie bijdrage was onmisbaar. BEDANKT aan al mijn lieve collega's in Leiden en in Rotterdam, voor jullie hulp en steun als het even wat minder soepel verliep, maar ook voor alle gezellige momenten in de afgelopen jaren. In het bijzonder BEDANKT aan: de leden van koffiecorner "de Gezellige Gang", de leden van de spelletjesclub, de meiden van de Leidse AiO-borrel en van de "Soep-&-Sla"-avonden. Ik prijs me gelukkig dat ik niet alleen een titel, maar ook een groep vrienden rijker ben! BEDANKT aan mijn nieuwe collega's bij de EUR voor het warme bad waarin ik beland ben. BEDANKT aan al mijn vrienden voor jullie interesse, steun, humor, geduld en goede adviezen in de afgelopen jaren. Er is hier te weinig ruimte om jullie allemaal persoonlijk te bedanken, maar de waardering is daar niet minder door. In het bijzonder BEDANKT aan Denise, Linda en Lotte: ik hoop dat we nog lang samen mogen opgroeien. En tot slot BEDANKT aan Pap, Mam, Manon en Mike. Dankzij jullie onvoorwaardelijke liefde, steun, vertrouwen en broodnodige relativering zijn dit proefschrift en ik geworden zoals we zijn.

Curriculum vitae

Rianne Kok werd geboren op 8 juni 1985 in Zaanstad. In 2002 behaalde zij haar Gymnasium diploma aan het Zaanlands Lyceum te Zaanstad. In hetzelfde jaar begon zij aan de opleiding Psychologie aan de Universiteit van Amsterdam. In 2007 is zij cum laude afgestudeerd met als specialisatie Klinische Neuropsychologie. Na haar afstuderen heeft Rianne gewerkt als promovenda bij de afdeling Algemene en Gezinspedagogiek (AGP) van de Universiteit Leiden. Zij deed onderzoek naar de rol van opvoeding en biologie in de ontwikkeling van zelfregulatie in de vroege kindertijd. Dit onderzoek werd uitgevoerd binnen de Generation R studie aan het Erasmus Medisch Centrum (EMC) te Rotterdam. De resultaten van haar onderzoek zijn beschreven in dit proefschrift. Tijdens haar promotietraject heeft Rianne de research master *Developmental Psychopathology in Education and Child Studies* aan de Universiteit Leiden afgerond. Naast haar aanstelling als promovenda heeft Rianne gewerkt als docent bij AGP en haar Basiskwalificatie Onderwijs behaald. Daarnaast heeft zij ervaring opgedaan als psycholoog bij de polikliniek Kinder- en Jeugdpsychiatrie van het Sophia Kinderziekenhuis te Rotterdam. In 2012 is zij gestart als docent aan de afdeling Pedagogische Wetenschappen van de Erasmus Universiteit Rotterdam. Daarnaast is Rianne betrokken als co-promotor bij het onderzoeksproject *Parenting Capacity in Mothers with a Severe Mental Illness* aan het EMC te Rotterdam, gesubsidieerd door de Sophia Stichting.

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