Chapter 10
How Being Mothered Affects the Development of Mothering

Viara R. Mileva-Seitz and Alison S. Fleming

For better or for worse, parents draw on past experiences, sometimes repeating the behaviour of their own parents. Yet how precisely do they do so? What aspects of their early 'experience' become influential to new parents, and by what mechanisms? As with any complex behaviour, the transmission of parenting from one generation to another is unlikely to follow a single pathway or mechanism. Social and biological processes are intertwined. Advances in genetic and epigenetic techniques allow us to probe mechanisms underlying this transmission across generations. Such research also bears a responsibility. It must ultimately answer the following questions: What dimensions of parenting tend to be transmitted across generations? Are these dimensions at the mercy of biological and environmental programming? How flexible is the intergenerational transmission of parenting? Here we will review some major aspects of intergenerational transmission of mothering.

Parenting is a hugely complex and potentially stressful time of life. Sometimes parental stress leads to less-than-optimal parental behaviours, which can be strongly influential for subsequent generations. The identification of mechanisms of transmission of parental behaviour across generations will help to eventually shape interventions and policies aimed at reducing parental stress and abuse and neglect of the offspring. One potential such mechanism which we discuss below is the following: maternal stress can alter aspects of psychobiological function in offspring such that daughters grow up to mother in the same way (e.g. low-licking moms produce daughters who grow up to be low-licking moms). The focus on mothering—versus other types of caregiving—is due to the overall lack of research into fathers, grandparents, and other caregivers.

V.R. Mileva-Seitz (✉) · A.S. Fleming
Department of Psychology, University of Toronto, Toronto, Canada
e-mail: viara.mileva@gmail.com

A.S. Fleming
e-mail: Alison.fleming@utoronto.ca

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Variations in Mothering

Animals (including humans) exhibit natural variations in the types and quantities of species-specific maternal care they exhibit. Studying animals in the laboratory is useful to untangle some of the underlying influences on maternal behaviour and on the transmission of behaviour across generations. One of the most widely studied animal models of parenting is the rat. Rats exhibit stereotyped maternal behaviours: they nurse, lick, and groom their pups, build a nest, and retrieve the pups back to the nest. The mother and the nest provide nutrition, warmth, and protection. They also provide social and other stimuli that affect pups' neural and endocrine development and later behaviour (Lonstein, Lévy, & Fleming, 2015). Moreover, the young learn to prefer their mother's odour over time, which guides subsequent social interactions and even their responses to their own offspring later on (Abel, Ronca, & Alberts, 1998; Hofer & Sullivan, 2001; Shah, Oxley, Lovic, & Fleming, 2002; Wilson & Sullivan, 1994). Maternal licking has a particularly pronounced effect on offspring development. The somatosensory stimulation has long-term effects on the quality of mothering pups adopt towards their own young. The most effective period for transmission of licking effects seems to be in the first post-partum week when the rat brain is still rapidly developing (Champagne, Francis, Mar, & Meaney, 2003; Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001). Licking and grooming during early life thus have a non-genetic influence on the next generations and are therefore crucial for optimal development. The absence or disruption of licking and grooming, such as during maternal separation or deprivation, has documented developmental consequences as well.

In humans, as in other mammals, there also occurs a continuity of parenting styles (subtypes of parental behaviours) across generations (Bailey, Hill, Oesterle, & Hawkins, 2009; Belsky, Jaffee, Sligo, Woodward, & Silva, 2005; Conger, Neppl, Kim, & Scaramella, 2003; Neppl, Conger, Scaramella, & Ontai, 2009; Scaramella, Neppl, Ontai, & Conger, 2008). For instance, a large prospective study with direct parent–child behavioural observations during a puzzle task showed continuity in both positive parenting (supportive, warm, helpful, and involved parenting during the task) and negative/harsh parenting (critical, aggressive, unkind, irritable, and 'pressureful' parenting during the task) (Scaramella et al., 2008). Moreover, human studies suggest a bi-directional role for parent–child interactions in the developmental process. On the one hand, early parenting might influence developmental trajectories. On the other hand, children's own behaviours might elicit specific types of parenting through evocative effects and—given shared genetic factors—through evocative gene–environment correlations (Ge et al., 1996; Jaffee & Price, 2008; Maccoby, 2000).

