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REVIEW

PARENTING BEGETS PARENTING: A NEUROBIOLOGICAL PERSPECTIVE ON EARLY ADVERSITY AND THE TRANSMISSION OF PARENTING STYLES ACROSS GENERATIONS

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Abstract—The developing brains of young children are highly sensitive to input from their social environment. Nurturing social experience during this time promotes the acquisition of social and cognitive skills and emotional competencies. However, many young children are confronted with obstacles to healthy development, including poverty, inappropriate care, and violence, and their enhanced sensitivity to the social environment means that they are highly susceptible to these adverse childhood experiences. One source of social adversity in early life can stem from parenting that is harsh, inconsistent, non-sensitive or hostile. Parenting is considered to be the cornerstone of early socio-emotional development and an adverse parenting style is associated with adjustment problems and a higher risk of developing mood and behavioral disorders. Importantly, there is a growing literature showing that an important predictor of parenting behavior is how parents, especially mothers, were parented themselves. In this review, we examine how adversity in early-life affects mothering behavior in later-life and how these effects may be perpetuated intergenerationally. Relying on studies in humans and animal models, we consider evidence for the intergenerational transmission of mothering styles. We then describe the psychological underpinnings of mothering, including responsiveness to young, executive function and affect, as well as the physiological mediators of mothering behavior, including hormones, brain regions and neurotransmitters, and we consider how development in these relevant domains may be affected by adversity experienced in early life. Finally, we explore how genes and early experience interact to predict mothering behavior, including the involvement of epigenetic mechanisms. Understanding how adverse parenting begets adverse parenting in the next generation is critical for designing interventions aimed at preventing this intergenerational cycle of early adversity.

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Key words: early adversity, intergenerational effects, gene-environment interactions, mothering, parenting styles.

Contents

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Abbreviations: ERP, event-related potentials; fMRI, functional magnetic resonance imaging; GxE, gene by environment; HPA, hypothalamic–pituitary–adrenal; mPFC, medial prefrontal cortex; MPOA, medial pre-optic area; OXT, oxytocin peptide; OXTR, oxytocin receptor.

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INTRODUCTION

Early childhood is a period of unprecedented change and integration at both the biological and social level characterized by a high degree of plasticity in brain organization (Kolb et al., 2003a,b; Marshall and Kenney, 2009). Young children's rapidly developing brains are highly sensitive to input from the social world, which allows for the rapid acquisition of language, cognitive skills, and emotional competencies. Nurturing social experiences in the early years have lifelong benefits, including an increased ability to learn, greater achievement, involvement in community activities, active participation in the labor market and overall quality of life (Ermisch et al., 2012; Boivin and Bierman, 2013). Unfortunately, too many infants and young children are confronted with adverse experiences, such as poverty, inappropriate care, and violence, which pose enduring obstacles to their healthy development (Boivin et al., 2005; Evans and Kim, 2007; Wadsworth and Santiago, 2008; Brown et al., 2009). Disparities emerge early in life in children's physical, social/emotional, and language/cognitive development that are largely attributable to the interplay of genetic factors and systematic differences in the nurturing qualities of their early environments: nutrition, bonding/attachment, stimulation, and opportunities for participation (Grantham-McGregor et al., 1997; Boyden and Levison, 2000; Barker et al., 2008; Côté et al., 2009; Forget-Dubois et al., 2009; Petitclerc et al., 2009, 2011; Lacourse et al., 2014; Battaglia et al., in press). During those early years, a dense, hierarchically connected series of sensitive periods occur in the brain, such that early experiences can embed themselves in brain circuitry and other biological systems (Hertzman and Boyce, 2010).

Young children's enhanced sensitivity to their social world means that they are highly susceptible to adverse social experiences, including short-term, dramatic events such as discrete episodes of physical or sexual abuse, as well as the chronic daily stressors within the home and community. One source of social adversity in early life can also stem from parenting behavior that is harsh, inconsistent, non-sensitive or hostile. Generally perceived as the cornerstone of early socio-emotional development (Bornstein, 1995), parenting behaviors are especially important in the early years when the maturation of neurophysiological systems makes the infant particularly receptive to, and dependent on sensitive parenting care for his/her emotional and behavioral regulation (Kochanska et al., 1998). In most cases, a child's parents and immediate family provide the early and influential proximal environment through which a child's potential for "effective psychological function" begins to evolve and manifest (Bronfenbrenner and Ceci, 1994). Unfortunately, not all children benefit from this nurturing contribution. Early signs of adjustment problems have been associated specifically with inconsistent, non-sensitive, and hostile parenting behaviors (Lyons-Ruth et al., 1991; Wakschlag and Hans, 1999; Tremblay et al., 2004; Huijbregts et al., 2008). Furthermore, epidemiological studies demonstrate that children who are exposed to early adverse experiences associated with disrupted bonding and attachment are at a higher risk for developing anxiety, depression, and other stress-related illnesses during adolescence (Rey, 1995; McCauley et al., 1997; Martin et al., 2004) and adulthood (Enns et al., 2002; Putnam, 2003).

There is a growing literature showing that one of the most powerful predictors of parenting behavior is how parents, especially mothers, were parented themselves. In this review we examine the relationship between early adversity and parenting behavior and its intergenerational perpetuation. We begin by outlining our conceptual perspective on parenting, focusing particularly on mothering. We then review evidence for intergenerational recurrence of mothering styles relying on evidence from both human and animal studies. This is followed by a description of what is known about the psychological underpinnings of mothering, including perception, executive function and emotion and the impact of early adversity on offspring development in these domains of psychological functioning. We then discuss the putative physiological mediators associated with mothering, including the role of hormones, key areas of the brain, and neurotransmitters, and we examine how early adversity influences these physiological mediators. A final section explores what is known about how specific genes and the early environment interact to predict mothering behavior, as well as the potential involvement of epigenetic mechanisms through which early adversity may affect the mechanisms of mothering. We close the review with a summary of the material presented and some tentative conclusions aimed at informing targeted interventions to break intergenerational cycles of problematic parenting behaviors.

CONCEPTUALIZATION OF PARENTING

Parenting is embedded in a complex social system. It is influenced by parent and child characteristics, but also by contextual stressors and supports (Belsky, 1984). Parents bring their personality and personal history to their early interactions with the young child, and this background, as well as more immediate environmental constraints, may influence their beliefs and expectations about parenting and their parenting practices (Boivin et al., 2005). The concept of normative-adaptive or species-typical parenting behavior is implied throughout the present review, but we acknowledge that among all species, especially humans, there are large individual and cultural differences in parenting behaviors, in feelings and attitudes toward infants, as well as in motivation to parent. In fact, individual differences are the hallmark of human behavior within and across cultures, and it is important to understand how both environmental and genetic factors, as well as their interactions, contribute to these individual differences. This review points to features of parenting that create an environment in which healthy development can occur, but always with the view that both 'positive' and 'negative' parenting, as well as 'desirable' child outcomes cover a range of approaches,

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styles, and behaviors that vary across individuals, societies, and cultures (Keller et al., 2004, 2005).

Most of the research we review focuses on parenting by the mother, reflecting the state of the existing literature. Nevertheless, we recognize that fathers play a significant role in children's development (Amato, 1994; Williams and Radin, 1999; Chang et al., 2003; Tamis-LeMonda et al., 2004; Sarkadi et al., 2008). In addition, fathers and mothers exist within a family context, affect one another's parenting, and participate in a family dynamic that also contributes to children's development (Quinton and Rutter, 1984a,b; Jenkins et al., 2012; Meunier et al., 2012; Stover et al., 2012; Tamis-LeMonda et al., 2004). Finally, in many homes and cultures, other relatives, friends, and professional caregivers also contribute to children's development (Peisner-Feinberg et al., 2001; NICHD Early Child Care Research Network, 2002; Côté et al., 2007; Geoffroy et al., 2010; Herba et al., 2013). These forms of caregiving, while extremely important, are beyond the scope of the present review.