In addition to normal variations in parenting affecting the parental behaviour of the next generation, there is ample evidence both in non-human animals and in humans that manipulated extremes in parenting affects the offspring and their subsequent parental behaviour. This has been well demonstrated in rats (Fleming et al., 2002; Hofer, 2002). The most severe rat deprivation paradigm involves

raising pups without a mother in an artificial rearing variant on Hall's 'pup-in-a-cup' environment, and then comparing these pups to mother-reared sibling controls (Hall, Wilkinson, Humby, & Robbins, 1999; Thoman & Arnold, 1968). This animal model is reminiscent of the environment provided by human institutionalization and produces many of the same effects on young (Brett, Humphreys, Fleming, Kraemer, & Drury, 2015). Unlike the limited deprivation during short-term daily separations and reunions (short-term stress), the 'pup-in-the-cup' procedure is a continuous isolation, where pups never know their mothers and siblings but are raised alone, with some human contact. As adults, these pups show deficits in maternal licking and crouching over their pups, consistent with the extent of the adversity or separations experienced in early life (Gonzalez et al., 2001; Lovic & Fleming, 2004; Lovic, Gonzalez, & Fleming, 2001; Rees & Fleming, 2001). Short-term deprivations produce the least deficits, whereas artificially reared pups produce the greatest reductions in pup body licking, genital licking, and crouching subsequently as adults (Fleming et al., 2002; Gonzalez et al., 2001; Liu et al., 1997). Yet when artificially reared pups are given additional licking-like stimulation by 5–8 daily strokes with a paintbrush, or if they are reared more socially with another single sibling, the isolation effects on subsequent behaviour are considerably reduced (Lomanowska & Melo, 2016).

Hence a deficit experienced by isolated pups resides in how much somatosensory, vestibular, and tactile stimulation (and possibly contingent interactions) they receive in their pre-weaning life (Hofer & Sullivan, 2001). Most relevant to the current discussion is that the effect of artificial rearing *persists across generations*. Offspring of isolated pups who were not themselves isolated or maternally deprived, also show disrupted mothering as adults (Champagne et al., 2003; Fleming et al., 2002; Gonzalez et al., 2001; Hofer & Sullivan, 2001; Kraemer, 1992; Lévy, Melo, Galef, Madden, & Fleming, 2003; Lomanowska & Melo, 2016; Lovic & Fleming, 2004; Melo et al., 2006; Numan, Fleming, & Levy, 2006; Palombo, Nowoslawski, & Fleming, 2010; Wilson & Sullivan, 1994). Similar effects are seen in non-human primates (Champoux et al., 2002; Fleming et al., 2002; Maestripieri, 2005; Maestripieri et al., 2006; Maestripieri, Lindell, & Higley, 2007; Suomi, 1999).

In humans as well, extreme parental abuse, neglect, or deprivation and social isolation have serious consequences that affect the behaviour of subsequent generations. About 30% of women abused as children go on to abuse their own children, a rate of abuse substantially higher than that in the general population of 5% (Kaufman & Zigler, 1987; Knutson, 1995). Some of the associated outcomes of early abuse or neglect include more aggressive, intrusive, or generally 'poor' parenting (Moehler, Biringen, & Poustka, 2007; Newcomb & Locke, 2001), a decreased female interest in becoming a mother, higher levels of child neglect, diminished parental confidence and self-appraisal, greater use of physical punishment, and a lack of emotional control in parenting situations (Roberts, O'Connor, Dunn, & Golding, 2004). Less severe negative early experiences (e.g. harsh parenting and high levels of family discord) are also transmitted intergenerationally (Capaldi, Pears, Patterson, & Owen, 2003). For instance, mothers who experienced

early parental rejection show more negative affect towards their children (Belsky, Youngblade, & Pensky, 1989).

Positive early experiences also influence later maternal behaviour (Belsky et al., 2005; Chen & Kaplan, 2001; Chen, Liu, & Kaplan, 2008). Mothers who had positive childhood relationships with their own parents are more responsive towards their children (Gara, Rosenberg, & Herzog, 1996). Less authoritarianism, more positive family 'climate', and a positive attachment in childhood are predictive of warm, sensitive, and stimulating maternal behaviour in adulthood (Belsky et al., 2005). Early life experiences are thus part of a spectrum, from very negative to very positive (Belsky et al., 2009), and both the 'good' and the 'bad' can be transmitted cross-generationally. The most evident question arising from this intergenerational research is the question of *how* parental behaviour is transmitted, particularly when it appears to happen sometimes in the absence of the very same environment that triggered particular parental behaviours in previous generations.

Is Parenting Stable Over Time?

The quest for finding mechanisms of intergenerational transmission of parenting begins with the assumption that parenting practices are, to a degree, stable over time for a given parent. The evidence only partially corroborates this view, however. For instance, some studies indicate maternal sensitivity is stable over time (Behrens, Hart, & Parker, 2012; Vereijken & Marianne Ri, 1997), whereas others report the opposite (Lohaus, Keller, Ball, Voelker, & Elben, 2004). Therefore, single snapshots of mother–infant interactions may not be optimal for assessing the true nature of maternal sensitivity (Lindhiem, Bernard, & Dozier, 2011).