EARLY EXPERIENCES AND INTERGENERATIONAL TRANSFER OF PARENTING STYLES

In humans, important aspects of early experiences with the mother are the warmth expressed by the mother, engagement in physical contact and play, visual mutuality and/or vocal exchanges, and the extent to which a mother responds to her infant in a timely and appropriate way (that is, 'contingently') (Tamis-Lemonda and Bornstein, 1989; Tamis-Lemonda et al., 2001). The expression of these mothering behaviors, however, is associated with prior life experiences. In this section we review evidence for the relationship between early-life adversity in mothers and subsequent mothering behavior, as well as offspring outcomes. We then examine studies using animal models that shed light on the causal nature of this relationship.

Maternal history and parenting

A number of studies have demonstrated that a woman's history of adverse early experiences is associated with difficulties in parenting. Moehler et al. (2007) measured emotional availability during mother-infant interactions and found that mothers with a history of sexual or physical abuse were significantly more intrusive toward their children than were non-abused mothers. Roberts et al., (2004) also reported that mothers who had experienced sexual abuse in early life were less interested in becoming mothers themselves and when they did, they exhibited impaired parenting skills, such as higher levels of child neglect, diminished confidence in their own parenting skills, more negative self-appraisal as a parent, greater use of physical punishment, and a lack of emotional control in parenting situations. In addition, Knutson (1995) reported that a substantial proportion of mothers who were abused during childhood go on to subsequently abuse their own children, when compared to mothers who did not report abuse.

Furthermore, adjustment problems in offspring are often associated sequelae of cross-generational early abuse experiences. Using the Avon Longitudinal Study of Parents and Children, Collishaw et al. (2007) found that the more severely the mothers rated the impact of their own childhood maltreatment, the worse the adjustment of their offspring. Adjustment problems in offspring were also more chronic when mothers reported severe abuse than when they reported less severe adversity. Moreover, the effects were cumulative wherein problems in offspring were greater when maternal exposure was to several types of abuse as compared to only one type. Offspring of maltreated mothers were also at an increased risk of experiencing aversive events and physical assaults. In addition, changes in the structure of their families, such as separations from caretakers and parents, and the acquisition of new parent figures, were more frequently reported. Finally, maltreated mothers' offspring also faced a wider range of stressful life events, such as moving into another neighborhood, changing schools, and losing contact with friends.

Positive early experiences also predict later maternal behavior (Chen and Kaplan, 2001; Belsky et al., 2005; Chen et al., 2008). For instance, the experience of less authoritarian parents in early childhood, a more positive family 'climate' in middle childhood, and more positive attachment in adolescence, are all predictive of warm, sensitive, and stimulating maternal behavior in adulthood (Belsky et al., 2005). In sum, early life experiences can be viewed as part of a spectrum from very negative to very positive, and as discussed next, both positive and negative parenting behaviors can be reproduced intergenerationally.

Intergenerational continuity of parenting

There is growing evidence for some form of intergenerational continuity of parenting style (Conger et al., 2003; Belsky et al., 2005; Scaramella et al., 2008; Bailey et al., 2009; Neppl et al., 2009). The emphasis of this research has been both on the developmental "sequelae" of parenting behavior and the outcomes associated with positive and negative aspects of parenting. These associations were initially established by studies in which the early experiences were recalled retrospectively. Recently and more convincingly, these associations were also documented in prospective studies in which families and children were followed from childhood through adulthood, and the style of parenting of the first generation and the second generation was observed directly (Belsky et al., 2005; Scaramella et al., 2008).

Scaramella and colleagues (2008) reported a particularly informative prospective study of intergenerational parenting that eliminated bias associated with retrospective reports and had the advantage of a relatively large sample size (well over 100 subjects at each time point), direct behavioral observations and reliable coding, as well as independent characterizations of parents and adolescents allowing statistical separation of their individual contributions in parent–child interactions. Observations of parenting in the first and second generation showed a significant degree of continuity in both harsh and positive

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parenting among both males and females across the two generations. Harsh parenting in this context was defined as critical, aggressive, unkind, irritable, and 'pressureful' in a structured puzzle task. Positive parenting was defined as supportive, warm, helpful, and involved during the task. Harsh parenting was associated with 'externalizing' and disruptive behavior in adolescents, whereas positive parenting was associated with competent behaviors in adolescents. The children displaying these behaviors as adolescents also tended to behave similarly as adults, which in turn may account for the differing parenting styles the adolescents exhibited as adults parenting their children (third generation). Because personality and behavioral characteristics of a child are also correlated with parenting, the study helps disentangle the contributions of each factor of the parent–child interaction; for instance, when harsh parenting is associated with externalizing behaviors in a child, these behaviors then contribute to that child becoming a harsh parent toward his/her own children. Hence, this study documents the important role of the child as a mediator in the apparent continuity of parenting.

These results are consistent with other analyses and with other prospective studies of intergenerational transmission of parenting (Belsky et al., 2005; Bailey et al., 2009). They are also consistent with the view that the problematic nature of some teenage mothering (de Paul and Domenech, 2000; Rebollo and Montero, 2000; Giardino et al., 2008) could be accounted for by an intergenerational process whereby teen mothers who experience adverse parenting may in turn become poorly adjusted mothers (Furstenberg et al., 1987). The studies also point strongly to the critical nature of the parent–child interplay in long-term outcomes for offspring and to the bidirectional character of this developmental process. That is, parenting in early childhood may influence the child's developmental trajectory, but also, the child may influence the nature of parenting received through an interplay of social and/or genetic factors (Boivin et al., 2005).

Buffers to the adverse effects of abuse

In spite of these apparent associations between early adversity, including physical abuse (and/or retrospective perception of that adversity), and later emotional and parenting problems, it remains that a large proportion of mothers who were abused will NOT, in turn, abuse their own children. This suggests that a myriad of factors protect future mothers from the risks accrued through early experiences. Among these, social support to the mother or to the developing child (Wind and Silvern, 1994; Kaufman et al., 2004; Jaffee et al., 2007), as well as forming a relationship with a supportive partner in adulthood (Seeman et al., 2002) appear to play an important role. Although experiences during early developmental periods may well have a greater impact than occurrences in later development periods (Heim and Nemeroff, 1999; McEwen, 2003), and form the stepping stones for the development of personal qualities underlying appropriate mothering, experiences acquired later in life can reverse previous effects, and/or result in development to follow a different path. McEwen (2003) in a review of the effects of early life adversity on brain development concludes that problems brought about by unstable or abusive care-giving during childhood are not irreversible, and may be ameliorated by a social support system or a caring and loving relationship with a partner.

Animal studies of early adversity, mothering, and intergenerational effects

In non-human primates and rodents, adequate maternal care is necessary for the establishment of normal behavioral and physiological functioning in the offspring; variations in this care early in life predict variations in a wide variety of developmental outcomes, including the type of maternal care that offspring provide when adults (Francis and Meaney, 1999; Champoux et al., 2002; Champagne et al., 2003a,b; Maestripieri et al., 2006). Furthermore, the early care the young receive from their mothers is a reliable predictor of the type of care they provide when they become mothers (Gonzalez et al., 2001; Fleming et al., 2002a,b; Maestripieri, 2005; Maestripieri et al., 2007; Suomi, 1999).

The effects of early experience of mothering has been extensively studied in the rat using an artificial rearing approach that allows for experimental control of the early rearing environment, including the removal of the mother followed by artificial replacement of relevant maternal stimuli (Lovic and Fleming, 2015; Lomanowska and Melo, in press). This early experience of isolation from maternal contact does not completely disrupt the rat's ability to engage in species-specific maternal behaviors, but it impairs the frequency and organization of these behaviors. For instance, artificially reared mothers retrieve pups to the nest, lick and groom them and display hovering, crouching, and nursing behavior, but compared to control rats, they spend significantly less time engaging in these behaviors (Gonzalez et al., 2001; Fleming et al., 2002a,b; Melo et al., 2006, 2009; Palombo et al., 2010; Afonso et al., 2011; Lovic et al., 2011b; Shams et al., 2012). Importantly, these effects can be partially reversed by artificially administering maternal licking-like tactile stimulation to the pups (Gonzalez et al., 2001; Gonzalez and Fleming, 2002; Lovic and Fleming, 2004; Novakov and Fleming, 2005). This reversal highlights the direct influence of early-life maternal care on the development of subsequent maternal behavior. Furthermore, in line with the human studies discussed above, the disruption of maternal behavior resulting from artificial rearing, such as deficits in maternal licking and crouching, is also transferred to the subsequent generation (Gonzalez et al., 2001). Therefore, results from animal studies provide strong support for the causal nature of the association between early experience and the later development of maternal behavior, and also for the trans-generational expression of these effects.

EARLY ADVERSITY AND PSYCHOLOGICAL MEDIATORS OF PARENTING

Parenting encompasses a complex set of behaviors that depend on different psychological processes, from perceiving and attending to child-associated cues,

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including their motivational and emotional valance, to responding appropriately to these cues while attending also to the context of the surrounding environment (Barrett and Fleming, 2011; Lonstein et al., 2015). The existing literature on early adversity demonstrates linkages with different domains of psychological functioning in humans, while studies in animal models support the causal nature of the associations between early experience and the development of various aspects of behavior and cognition. In this section, we examine the putative contributions of early adversity to perceptual, cognitive and emotional functions that are implicated in the expression of parental sensitivity and behavior. We discuss this evidence with the aim of understanding the more proximate psychological mechanisms mediating the effects of early adversity on parenting.

Early adversity and perceptual responsiveness

Early adversity has been associated with heightened responsiveness to all stimuli, but especially with a bias toward stimuli with negative valence. Children who were abused and/or neglected show a negative bias, and are more attentive to negative pictures than to positive pictures. Measuring brain electrical responses through event-related potentials (ERP), a measure of neural activity, Pollak et al. (1997, 2001) have shown that one of the wave forms of the ERP, the P3b component, which reflects attention and interest, has a greater amplitude in abused, as opposed to non-abused, children when they are presented with an angry face or vocal expressions of anger, and especially faces of their own mothers. The amplitude of P3b has also been associated with the severity of physical maltreatment (Pollak et al., 1997, 2001; Shackman et al., 2007). However, this pattern of association was not shown in response to happy faces. Moreover, abused children had more difficulties disengaging from attending to angry faces even when they were instructed to avoid them. As a result, they performed worse than controls on neutral goal-directed tasks in the presence of an angry face (Shackman et al., 2007). The pattern of responsiveness to environmental cues associated with early adversity suggest that some children may develop greater reactivity to negative features of the environment, particularly socially-relevant information, and they may adopt a more negative world view later in life. In future studies, it will be important to explore how this pattern of responsiveness relates to future parental sensitivity.

Responsiveness to environmental cues in relation to early social adversity has also been studied in rats and non-human primates. In rats, limited experience with the mother during early-life result in changes in the perceived value of environmental stimuli ('stimulus salience') (Lomanowska et al., 2006, 2011), increased locomotor reactivity to a novel environment (Gonzalez et al., 2001), increased motor impulsivity (Lovic et al., 2011a,b), reduced attention in an attention set-shifting task (Lovic and Fleming, 2004), as well as alterations in perceived reward value of pups (Afonso et al., 2009, 2011). These patterns of behavior, particularly inattention and impulsivity, have also been related to impairments in mothering behavior in rats, including the duration of pup licking and hovering over the pups (Lovic and Fleming, 2004, 2015; Lovic et al., 2011b). Conversely, rat mothers who received adequate parenting as neonates tend to show a balance in approach and avoidance behaviors in novel environments and with their pups; specifically, they show less fearfulness and enhanced attentiveness, and respond more positively to features of their young (Fleming and Li, 2002). In non-human primates, peer-reared, as compared to mother-reared rhesus monkeys showed enhanced responding to an attractive stimulus in the form of sweet aspartame (Nelson et al., 2009). Nelson et al. (2009) have suggested that this increased responding to appetitive stimuli may act as a behavioral suppressant for negative emotions, which are often enhanced in animals reared in adverse conditions (Volkow, 2004). In other words, early adversity may create inconsistent propensities in offspring; that is, to produce a long-term underlying negative emotion bias while enhancing short-term reactivity to both positive and negative stimuli presented by the environment. These studies in animal models demonstrate a direct relationship between changes in perceptual and attentional processes and effects on mothering behavior following early adversity. The association between impulsive-inattentive behaviors and disrupted parenting has also been documented in humans, although in a few studies only and not always with detailed measures of parenting (Chen and Johnston, 2007; Johnston et al., 2012; Moffit et al., 2013). Future research in this area needs to explore how early adversity relates to perceptual and attentional processes in the context of parenting.

Early adversity and executive function

In both the animal and human literature there is strong evidence showing that social adversity during an offspring's early years results in disrupted development of many of the executive functions that are necessary for well-regulated mothering. Studies in rats have demonstrated the lasting effects of early adverse social experiences on performance of tasks involving executive function-related processes. For instance, being reared without the mother results in offspring that show deficits in attention and ability to shift attention when needed (Lovic and Fleming, 2004; Burton et al., 2006; Garner et al., 2007). Early adversity studies in children have also demonstrated a stable relationship between abuse or neglect and executive function (Kreppner et al., 2001; De Bellis, 2005; Pears and Fisher, 2005; Bos et al., 2009). Bos and colleagues (2009) investigated executive function in children that had a history of early deprivation due to institutionalization and reported that early adversity is associated with deficits in performance on tasks that involve planning and working memory. Early adversity resulting from familial violence has also been associated with deficits in a wide range of executive functions, including working memory, problem solving, inhibition and attentional control (Nolin and Ethier, 2007; Pears et al., 2008; Fishbein et al., 2009). While we expect that these deficits continue into adulthood, less is known about the predictive relationship

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between early adversity and executive function in adulthood.

Thus, for both perceptual responsiveness and executive functions, there is evidence of a link between adverse early experience of parenting and later-life deficits in functioning in these domains. These cognitive functions are relevant for parenting behavior, but evidence providing a more direct link between early adversity (i.e., parenting received), these cognitive functions, and later-life parenting behavior is lacking at this point.

Early adversity and emotional dysfunction

In addition to the relationship discussed above between early adversity and heightened responsiveness to emotionally-relevant cues, early adversity is also a significant factor in affective disorders in later life. Spertus and colleagues (2003) showed that a woman's history of neglect and emotional abuse was related to increased depression, anxiety, post-traumatic stress and physical symptoms, and that some of these scars persisted over time, specifically, poorer physical and emotional functioning. Early adversity has also been related to earlier onset of depression, a greater number of depressive episodes, a more chronic course of the illness and a greater likelihood of suicide (Brown and Moran, 1994; Lizardi et al., 1995; McCauley et al., 1997; Bernet and Stein, 1999; Brown et al., 1999; Bifulco et al., 2002; Harkness and Monroe, 2002; Moskvina et al., 2007). The timing of early adversity (earlier in childhood is considered a more vulnerable period), gender (men are less vulnerable), stressful experiences in later life and hypothalamic–pituitary–adrenal (HPA) axis functioning throughout life, as well as genetic characteristics are all factors that moderate and/or mediate the relationship between early adversity and depression (Heim and Nemeroff, 1999; Heim et al., 2004).

Emotional liability following early adverse social experience has also been studied in animal models. Repeated separation of pups from the mother during early life has been shown to increase the pup's fearfulness and anxiety in later life (Anisman et al., 1998; Huot et al., 2001; Sanchez et al., 2001; Kalinichev et al., 2002), with effects varying as a function of the duration and frequency of maternal separation (Matthews, 2002). Rats that were reared artificially in isolation from the mother and litter have also been shown to exhibit increased fearfulness and anxiety in response to novel environments and in investigating novel objects (Gonzalez et al., 2001; Burton et al., 2006; Melo et al., 2009), although some of these effects may depend on the sex of the animals and the testing conditions (Burton et al., 2006; Lomanowska et al., 2006).