Mothers may get more comfortable over time and repeated assessments, or they may gradually fall into more stable patterns of interactions with their infants over the first year (Pauli-Pott, 2008). As well, mothers clearly respond differently to different children within the family, and family effects at one time can feed back and affect mothers' relationship with different children at later times (Jenkins, McGowan, & Knafo-Noam, 2016). Furthermore, individual susceptibility to parenting effects might also be only moderately stable. That is, there might be different sensitivity periods (Windhorst et al., 2015), so that the interactions between parenting and the child's susceptibility alleles might change over time. This has not been well explored, and nothing is known about the stability of gene–environment interactions in mothers lives as they acquire experience with their own children.

Mechanisms for the Intergenerational Transmission of Parenting

The effects of early rearing experiences on later parenting might be mediated by shared genetics, shared environment, physiology, brain development, and epigenetic modifications. We will briefly review evidence for each of these multiple mechanisms. New rat mothers who themselves experienced adequate early parenting in infancy, when compared to mothers who experienced varying periods of separation from mother, show a good balance in approach-withdrawal behaviours when in both novel environments and when with their pups; they show reduced fearfulness and enhanced attentiveness, and they are better able to respond to positive features of their young (Barrett & Fleming, 2011; Fleming & Li, 2002; Lomanowska, Boivin, Hertzman, & Fleming, 2016; Lonstein et al., 2015). In contrast, early adversity and isolation results in changes in the animals' fearfulness in an elevated plus maze (Lomanowska & Melo, 2016; Lomanowska, Rana, McCutcheon, Parker, & Wainwright, 2006), produces hyperactivity in an open field and in activity boxes (Gonzalez et al., 2001), increases overall impulsivity assessed in a DRL paradigm (Lovic & Fleming, 2015), enhances inattention in a set shifting task (Lovic & Fleming, 2004), and alters the hedonic value of pups in the new mother (Afonso, King, Chatterjee, & Fleming, 2009). Paradoxically, early deprivation also enhances an animal's responsiveness to natural or conditioned cues associated with a primary reward (Lomanowska et al., 2011; Lomanowska & Kraemer, 2014). Thus, early experiences affect reward processing and executive functioning in animals. These cognitive processes are important to mothering, and therefore offer an indirect neural mechanism by which early experiences affect subsequent maternal behaviour in rats.

We believe a similar set of relations applies to human mothers. After giving birth, mothers are more attracted to infant odours and more sympathetic to infant cries than are non-mothers, and the extent of sympathy or attraction is associated with mothers' expressed maternal behaviour and their heart-rate and cortisol responses to those cues (Fleming et al., 1993; Fleming, Steiner, & Corter, 1997; Giardino, Gonzalez, Steiner, & Fleming, 2008; Porter, Cernoch, & McLaughlin, 1983; Porter, Makin, Davis, & Christensen, 1991; Stallings, Fleming, Corter, Worthman, & Steiner, 2001). Infant sensory cues are inherently rewarding to human mothers (Lonstein et al., 2015). They activate regions of the adult brain that are associated with reward and pleasure [e.g. (Kringelbach, 2008)]. Moreover, infant cues can grab and/or disrupt adult attention (Dudek, Faress, Bornstein, & Haley, 2016), depending on the valence of these cues.

Moreover, experience with salient infant cues enhances maternal attention to these cues, as illustrated in studies that examined attentional capture or bias by infant and adult faces in women during late pregnancy (Pearson, Lightman, & Evans, 2011). Mothers were much less able to disengage from a distressed infant face than from a non-distressed infant face, in order to attend to a neutral stimulus in the periphery. This differential maternal attention to distressed faces was related to

later maternal self-reported postpartum bonding with the infant. Also, a study of event-related potential (ERP) responses to infant cues (Proverbio, Brignone, Matarazzo, Del Zotto, & Zani, 2006) indicated that parents find infant cues more salient and better discriminate between different infant emotional expressions, suggesting heightened attention to infant features.

While too little attention bias to infant cues is clearly problematic for parenting, too much attention bias to infant cues can also interfere with parenting. Mothers who were overly distractible to infant cues and unable to selectively attend to a target task and ignore infant cries have greater insecure maternal attachment history (Haley & Ryan, personal communication, 2016) and less emotion regulation as indexed by reduced control of their autonomic activity (Haley & Jabrayan, personal communication, 2016). Finally, non-parents have been shown to display greater heart-rate reactivity than parents in response to hearing infant cries (Out, Pieper, Bakermans-Kranenburg, & van IJzendoorn, 2010). This, as Pedersen, Huffman, del Carmen, and Bryan (1996) suggested, might be due to the fact that parents perceive infant cries more accurately and can better select an appropriate response to infant cries (Pedersen et al., 1996). In general, parents have had more experience with infant cries than have non-parents and hence may simply be habituated to their effects. Taken together, mothers showing moderate attention biases to infant cues—rather than too little or too much—exercise greater cognitive flexibility and selective attention, which may enhance parenting experiences and parenting adequacy. Both experience and underlying biological factors are likely to shape individual differences in these attention biases.