The impact of early adversity on affective functioning in later-life may be especially relevant to subsequent parenting behavior. There is mounting evidence from human studies showing the link between depression in parents, especially post-partum depression in both mothers and fathers, and negative developmental outcomes among infants and children (Goodman and Gotlib, 2002; Kane and Garber, 2004; Tronick and Reck, 2009). Infants of depressed mothers are less interactive (Field et al., 2007), socially engaged (Feldman et al., 2009) and show more negative emotionality (Feldman et al., 2009). In addition, there is evidence for an association between maternal depression and infant cognitive and motor development (Tronick and Reck, 2009). In the early postpartum period, infants of depressed mothers are also less responsive to, and show less interest in faces and voices (Field et al., 2009). These findings could reflect higher arousal levels, less attentiveness, and perhaps altered sociability and empathy in the child. Indeed, infants of depressed mothers exhibit a distinct physiological profile, one that also is associated with heightened stress (Field and Goodman, 2002; Diego et al., 2004, 2006, 2010). In fathers, depression has been related to more spanking of the child, as well as less often reading or engaging positively with the child (Davis et al., 2011). In terms of later-life outcomes, parental depression has also been associated with internalizing and externalizing disorders in children (Connell and Goodman, 2002; Ramchandani et al., 2005, 2006). Furthermore, both maternal and paternal depression has been associated with physiological, cognitive, behavioral and emotional functioning across the lifespan of children, including an increased risk of developing psychopathology in adolescence or young adulthood (Cicchetti et al., 1998; Halligan et al., 2007; Brand and Brennan, 2009; Gump et al., 2009). Flouri and colleagues (McEwen and Flouri, 2009; Walton and Flouri, 2010) found that the behavior of fathers and mothers was associated with different aspects of adolescent emotional regulation, with maternal warmth being positively related to good regulation and psychological control being negatively related. Taken together, these studies demonstrate that parents' emotional dysfunction is persistently reflected in their children's psychological development, pointing to a source of socio-emotional adversity in early life that may be perpetuated across generations. It is important to note, however, that genetic vulnerability transmitted across generation should not be discounted in this context. Accordingly, it will be essential in future studies to dissociate the role of shared genetic vulnerability for emotional dysfunction and the contribution of environmental influences related to parenting behavior itself.

EARLY ADVERSITY AND PHYSIOLOGICAL MEDIATORS OF PARENTING

Parenting behavior is rooted in key physiological changes related to pregnancy, parturition, and responsiveness to young that involve interacting systems of hormones, as well as neural circuitry and neurotransmitters. It has now become clear that these physiological systems are sensitive to the influence of the early environment and can be perturbed by early adversity. In this section, we provide a brief overview of the physiological components underlying parenting behavior and we examine how their functioning may be affected by early adversity.

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Hormones and mothering

In most mammalian species that have been studied, the hormones associated with late pregnancy and childbirth enhance the likelihood that the new mother will respond appropriately to her newborn offspring. Mothers undergo a shift from being nonresponsive to acting responsively over the course of a short period before, during and after birth (Numan et al., 2006). The hormones that are implicated in this process vary across species, but most involve a configuration of hormones, including elevations in estrogen, and then prolactin and oxytocin, against a background of declining gestational progesterone (Numan et al., 2006). The neuropeptide oxytocin (primed by estrogens and affected by the glucocorticoids) has also been strongly implicated in the activation of nurturance in many species, including humans (Bardi et al., 2003; Feldman et al., 2010a,b; Gordon et al., 2010a,b).

Once females become 'biologically motivated' to respond maternally to their young, the behavior they exhibit is not strongly affected by hormones, but is primarily experience-based. Hormones, however, especially those of the HPA axis, cortisol in humans and corticosterone in rats, can affect the intensity of maternal behavior. The HPA axis or 'stress' system is a hormonal system critical for physiological adjustments to environmental challenges and 'stresses'. The HPA axis is key in regulating metabolism to insure energy availability for action and proper immune function, as well as having mobilizing effects to enhance attention and memory (McEwen, 1998; de Kloet et al., 2005). It is also a system that has adverse effects on the brain and body when activated without relief over long periods of time. Chronic stress can lead to dysregulation of the HPA system, producing changes in metabolism, disease susceptibility, in other aspects of physiology and in normal behavior (McEwen, 1998; de Kloet et al., 2005). There is substantial evidence that the HPA axis has both an activating and inhibitory effect on the maternal system, depending on the stage of postpartum, the parity and endocrine condition of the female, and an animal's earlier experiences (Numan et al., 2006; Rees et al., 2006; Brummelte and Galea, 2010).

In human mothers, postpartum cortisol concentrations soon after birth—which are extraordinarily high—are positively associated with many nurturing features of mothering. Women experiencing higher levels of cortisol engage in more contact with their babies, find baby odors to be more attractive, are better able to recognize their babies based on their odors, are more sympathetic when exposed to infant cries, and show altogether heightened feelings of wellbeing (Fleming et al., 1997; Stallings et al., 2001; Krpan et al., 2005; Giardino et al., 2008). Later in the postpartum period, when the priming effects of the childbirth hormones are no longer present, high cortisol does not appear to directly augment maternal behavior. Research in monkeys suggest that high cortisol at this time is quite deleterious to mothering behavior, especially in the context of the childbirth hormones (Bardi et al., 2005). This putative bimodal effect of cortisol has been demonstrated in a variety of contexts and suggests that a certain level may be necessary for alertness and adequate attention to young. However, if the levels are too high and hormonal priming by progesterone and estrogen is no longer present, maternal behavior can be disrupted (see Rees et al., 2006; Brummelte and Galea, 2010).

Early adversity and HPA axis function

There is a large literature in animal models demonstrating that the regulation of the HPA system is clearly affected by adverse childhood experiences and the resulting dysregulation can, in turn, affect parenting behavior in later-life. Importantly, both pre- and postnatal experiences of adversity can result in altered stress reactivity.

Numerous studies in animals have described the effects of manipulating the maternal/fetal environment on stress responsiveness, with the general consensus that stress applied experimentally (restraint stress as one example) during pregnancy leads to increased HPA activity in guinea pig, rat, and primate offspring (Kapoor et al., 2006; Kapoor and Matthews, 2008; Weinstock, 2008; Cottrell and Seckl, 2009; Bergman et al., 2010). These studies have also demonstrated that the timing in gestation when maternal adversity occurs has a major impact on the offspring HPA system functioning later in life (Kapoor and Matthews, 2005), but the effects are dependent on the age of outcome assessment, offspring sex and, in females, the phase of the menstrual cycle at which a given outcome is measured (Kapoor and Matthews, 2008). Several studies have now assessed the association between stressful experiences during pregnancy and HPA function in children (Glover et al., 2010; Tollenaar et al., 2011). The adverse maternal experiences that have been summarized in these studies are comprised of measures of 'daily hassles', life events (moving to a new house, death of a family member and so on) or domestic violence. An emerging consensus is that maternal stress is associated with a wide range of neuroendocrine disturbances in the offspring and related adverse developmental outcomes that include altered behavior and cognition (Weinstock, 2008; Entringer et al., 2009). A longitudinal study of mothers and their children suggested that self-reported maternal anxiety during late pregnancy predicted a higher awakening salivary cortisol secretion in the offspring at ten years of age (O'Connor et al., 2005). The prediction persisted after accounting for socio-demographic and obstetric factors, which included several postnatal assessments of maternal depression and anxiety. Another study demonstrated that prenatal anxiety (as indicated by fear about pregnancy outcome or giving birth and daily hassles) and maternal cortisol levels at week 16 of gestation were related to higher cortisol responses to starting school after the summer break in five-year-old offspring (Gutteling et al., 2005).

With respect to post-natal adversity, evidence from animal studies suggests that maternal separation and the quality of maternal care alters the development of several endocrine systems, including the HPA axis (Champagne and Meaney, 2001). Rat mothers that were raised without their mothers or raised by mothers that showed low levels of maternal licking demonstrated ele-

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vated stress activated HPA function (Francis et al., 1999; Burton et al., 2007; Belay et al., 2011). Studies of early adversity in primates, where maternal separation or stress paradigms that more closely resemble that of human mothers and infants, have led to more varied results; some studies demonstrating HPA-axis hypoactivity (Rosenblum et al., 1994, 2002; Coplan et al., 1995) and others HPA hyperactivity (Higley et al., 1991, 1992; Fahlke et al., 2000).

Hertzman and Boyce (2010) have reviewed the role of adversity in HPA activity in humans. Adversity in terms of low socioeconomic position over a lifetime is associated with substantially higher levels of awakening cortisol, 8–10% higher levels of cumulative cortisol secretion during the early day hour, and an increased risk by 60–91% of having an abnormal cortisol secretion pattern (Hertzman and Boyce, 2010). Under less chronic, but more extreme, conditions, children who have been exposed to severe neglect through institutionalization during the first 6 months of life show hyper-secretion of cortisol to stressful situations in addition to showing emotional and social dysregulation (Hertzman and Boyce, 2010). Whether these patterns associated with neglect are accounted for by the absence of early stimulation in general or by the absence of a parent figure is not known. However, HPA function is also associated with how well children are attached to their mothers. Disorganized and insecurely attached children show a prolonged HPA stress response to stress situations, whereas securely attached children tend to show a robust but short-lived response (Gunnar et al., 1996; Nachmias et al., 1996; Rao et al., 2008).

Dysregulation of the HPA axis activity is also associated with other behavioral indices of distress, as well as with emotional and cognitive problems, especially in later adolescent years and adulthood. A series of studies showed that mothers who were either at-risk teens or clinically depressed were more likely to show less affectionate and disrupted interactions with their babies as well as demonstrating elevated basal cortisol levels (Krpan et al., 2005; Gonzalez et al., 2012). Teen mothers with this endocrine and behavioral profile were also more likely to report (retrospectively) having experienced inconsistent care and multiple and changing caregivers (Krpan et al., 2005). In addition, adult mothers with a history of early adverse experiences (inconsistent care and/or maltreatment) showed higher levels of diurnal cortisol and were less sensitive when interacting with their infants (Gonzalez et al., 2012).

Taken together, these studies suggest that HPA dysfunction is associated both with concurrent stress and with earlier life stress or adversity and, in addition, that these dysregulations have been associated with mothers' sensitivity and interaction patterns with their infants. Still elusive is whether the elevated cortisol levels in high-risk mothers are particularly related to the postpartum period or were present throughout childhood and generally in adulthood. In fact, in a retrospective study outside of the postpartum period, women who were abused as children demonstrate elevated peak adrenocorticotropic hormone (ACTH) responses to stress and more prolonged cortisol responses. This pattern is strongly associated with a woman's current mood state, such that abused women without current depression demonstrate lower cortisol responsiveness and basal cortisol levels, while women who were abused with depression show features more consistent with hyperactive HPA function (Heim et al., 2004). These data indicate that when interpreting studies using cortisol as a marker for stress, it is important to know the context of the cortisol assessment and the life history and circumstances of the person being assessed. Future work should focus on prospective measures and/or intervention studies to more clearly establish causal pathways and to further elucidate the pattern of HPA axis functioning in women with a history of early adversity who will subsequently become mothers.

The brain, neurotransmitters and mothering

What we know about the maternal brain and its neural circuitry is derived almost exclusively from experimental research based on lesion, stimulation, and pharmacologic studies with rats and monkeys (Fleming and Li, 2002; Numan et al., 2006; Barrett and Fleming, 2011; Numan, 2012). Broadly speaking, this body of work shows that the circuitry involves lower-level systems in the hypothalamus and midbrain that can be thought of as the 'final common path' for the expression of maternal behaviors. Interconnecting this system are projections from limbic structures, including the olfactory system, the amygdala, and the nucleus accumbens that mediate the expression of olfactory-based hedonics, affect, and reward processing, respectively. Intersecting with both the hypothalamic and the limbic systems are cortical systems, including the prefrontal, orbitofrontal, and cingulate systems that regulate planning, attention, working memory and social-emotional expression. See Fig. 1 for a schematic of this maternal circuitry in the rat. Within the maternal circuitry, one system that has been studied heavily is the limbic-amygdala system, known for its involvement in emotion regulation, fear expression, fear conditioning, and affect in general (LeDoux, 2003). With respect to mothering, this system is implicated in the change the new mother rat undergoes during parturition when she transforms herself from an animal that is fearful and withdraws from young into one that approaches and engages with the young (Fleming and Li, 2002; Numan et al., 2006; Numan, 2012).

There has also been a plethora of human functional magnetic resonance imaging (fMRI) studies focusing on the brain activation patterns of mothers and others to infant-related stimuli. These studies show a pattern of activation in humans that matches quite well the pattern derived from animal experimental studies, with activation in limbic structures, but especially in cortical structures (Seifritz et al., 2003; Bartels and Zeki, 2004; Leibenluft et al., 2004; Swain, 2008; Swain and Hoa, 2010; Musser et al., 2012). See Fig. 2 for a schematic of the maternal circuitry in humans. For example, focusing quite directly on sites within the brain known to be important among other mammals, Barrett and colleagues (Barrett and Fleming, 2011; Barrett et al., 2012) pre-

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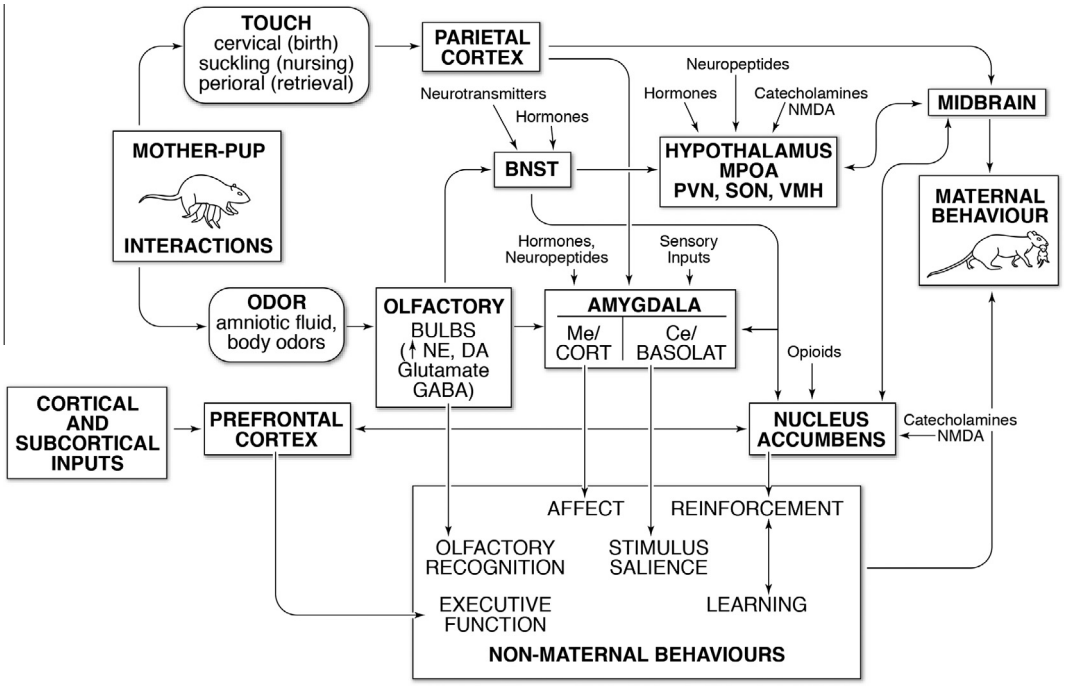

Fig. 1. The functional neuroanatomy of maternal and related non-maternal behaviors in mammals. Neuroanatomical structures comprise the olfactory bulbs, the amygdala, the nucleus accumbens, the bed nucleus of the stria terminalis (BNST), the medial preoptic area (MPOA), the ventromedial hypothalamus (VMH), the periventricular nucleus (PVN), the supraoptic nucleus (SON), the midbrain, and the parietal cortex. Neurochemical systems include the catecholamines, norepinephrine (NE) and dopamine (DA), the neuropeptides, and the opioids (from Barrett and Fleming, 2011, used with permission).