Early experiences of adversity likely affects human mothers' attraction to infants and their reinforcing value, although this has not been specifically addressed (summarized in Afonso, Grella, Chatterjee, & Fleming, 2008; Barrett & Fleming, 2011). Correlational behavioural and imaging studies suggest that early adversity affects reward processing (Boecker et al., 2014; Pechtel & Pizzagalli, 2011). Furthermore, indirect evidence is mounting that early experiences with parenting influence brain development and behaviour in the child. For instance, child neglect and institutionalized rearing is associated with later-life difficulties of inhibitory control that may reflect altered attribution of salience to external stimuli (Brett et al., 2015). Even less severe early negative experiences, such as harsh parenting and low maternal sensitivity, have been associated with decreased inhibitory control in children (Lucassen et al., 2015).

Early neglect or adversity also appears to have neurological consequences for children. For instance, early maltreatment is associated with reductions in hippocampal volume (Riem, Alink, Out, Van IJzendoorn, & Bakermans-Kranenburg, 2015), whereas more sensitive parenting is associated with larger grey matter volume (i.e. neuronal density), and total brain volume (Kok et al., 2015). Positive maternal behaviour in early childhood is also associated with an attenuated growth of the amygdala of adolescents (Whittle et al., 2014). Such attenuation (e.g. reduced hippocampal volume) might relate to decreased emotional reactivity, though further research is needed to implicate this in a cross-generational effect on subsequent parenting. In general, however, if early experience-associated changes in brain

morphology and executive functioning persist into adulthood, they are likely to have effects on parenting.

Genetic and Physiological Mediators of Mothering

Early experiences and environmental influences affect the quality of exhibited mothering, and yet not all mothers respond in the same way to these environmental influences. Mothers vary in their susceptibility to environmental effects, possibly owing at least in part to mothers' genetic profiles. Some genetic variants might make individuals more susceptible to specific types of environmental input, and there is a growing literature on this topic. A caveat to this research is that studies have been mostly correlational and associations between a genetic variant and an environmental susceptibility are modest at best. Since human maternal responsiveness is a highly complex phenotype, it is unlikely scientists will find individual genetic variants with large influences on such phenotypes. Effects are likely to be small, polygenic, and involve numerous, ongoing, interactions with environmental factors. The search for candidate genes associated with human parenting has centred on three key neurotransmitter/neuropeptide systems (Mileva-Seitz, Bakermans-Kranenburg, & van IJzendoorn, 2015): dopamine, oxytocin, and serotonin. Because of their clear involvement regulating animal parental responsiveness and processing of infant cues, the following discussion focuses on the first two: dopamine and oxytocin.

Dopamine and Mothering

Dopamine is a major catecholaminergic neurotransmitter implicated in reward, mood, attention, and mothering, at least in non-humans. Dopamine reflects and enhances the rewarding properties or salience of stimuli. Depending on an animal's 'motivational' state, relevant stimuli are food (to the hungry animal), a sexually experienced male (for an oestrous female), or pups (for a new mother) (Afonso et al., 2008, 2009; Afonso, King, Novakov, Burton, & Fleming, 2011; Berridge & Robinson, 1998). In the new mother rat, progesterone and oestrogen suppress baseline activity of the dopamine system in the nucleus accumbens (NA); in hormonally primed non-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 (Afonso et al., 2011). Therefore, the 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).

Rat dams exhibit individual differences in levels of dopamine release into the nucleus accumbens (e.g. high-lickers and groomers have greater dopamine release than low-lickers and groomers; Champagne et al., 2004). Postpartum females have

naturally suppressed dopamine baseline levels, but these levels increase significantly when they are exposed to pups (Afonso et al., 2009), or following reunion with pups after a separation (Hansen, Bergvall, & Nyiredi, 1993). Pups are so rewarding that new rat mothers prefer pups to cocaine until about day eight postpartum (Mattson, Williams, Rosenblatt, & Morrell, 2001). Even cycling (non-postpartum) females, who normally avoid pups, when exposed to pups show dopamine increases proportional to their prior pup exposure (Afonso et al., 2008).

In addition to looking at dopamine levels associated with mothering, there is substantial evidence that dopamine receptors which determine the sensitivity of the brain to the dopamine that is released also change in the new mother, and that in different sites different receptors are activated. For instance, the expression of dopamine receptor genes D1 and D2 (DRD1 and DRD2, respectively) is up-regulated during pregnancy in the rat (Mann, 2014), and dopamine receptor D4 (DRD4) and dopamine transporter (DAT1) mRNA increase in the medial pre-optic area following pup exposure, regardless of maternal parity (Akbari et al., 2013). This evidence implies that dopamine, known to be implicated in stimulus salience and 'reward', is one of the major neurotransmitters involved in rat maternal regulation.