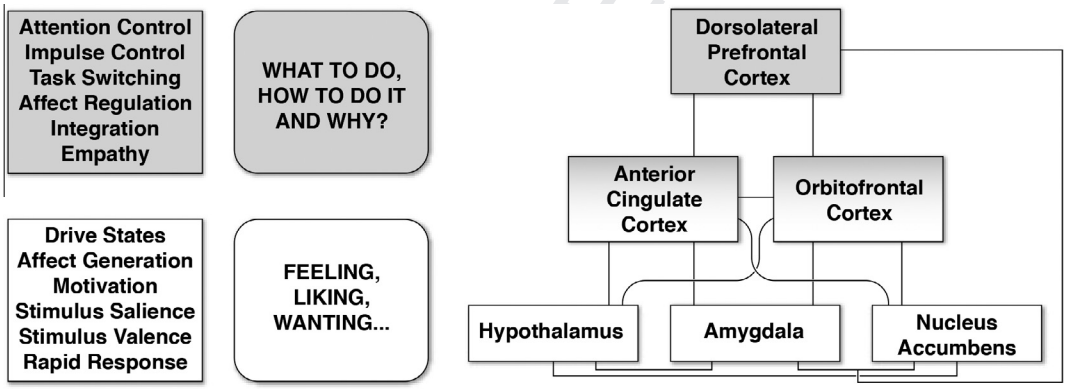

Fig. 2. The putative human maternal circuit. Subcortical brain regions implicated in reward, affect, and motivation serve to promote the salience of baby stimuli as strongly reinforcing factors that stimulate the mother to care for, be responsive to, and show affection to the baby. Higher-order cortical functions regulate maternal behavior in the context of the internal and external environment and overarching goals, standards, mores, and intentions. Regions such as the anterior cingulate cortex and orbitofrontal cortex operate at the interface of the two systems (from Barrett and Fleming, 2011, used with permission).

sented pictures of their own infants and other infants to new mothers. They found that mothers responded most positively to faces of their own infants smiling (as opposed to crying) and that the brain areas that became activated to the familiarity dimension and affect dimensions of their own infant faces compared to the control condition included many of the same sites described in the animal models, including the nucleus accumbens, the amygdala, and the cingulate cortex. Furthermore, in line with the involvement of the limbic-amygdala system in emotional regulation in the context of mothering, these response patterns related quite clearly to maternal levels of anxiety and depression (Barrett et al., 2012).

While many neurotransmitters play a role in the onset of mothering, dopamine, has been clearly implicated in reward, mood, attention, and mothering, at least in non-humans. The general function of dopamine is to reflect and enhance the rewarding properties or salience of stimuli for an animal (Berridge and Robinson, 1998). Depending on an animal's 'motivational' state, relevant stimuli are food to the hungry animal, a sexually experienced male for an estrous females, or pups for a

new mother (Berridge and Robinson, 1998; Afonso et al., 2008, 2009, 2011). In the new mother rat, hormones progesterone and estrogen suppress baseline activity of the dopamine system in the nucleus accumbens. In hormonally primed new mother rats, subsequent pup stimulation produces an increase in dopamine over baseline, which is proportionally greater than it would be if the baseline were high. Therefore, this hormonal effect acts to tune the dopamine system by enhancing the ratio of dopamine signal to baseline noise when pups are presented (Afonso et al., 2011, 2013).

An important point to consider with respect to the neurobiology of mothering is that the brain and neurotransmitter systems that become activated by infant stimulation in new mothers are not specific to mothering or to infants; instead they reflect activation of general processes that are recruited, utilized, or activated by different stimuli at different life stages and under different endocrine, experiential, and motivational conditions.

Early adversity and development of brain function

Animal models show that the nature of the early experience of being mothered affects the development of the brain systems important for mothering. For instance, in comparison to offspring of high licking rat mothers, offspring of low-licking rat mothers grow up to have lower levels of receptors in the brain for the hormones estrogen and oxytocin (Francis et al., 2000; Champagne et al., 2003a,b), and lower levels of receptors for corticosterone (van Hasselt et al., 2012). These receptors are all involved in the activation or modulation of maternal behavior. Studies of maternal deprivation in rats have also provided a wealth of information regarding the effects of this type of early adversity on brain development. Raising rat pups without their mothers, in comparison to mother-reared pups, results in animals that show reduced neural activation in the subcortical brain regions important for mothering, including the medial pre-optic area (MPOA), and the piriform and parietal cortices, as measured in the pup sensitization paradigm in juvenile females (Gonzalez et al., 2001). Similarly, changes in the profile of dopamine release in the nucleus accumbens in response to pups are observed in postpartum females who were raised without their mothers (Afonso et al., 2011). In both cases, additional touching and stroking stimulation during early life normalizes brain function and prevents the effects of deprivation. Similarly, early deprivation disrupts normal development of some, but not all, maternal neural circuits by reducing the production of proteins associated with the development of neurons in a number of brain sites important for mothering (Akbari et al., 2007; Burton et al., 2007; Chatterjee et al., 2007; Chatterjee-Chakraborty and Chatterjee, 2010). Finally, there is evidence that many of these effects are initiated during the first week of life in rats, since by day seven of postnatal rearing, maternally deprived animals show a reduction in normal 'programed cell death' (apoptosis) and reduced production of proteins that promote cell death (Chatterjee-Chakraborty and Chatterjee, 2010). It is important to note that, in all these studies, providing replacement maternal licking-like stimulation prevents the brain deficits.

In humans, the evidence that early adversity is predictive of the neural underpinnings of later mothering behavior is less direct. However, some initial data suggested by studies of abused and neglected women, and of individuals raised in the early years of life in institutions who have many deficits in brain structure and function, indicate that early adversity may well disrupt the maternal circuitry. A number of brain differences associated with early life adversity have been reported in adults, including reduced volume or development of brain areas in the cortex and subcortex (Teicher et al., 2003). Moreover, in children, the orbitofrontal cortex involved in social-emotional regulation is considerably less active and smaller in maltreated children than in non-maltreated children, and again this reduction is related to the extent of early stress experienced (Bachevalier and Loveland, 2006; Hanson et al., 2010). Similar reduced size has also been reported in institutionalized children; in this case in a portion of the cerebellum that is involved in social regulation, such that children with smaller posterior-superior lobes showed poor executive control (Pollak, 2005, 2008; Bauer et al., 2009). Youths with a prior history of institutionalization have also been shown to exhibit an altered pattern of activation in the amygdala in response to faces of their mothers and strangers by comparison to controls (Olsavsky et al., 2013). Institutionalized youth showed reduced amygdala discrimination toward these stimuli, and this reduction in activation was related to greater indiscriminate friendliness (Olsavsky et al., 2013). Moreover, adult individuals who experienced early maltreatment reported more flatness of affect and depressive symptoms, and displayed decreased neural activation in reward and learning brain regions compared to non-maltreated counterparts (Buss et al., 2007; Dillon et al., 2009). Maternal warmth was also associated with neural activation in the medial prefrontal cortex (mPFC) in response to different reward conditions and this relationship was particularly salient for individuals who were raised by depressed mothers (Morgan et al., 2014). Furthermore, mothers who reported more nurturing maternal care in childhood had larger gray matter volumes, indicating neuron cell bodies, in many regions of the cortex (Kim et al., 2010). They also exhibited greater brain activation to infant cries in many of the same cortical sites. However, there is still a lack of published research examining neurobiological processing in new mothers who themselves have experienced parental loss or personal trauma during early development.

GENES, GENE BY ENVIRONMENT (GXE) INTERACTIONS AND EPIGENETICS

Genetic influences may also account for variability in parenting behavior and in its transmission across generations. Importantly, however, there is evidence for GxE interactions in the expression of maternal behavior. This is apparent from the results of studies showing that the maternal genotype predicts different patterns of

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maternal behavior as a function of early experience, and other studies showing that the expression of certain genes associated with parenting behavior can vary in relation to particular early experiences. In this section, we describe studies in both humans and animal models that shed light on these processes.

Genetics and maternal behavior

The heritability of maternal behavior (e.g., positivity, warmth, physical affection, and control) was first indicated by studies with human twins (Perusse et al., 1994; Kendler and Baker, 2007). More recent genetic studies have focused on candidate genes implicated in systems underlying maternal behavior, including the dopamine, serotonin, and neuropeptide oxytocin and arginine vasopressin systems (Mileva-Seitz et al., in press). In these studies, the maternal genotype is defined by the expression of different variants, or polymorphisms, of candidate genes. Gene expression in mothers is then related to observed maternal behavior.

Due to the importance of dopamine in the motivational aspects of mothering, a number of genes involved in the functioning of the dopamine system have been studied. Variation in the dopamine transporter (DAT1) gene associated with the metabolism of dopamine has been related to differences in 'negative parenting' and the frequency of maternal verbal commands during a structured mother–child interaction (Lee et al., 2010). Furthermore, polymorphisms of dopamine genes for the D4 receptor (DRD4) and catechol-O-methyltransferase (COMT) related to 'less efficient transmission' of the neurotransmitter predicted lower maternal sensitivity in mothers with high levels of self-reported daily hassles (Van Ijzendoorn et al., 2008). Importantly, in both of these studies, GxE interactions were also reported in relation to the disruptive behavior of the child (Lee et al., 2010) or the level of daily hassles (Van Ijzendoorn et al., 2008). A similar GxE interaction was also found when infant fussiness was considered within the context of maternal sensitivity. Mothers with a variant of the DRD4 dopamine receptor gene (the DRD4 7-repeat allele) behaved more sensitively to fussy babies and less sensitively to non-fussy babies than did mothers with an alternate variant, without the 7-repeat allele (Kaitz et al., 2010). Another study relating dopamine genes to mothering at 6 months postpartum focused on two other dopamine receptor genes, (DRD1 and DRD2). Variation in the DRD1 receptor gene was significantly associated with the time mothers spent disattending to the infant (Mileva-Seitz et al., 2012). This finding is consistent with the idea that dopamine acts at this receptor to enhance the salience and thus attention toward infant stimuli. In contrast, variation in the DRD2 receptor gene was significantly associated with maternal vocalizing/speech to the infant (Mileva-Seitz et al., 2012).

A similar association between mothering behavior and gene variants coding for the serotonin transporter 5HTT has also been reported. Specifically, the 5HTT genotype was found to predict observed maternal sensitivity in response to 2-year-old toddlers (Bakermans-Kranenburg and van Ijzendoorn, 2008), 6-month-old infants (Mileva-Seitz et al., 2011), and during repeated measurement time points at 14, 36, and 48 months of age (Cents et al., 2014). Two of the initial studies reported opposite effects, however, where mother carrying the S-allele of the serotonin transporter showed lower (Bakermans-Kranenburg and van Ijzendoorn, 2008) or higher (Mileva-Seitz et al., 2011) levels of sensitive parenting. The more recent study by Cents et al. (2014) of a much larger cohort of mother–child dyads, with tests of maternal sensitivity performed at different time points during child development, supported the findings of the S-allele being associated with higher levels of maternal sensitivity as observed by Mileva-Seitz et al. (2011). Of importance to the focus of this review, Mileva-Seitz et al. (2011) also reported a GxE interactive effect between polymorphisms of the serotonin transporter gene and the reported quality of care that the mothers received from their own parents on the frequency of orienting away from the infant during a 30-min mother-infant interaction and perceived attachment to the infant.

Furthermore, a number of studies have reported an association between maternal behavior and genes implicated in the functioning of oxytocin, a neuropeptide important in affiliative behaviors. Several gene variants, including those coding for the oxytocin peptide (OXT), the oxytocin receptor (OXTR) and an ectoenzyme mediating the release of brain oxytocin (CD38), have been associated with observed maternal behavior, including maternal sensitivity (Bakermans-Kranenburg and van Ijzendoorn, 2008), maternal warmth (Klahr et al., 2015), positive parenting (Michalska et al., 2014), parental touch and parent-infant gaze synchrony (Feldman et al., 2012), maternal vocalizing to the infant (Mileva-Seitz et al., 2013) as well as neural and physiological responsiveness to infant cues (Riem et al., 2011; Michalska et al., 2014). Similarly to studies of the serotonin system, interactive GxE effects of mother's genetics and early experience on mothering behavior have also been observed for gene variants of oxytocin (Feldman et al., 2012; Jonas et al., 2013; Mileva-Seitz et al., 2013). Feldman et al. (2012) found that parents who reported greater parental care in early life, and who were also carriers of CD38 alleles associated with lower risk of social dysfunction displayed more touch toward their infants. Mileva-Seitz et al. (2013) also reported a relationship between OXT gene variants, the reported quality of early-life parental care, and variation in observed maternal instrumental care and post-partum depression. Jonas et al. (2013) also found that a similar interaction between OXT gene variants and early-life adversity predicted the duration of breastfeeding as well as postpartum depression.

Variation in the gene for arginine vasopressin, another neuropeptide implicated in affiliative behavior, has also been associated with mothering. Mothers with different alleles of the arginine vasopressin 1a receptor gene AVPR1A differed in maternal sensitivity (Bisceglia et al., 2012) and supportive and guiding behavior toward their children (Avinun et al., 2012). Importantly, there was also a significant GxE interaction between the AVPR1A gene variants and self-reported early adversity, such that

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women who scored lowest on measures of maternal sensitivity were those who experienced high levels of early adversity and who had two copies of the RS3 long alleles of the gene (Bisceglia et al., 2012).

Overall, these findings illustrate that different genetic variants can relate to different behavioral endpoints within the context of mothering behavior. Furthermore, mothers with different genetic profiles may be differentially affected by their early life experience, which can also play a role in maternal behavior.

Early adversity, epigenetic mechanisms and mothering

One intriguing mechanism through which early adversity could affect later mothering is epigenetic modification of gene expression (McGowan and Roth, 2015). Reduction or silencing of gene expression, through retention of methylation, is a biological mechanism through which an early adverse experience, as opposed to a positive and healthy experience, could have a long-term impact on processes underlying mothering behavior. Such a mechanism has been documented in rodents with respect to the expression in the brain of receptors of steroid hormones important for mothering, including estrogen and corticosterone (Champagne et al., 2006; Pan et al., 2014). Female offspring of low-licking mothers showed both a reduced expression of the estrogen alpha receptor gene in the MPOA (and hence are less sensitive to estrogen action), as well as an increased DNA methylation of its promoter region, which functionally reduces or silences gene expression (Champagne et al., 2006). In another study, a difference in the level of methylation of the glucocorticoid receptor gene promotor, a promotor for the receptor to which corticosterone binds, was found in the hippocampus of female offspring that experienced different amounts of maternal licking in early life (Pan et al., 2014). A similar epigenetic process has also been implicated in the altered expression of the BDNF gene, a gene involved in growth and plasticity in the brain, in the prefrontal cortex of female offspring following adverse early experiences (Roth et al., 2009; Roth and Sweatt, 2010).