Rat pups might be partially responsible for the onset and ongoing maintenance of maternal behaviour (Rosenblatt, 1967), via stimulation of gene expression in the mother. Natural bursts of dopamine-firing neurons in the mammalian striatum are said to be key for the pup-regulated aspects of maternal care (i.e. maternal care in response to pup-cues) (Robinson, Zitzman, & Williams, 2011). Other rodent models provide additional evidence for the dopamine-mothering link. In hypodopaminergic mice (genetically engineered to express less dopamine), striatal dopamine is key for 'active' maternal behaviours such as pup-retrieval and liking/grooming of pups, but not for 'passive' behaviours such as nursing (Henschen, Palmiter, & Darvas, 2013). In voles, the dopamine antagonist haloperidol has similar effects on parenting behaviour as in rats, reducing 'active' components of maternal behaviour (e.g. duration of licking), although species-specific differences in the effects can be seen (Lonstein, 2002).

Much of these natural variations in rodent dopamine levels are not clearly associated with underlying genotypes, suggesting that genetic association studies may not be useful. However, in humans, genetic association studies offer one of the only ways to study natural variation in dopamine levels. This is because the invasive procedures used in animal research (e.g. extraction of region-specific brain tissue for genetic expression analyses) are not possible in humans. Human studies rely mostly on the genotyping of specifics genes or gene loci to determine whether genetic variation is associated with differences in behavioural phenotypes.

Other ways to study possible relationships between genetic factors and parental behaviour in humans are by using brain imaging studies. Functional magnetic resonance imaging (fMRI) studies in which mothers were exposed to infant vocalizations (Lorberbaum et al., 2002; Sander, Frome, & Scheich, 2007; Seifritz et al., 2003), pictures (Barrett et al., 2011; Bartels & Zeki, 2004; Leibenluft, Gobbini, Harrison, & Haxby, 2004; Nitschke et al., 2004; Strathearn, Li, Fonagy, &

Montague, 2008), or video fragments (Noriuchi, Kikuchi, & Senoo, 2008; Ranote et al., 2004), report activation of either dopaminergic regions, or regions that directly interact with dopaminergic regions (Georges & Aston-Jones, 2002). Candidate gene studies have explored dopamine genetic polymorphisms in association with human parenting. Genetic polymorphisms in DRD1, DRD2, DRD4, COMT (coding for catechol-*O*-methyltransferase, a dopamine deactivating enzyme), and DAT1 have all been associated with differences in maternal behaviours, including sensitivity and vocalizing (Lee et al., 2008; Mileva-Seitz, Fleming, et al., 2012; van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008). Not all studies find significant associations, however. Mills-Koonce et al. (2007) reported no significant association between maternal genotype at a dopamine-related polymorphism on the gene ANKK1 and observed maternal sensitivity. These studies used observed measures of parenting, which is a significant strength because they represent a more objective and unbiased assessment of parental behaviour than can be obtained by parental self-report questionnaires (the alternate method for assessing parenting differences). Yet further replication is crucial before the role of dopamine gene polymorphisms in human maternal behaviour is clear.

A central limitation to the molecular genetic studies of parenting is the indirect way in which genotype is used as a proxy of actual gene expression in the brain, and this is particularly so for genotypes that have no known functional significance (i.e. genotypes that are not readily linked with up- or down-regulation of gene expression). Another limitation is that genetic variants interact with non-genetic factors (e.g. early rearing history) in ways that are not yet fully understood. This limits the ability to detect main effects of genotype alone. Furthermore, there is ongoing discussion whether main effects of higher order interactive effects are, in fact, more plausible. Given relatively small sample sizes, particularly when it comes to human behavioural studies, it is an added challenge to find these interactive effects in the first place. The future of parenting research will likely see small strides towards elucidating these important but complex mechanisms.

Oxytocin/Vasopressin and Mothering

In many non-primate mammalian species, the nine-amino-acid peptide oxytocin is key to regulating the onset of maternal behaviour (Fahrbach, Morrell, & Pfaff, 1985; Kendrick, 2000; Numan, 2015; Pedersen, Caldwell, Walker, Ayers, & Mason, 1994). Individual differences in centrally inducible oxytocin receptors predict rat maternal behaviour (Champagne, Diorio, Sharma, & Meaney, 2001). Oxytocin might also mediate maternal behaviour in rat dams indirectly by modulating anxiety levels, which in turn affect maternal behaviour (Bosch, 2010). In sheep, oxytocin administration results in maternal behaviour towards foreign lambs (Keverne & Kendrick, 1992) and decreases aggression and aversion to newborn

lambs (Insel & Young, 2001). In oxytocin receptor knockout mice, maternal behaviour is impaired (Takayanagi et al., 2005).

In primates, oxytocin is not essential for the establishment of maternal care, but is associated with post-parturition bonding and maternal behaviour (Broad, Curley, & Keverne, 2006; Saltzman & Maestripieri, 2010). Pregnancy hormones prime the mesolimbic dopamine projections to the NA and up-regulate oxytocin receptors in the brain. These modulations of the reward system facilitate mother–infant bonds at birth (Broad et al., 2006). Additionally, peripheral administration of an oxytocin receptor blocker in rhesus macaques reduces interest in the infant (e.g. lip-smacking, approaching, touching) (Boccia, Goursaud, Bachevalier, Anderson, & Pedersen, 2007). Whereas cerebrospinal (hence, 'central') levels of oxytocin in multiparous rhesus macaque females do not correlate with mother–infant interaction (Cooke et al., 1997), *plasma* (hence, peripheral) levels of oxytocin are highly correlated with 'maternal warmth' (Maestripieri, Hoffman, Anderson, Carter, & Higley, 2009).

The evidence in primates points to the numerous functions of oxytocin, and the complex regulation mechanisms that peripheral versus central oxytocin might be involved in. However, as is true of many of the other maternal hormones, oxytocin enhances responsiveness but it does not cause it, and in many instances maternal behaviour will be exhibited in the absence of the polypeptide. If virgin female rats are administered progesterone followed by oestrogen in a series of silastic capsules, they will exhibit maternal behaviour to foster pups without the addition of oxytocin —and in the rat, oxytocin will not affect maternal behaviour onset without prior oestrogen priming (see reviews by Bridges, 2016; Lonstein et al., 2015).

Turning to humans, increased plasma oxytocin from early to mid-late pregnancy correlates with higher scores on ratings of attachment to the foetus (Levine, Zagoory-Sharon, Feldman, & Weller, 2007), indicating the important role of oxytocin for bonding even before birth. Maternal and infant salivary oxytocin levels are correlated with each other and with mother–infant affect synchrony (Feldman, Gordon, & Zagoory-Sharon, 2010), and high levels of plasma oxytocin predict high levels of affectionate touch towards infants (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010). Increased oxytocin levels are found in mothers who recently touched or interacted with their infants (Light et al., 2000). Oxytocin is thus important in human parenting (Galbally, Lewis, van IJzendoorn, & Permezel, 2011), not purely during parturition and breastfeeding but during the expression of behavioural and attachment responses to infants. However, oxytocin has a multiple-site release, many functions, and a diurnal rhythm in the cerebrospinal fluid but not peripherally (Amico, Tenicela, Johnston, & Robinson, 1983), making it difficult to accurately measure. Since it does not cross the blood–brain barrier in adults (Saltzman & Maestripieri, 2010), plasma and cerebrospinal fluid levels may not be identical, although they are highly correlated (Carson et al., 2014). Again, this makes research with oxytocin genotypes challenging, as a simple DNA sequence along oxytocin-related genes does not necessarily indicate whether central or peripheral gene expression is associated with this genotype, and how this might relate to parenting.

Candidate gene studies of oxytocin in humans have shown significant association between polymorphic variants and parental behaviour. For instance, the rs53576 polymorphism on the oxytocin receptor gene (OXTR) is associated with parental sensitive responsiveness (Bakermans-Kranenburg & van IJzendoorn, 2008), maternal warmth (Klahr, Klump, & Burt, 2014), positive parenting, and neural activation of brain regions previously associated with positive parenting (Michalska et al., 2014). This polymorphism is also associated with differences in maternal cardiac reactivity to infant cries, moderated by maternal depressive symptoms (Riem, Pieper, Out, Bakermans-Kranenburg, & van IJzendoorn, 2011). However, although this polymorphism might influence oxytocin function (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011) and to represent an important direction in parenting research (Taylor, 2008), a meta-analysis of 48 studies (N = 17,559) found no significant effect for five domains of outcomes (biology, personality, social behaviour, psychopathology, and autism) (Bakermans-Kranenburg & van IJzendoorn, 2014). This further emphasizes the limitation of using genetic polymorphisms with unclear functional significance in human candidate gene studies.

Other single nucleotide polymorphisms (SNPs) in OXTR-related genes have also been explored in relation to differences in human parenting. For instance, parents with the CD38 CC genotype and the OXTR rs1042778 TT genotype touched their infants less frequently than parents with other genotypes (Feldman et al., 2012). CD38 regulates oxytocin release and is related to autism spectrum disorders (Munesue et al., 2010). Mice-knockouts for the CD38 gene exhibit reduced oxytocin levels and deficits in social and maternal behaviour (Jin et al., 2007), suggesting some possible function for these in human parenting. Another study showed that two SNPs in the oxytocin peptide-coding gene (OXT rs2740210 and OXT rs4813627) were significantly associated with differences in maternal vocalizing to the infant, but not maternal 'sensitivity' (Mileva-Seitz et al., 2013). That SNPs associate with some but not other maternal behaviour outcomes could indicate that the multiple dimensions of parental behaviour have differential genetic regulation. It also highlights the measurement issues inherent in complex behavioural research (such as parenting). 'Parenting' can be sliced in multiple ways, but the discriminant validity of specific parenting dimensions is often less than clear.