In human studies, early adversity has also been associated with differential methylation patterns in (postmortem) hippocampal tissue (McGowan et al., 2009; Labonte et al., 2012; Suderman et al., 2012). Furthermore, genome-wide DNA methylation differences were found between children raised in an institution compared to children raised by biological parents, including differences in genes for neural communication and brain development (Naumova et al., 2012). A recent study examined the association between early adversity, parenting, and methylation of the promoter region of the glucocorticoid receptor gene NR3C1 (Schechter et al., 2015). In mothers with a history of interpersonal violence and maltreatment, including experience of interpersonal adversity in early life, the severity of the mother's post-traumatic stress disorder symptoms and current parenting stress was negatively correlated with the level of methylation of NR3C1 (Schechter et al., 2015). In addition, the level of methylation of NR3C1 correlated positively with neural activity in the mPFC in response to videos of the mothers' interactions with their children during a play and separation session (Schechter et al., 2015). The results of this study demonstrate that patterns of epigenetic modifications important for the functioning of the HPA axis relate to both the mothers' experience of adversity, their present experience of mothering and their neural response to child-related cues.

Overall, research into the epigenetic mechanisms implicated in the long-term effects of early adversity is in its early stages and there is still limited information regarding outcomes related specifically to parenting. In future studies, it will be important to document whether the 'gene by early experience' interactions reported in relation to mothering involve differential methylation patterns of the genes implicated in mothering, such as genes involved in the functioning of the dopamine, serotonin, oxytocin or vasopressin systems. For instance, studies that examine the relationship between candidate gene polymorphisms and methylation patterns on these genes, in combination with an assessment of early parenting experience and current parenting style, will be critical in furthering our understanding of the mechanisms by which early experience affects parenting.

SUMMARY AND CONCLUSION

Adverse childhood experiences pose a challenge to healthy development with putative effects that may endure throughout life. As described in this review, these longitudinal associations also extend inter-generationally, by means of parenting behavior. Children who grow up neglected or abused by their parents, or under conditions of extreme distress within their families, are at risk of developing a host of unhealthy behaviors that affect their own lives. When these children grow up, they tend to be less equipped to take on a parenting role and, in the context of adverse circumstances and the absence of some form of social support and/or intervention, they are more likely to adopt parenting behaviors that perpetuate a cycle of adverse parenting across generations.

Based on a sizable literature in humans documenting the associations between early adversity and later-life outcomes, as well as animal studies that enable us to make stronger inferences of causality about the potential impact of early experiences on the development of offspring, we are now able to identify a number of psychological and physiological factors implicated in the perpetuation of early adversity through parenting behaviors. A number of perceptual, cognitive and emotional deficits associated with early adversity could play a significant role in the context of parenting. These include perception and responsiveness toward offspring stimuli, difficulties in regulating of parenting behavior, as well as depression. Parents (mothers) who are reactive, inattentive, impulsive, aggressive, depressed or simply not interested in their children are more likely to adopt problematic parenting behaviors, especially in stressful situations. The perceptual, cognitive, and emotional deficits that many mothers experience may affect their

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children in various ways. For instance, impulsive and inattentive mothers have greater difficulty interacting contingently and sensitively with their infants. Furthermore, depressed mothers, if untreated, can put their children at risk for depression and other affect problems, whereas children who are physically abused or the target of harsh parenting may come to show externalizing behavior and harsh parenting themselves.

The underlying mechanisms linking early adversity and later parenting difficulties imply a disruption of behavioral and physiological processes involved in typical parenting behavior. In particular, early adversity can disrupt the regulation of HPA axis activity, which, as discussed, has been shown to modulate how mothers respond to offspring. Furthermore, animal studies of early adverse experience reveal effects on a number of neural systems implicated in mothering, including changes in oxytocin, estrogen, and corticosterone receptors levels, reduced neural activation in relevant brain regions of the maternal circuit and altered patterns of dopamine neurotransmission in response to offspring stimuli. In humans, evidence of changes to the neural substrates of mothering following early adversity is less direct, but a number of structural and functional alterations have been reported in individuals with a history of various adverse early experiences. Importantly, however, genetically informative studies show that there is a GxE interaction between gene polymorphisms for several neuropeptides and neurotransmitters implicated in mothering and early-life experiences. In other words, endpoints associated with the type of parenting received and early adversity depend on the gene polymorphisms that individuals carry. Adverse early experience has also been related to epigenetic changes that affect gene expression levels of brain steroid hormone receptors that are implicated in mothering. However, the research examining GxE interactions in parenting is still in its infancy, and it is important in future studies to examine this question within a polygenic approach, as well as through long-term prospective longitudinal studies. This research on the GxE underpinnings of parenting will also have to consider genetically associated "child effects" (i.e., genetically mediated child characteristics that may evoke parenting behaviors) to account for variations in parenting within family (Boivin et al., 2005; Henry et al., 2015). Furthermore, future research will need to focus more closely on the contribution of fathers to the intergenerational transmission of parenting behavior, as well as on the interaction of mothers' and fathers' contributions. There are some conflicting reports on the intergenerational transmission of fathering behavior (Capaldi et al., 2003; Smith and Farrington, 2004; Belsky et al., 2005). In the same vein, studies examining the mechanisms by which genetic and GxE factors influence parenting report both similarities (Feldman et al., 2012) and differences (Klahr et al., 2015) between findings for mothers and fathers. However, as discussed in previous sections, both mothers' and fathers' behavior is known to contribute to the developmental outcomes of children, and both male and female offspring are sensitive to parental influence, underscoring the importance of investigating the specific mechanisms relevant to the intergenerational transmission of different parenting behaviors in both sexes.

The GxE and epigenetic processes highlight the complexity of the relationship between environmental experience and parenting behavior. It is important to reiterate that in most cases, parents who experienced extreme adversity, such as physical abuse, will not adopt the same pattern of behavior with their child. Individual factors, such as genetics and temperament in both the parent and the child, as well as environmental factors, such as support from the partner, the family, and the community, could mitigate the risk of problematic parenting behavior (e.g., Caspi et al., 2002; Boivin et al., 2005; Lee et al., 2010). Mounting evidence shows that the role of early adverse childhood experiences in predicting negative developmental outcomes is not the same for all, but rather depends on children's characteristics, including their genetic make-up (that is, a gene by environment, or GxE interaction). For instance, there is now ample evidence that the environment can affect individuals differently depending on their genetic endowment, and likewise, that the same genetic endowment produces different outcomes depending upon the environment (Caspi et al., 2002; Boivin et al., 2005; Ouellet-Morin et al., 2008, 2009; Lee et al., 2010). The complexity of developmental processes is further augmented by the growing flow of negative feedback loops in development, whereby personal characteristics, including genetic factors, may lead to differential exposure to stressful social contexts (Boivin et al., 2013a,b). In other words, biological and environmental determinants are intertwined in developmental pathways. These complex transactions over time between the characteristics of the parent, the child, and their environment will ultimately determine the parenting outcomes of early adversity and their possible transmission across generations.

Understanding how adverse parenting begets adverse parenting in the subsequent generation is critical to the planning of timely interventions in order to prevent this intergenerational cycle of adversity. The extant research suggests that, in addition to policies at a societal level (aimed at reducing the burden of early adversity, such as poverty and low education), we also need to consider interventions that focus on parenting difficulties. Among the current approaches to interventions, we should stress the importance of programs aimed at enhancing parents' emotional regulation and impulse control, attentional and cognitive capacity, mood state, ability to cope with stress, and more specifically in the context of parent–child interaction, attention to infant signals, contingent responding and positive regard. By understanding the phenomenology of parenting, its roots and consequences, and its underlying mechanisms, we will be in a position to attend to the needs of the parents, to enhance their overall well-being and to help them gain the tools to more effectively attend to the needs of their children. At the same time, because most of the documented deficits in parenting have their roots in infancy, early interventions specifically directed at children at risk may also have long-term benefits and thus

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may go a long way in preventing or at least mitigating the likelihood of problematic parenting behaviors in later life.

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