Finally, polymorphic variation in the vasopressin receptor 1A gene associates with differences in maternal sensitivity (Bisceglia et al., 2012) and maternal structuring and support (Avinun, Ebstein, & Knafo, 2012). Vasopressin has structural similarity to oxytocin and evidence suggests it is involved in the regulation of social behaviour (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012; Heinrichs & Domes, 2008; Meyer-Lindenberg et al., 2011), so it is another potential system for candidate gene studies. However, the lack of knowledge about the function of many of these SNPs limits the conclusions that can be drawn. Replications and functional studies of oxytocin and vasopressin genes are necessary. One approach is to use candidate genes/alleles only if their function in cell or cellular networks is

known. However, this too, has the potential to bias our genetic research to specific known genetic polymorphisms. Thus, a combination approach would be most productive. For instance, a hypothesis-generating genome-wide association (GWA) approach might first be used to identify genetic loci that have not been obvious candidates from a functional perspective alone. Later, these regions could be more carefully probed in observational studies of parenting.

Furthermore, some of these studies provide suggestive evidence for a moderating role of the environment (e.g. Mileva-Seitz et al., 2011; van IJzendoorn et al., 2008). Gene–environment interplay is likely to involve multiple genes and multiple environmental conditions, and we are only beginning to understanding these complex effects. Gene–environment interactions and correlations may explain why parents are differentially affected by their experiences, by their early life, and by their current stressors. Studies of gene–environment interplay have grown substantially in number over recent years (Fortuna et al., 2011), increasingly supporting the *for better and for worse* paradigm of differential susceptibility. For instance, in a large cohort of American children (Lee, Brooks-Gunn, McLanahan, Notterman, & Garfinkel, 2013), mothers with one genetic variant on the ANKK1 gene—related to DRD2 function—exhibited differential susceptibility: for them, harsh parenting increased as macroeconomic conditions worsened but decreased as conditions improved. For mothers with the alternate genetic variant, harsh parenting was not related to changes in macroeconomic conditions.

A working hypothesis emerging from these studies is that under conditions of stress, parents carrying differential susceptibility alleles are among the less parentally sensitive parents (i.e. exhibiting less optimal parental behaviours), whereas under conditions of no stress, they are among the more sensitive parents (i.e. exhibiting more optimal parental behaviours). Additional support for this comes from studies indicating that the short allele on the serotonin transporter polymorphism (5HTTLPR) is associated with greater maternal sensitivity (Cents et al., 2014; Mileva-Seitz et al., 2011). This is an allele that unpublished work of ours suggests is also related to greater rates of depressive symptoms in these same, more sensitive mothers. Thus, mothers with this allele might not only be more likely to be influenced by more adverse experiences, but also might generally be more responsive to ongoing environmental input, of which the new infant forms a large proportion in the early postpartum period. In other words, a mother who is more emotionally labile or susceptible might also be *able,* under optimal conditions, to respond better to their infants.

From an evolutionary perspective, maintaining a diverse gene pool has allowed for some phenotypes that are able to cope with greater stress (the less susceptible parents) and whose behaviour is not greatly affected by the environment, and for other phenotypes that are highly reactive to ongoing environmental stimuli and whose behaviour might suffer as a result of high stress, but benefit as a result of low stress. With historical fluctuations in the levels of environmental stress (e.g. famines, war, drought), the maintenance of a full range of genotypes might have been facilitated. At any given slice in history, however, some phenotypes might be

more advantageous than others. Of course, this thinking is highly simplified and speculative. Much more work is required in this domain.

Epigenetic Effects on Mothering

If environmental interactions with genetic polymorphisms are codified, and they are passed across generations as well, how does this occur? Current theoretical and empirical evidence implicates 'epigenetic' mechanisms, an umbrella term covering processes by which the environment interfaces with, and changes the influence of, underlying genetic variants without altering those variants.

Complex epigenetic processes regulate gene expression in response to environmental input (Brookes & Shi, 2014; Kundakovic & Champagne, 2014; Meaney, 2010). In rats, licking/grooming and arch-back nursing can alter pup methylation patterns and gene expression and can be passed on to the pup's pups (e.g. Meaney, 2010; Szyf, Weaver, Champagne, Diorio, & Meaney, 2005). Thus, epigenetic changes can be acquired through experience and/or inherited (Meaney, 2010). Differential methylation of the glucocorticoid receptor (GR) gene as a result of early experience induces long-term changes in response to stress that span into the next generation (Weaver et al., 2004; Zhang & Meaney, 2010; Zhang, Labonté, Wen, Turecki, & Meaney, 2013). The first epigenetic study on human behavioural development showed GR gene expression in the hippocampus of suicide victims was decreased only in the group who had experienced child abuse (McGowan, Sasaki, & D'Alessio, 2009). Similar epigenetic changes have been found as a result of child maltreatment (Perroud et al., 2014) or structural neglect in orphanages (Naumova et al., 2012).

Aside from the involvement of direct DNA information carried by gametes, there are multiple suggested transmission mechanisms, including for example hormones, cytokines, and microorganisms (Toth, 2015). Mileva-Seitz et al. (2015) outlined a mediated moderation model of intergenerational transmission of parental behaviour. In this model, abusive grandparental behaviour might alter methylation patterns of multiple candidate genes of interest in the offspring, leading to altered parental behaviour set-points, and this behavioural system might be further moderated by existing genotypes in parental susceptibility genes, and existing environments, to affect the third generation.

The fact that there might be potential effects on several generations arising as a result of environmental or behavioural exposures in the first generation, presents a set of interesting challenges for the study of intergenerational transmission of parental behaviour. Moreover, it has consequences for interventions and policy-building. We feel that we are yet at too early of a stage to directly apply this epigenetic research and reasoning towards clinical implementations, but it is an exciting area of research that is rapidly gaining momentum. Large-scale human behavioural studies are beginning to examine epigenome-wide methylation differences and patterns within populations, with the potential to identify previously

unknown loci of interest that can in turn regulate the genetic variants we have been studying for years, and other, new genetic variants that genome-wide association studies are providing. There has arguably never been a more exciting time to be in parenting research.

Future Directions

'Human parenting' is in fact clusters of behaviours with underlying motivational, physiological, genetic, epigenetic, and environmental interactants. Parenting behaviours exhibit variation over time and place and culture (see Cassells & Evans, Chap. 2 this volume; Nomaguchi & Milkie, Chap. 3 this volume; Mileva-Seitz, Afonso, & Fleming, 2012; Mileva-Seitz & Fleming, 2011). To study the underlying mechanisms of transmission of such behaviours, we suggest it would be best to adopt a multi-pronged approach. On the one hand, we should continue to explore how broad parenting concepts (e.g. maternal 'sensitivity') are shaped by experience and biology. On the other hand, we ought to also dissect the broader phenotypes of parenting into smaller, discrete behavioural components. In animal research, this approach has been fruitful: the use of micro-behavioural analysis, quantifying exact behaviours and their durations, frequencies, and contingencies, has helped untangle some of the complexity. The smaller components of parenting might have more direct biological or environmental underpinnings.

Future research should also analyze interactions *between* multiple levels of influence: genetic, epigenetic, and environmental. Individuals with more environmentally 'susceptible' genotypes might have different epigenetic profiles, and we are only scratching the surface of these interactions to peek into the shaping of parental behaviour over time and place. Prenatal effects—which have been argued to constitute a form of early parenting (Mileva-Seitz et al., 2015)—must also be explored. The choices mothers make and behaviours they perform while pregnant might be just as important to the growing foetus, as the behaviours following birth. We recently showed that there are no large effects of prenatal maternal stress exposure on neonatal DNA methylation profiles (Rijlaarsdam et al., 2016), but these efforts require replication before we can dismiss prenatal stress as inconsequential.

Finally, it would be highly beneficial to peer into the parental brain. The field so far has used brain imaging and molecular genetics studies of genes thought to be expressed in the brain. Future techniques which allow a more direct view of the human parental brain—and genes expressed in different neural regions—would be the ultimate approach to understanding parental behaviour. Animal studies have a lot to offer, as they permit the use of invasive techniques to map and monitor gene expression in the brain. However, there are limits to the amount of extrapolation we can and ought to do from non-human to human parenting, imparted by the greater

complexity of human parenting behaviour and cortical organization (Lonstein et al., 2015).[1]

The many changes that new parenthood entails often bring about a large amount of stress. Parental ability to cope with stress is likely codified at multiple levels, from the genetic to the epigenetic. The expression of parental behaviour during stressful times is a hugely important predictor for children's well-being. Parenting scientists are only beginning to explore the mechanisms by which stress interacts with the biology of the parent to shape their behaviour (see Neuenschwander & Oberlander, Chap. 6 this volume; Crnic & Ross, Chap. 11 this volume). As far as impactful implications, we ought to focus on research that can give rise to predictable and replicable intervention strategies for those most at risk. From a research perspective, we are a long way from understanding the complexities of the systems that help shape parental behaviour, but we have made great strides by considering both animal and human research and tackling them both at multiple levels of influence, from the genetic to the behavioural.

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[1]Sections of the present chapter are based on Lonstein et al. (2015) and on Lomanowska et al. (2016), in which neural and molecular (non-genetic) mechanisms of early adversity and maternal behaviour are further explored.

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