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Genetic mechanisms of parenting

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ABSTRACT

This article is part of a Special Issue "Parental Care".

The complexities of parenting behavior in humans have been studied for decades. Only recently did we begin to probe the genetic and epigenetic mechanisms underlying these complexities. Much of the research in this field continues to be informed by animal studies, where genetic manipulations and invasive tools allow to peek into and directly observe the brain during the expression of maternal behavior. In humans, studies of adult twins who are parents can suggest dimensions of parenting that might be more amenable to a genetic influence. Candidate gene studies can test specific genes in association with parental behavior based on prior knowledge of those genes' function. Gene-by-environment interactions of a specific kind indicating differential susceptibility to the environment might explain why some parents are more resilient and others are more vulnerable to stressful life events. Epigenetic studies can provide the bridge often necessary to explain why some individuals behave differently from others despite common genetic influences. There is a much-needed expansion in parenting research to include not only mothers as the focus—as has been the case almost exclusively to date—but also fathers, grandparents, and other caregivers.

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Introduction: Mammalian mothering and its multiple influences

Colloquial references to a 'maternal instinct' or a 'maternal drive' are common and reveal a general presupposition about mothers: that there are innate rules shaped by the long course of evolutionary history and hardwired into the DNA, which drive all mothers to respond to, nurture, and protect their offspring (Rosenblatt, 1967). The focus of this review is to explore the current evidence of such a genetic component to mothering.

The evidence for intergenerational transmission of parental behavior is clear: mothering begets mothering (Fleming et al., 2002). Both positive and negative aspects of early experience being parented tend to be repeated by the next generation, in humans and animals alike (Belsky et al., 1989, 2005; Capaldi et al., 2003; Chen and Kaplan, 2001; Chen et al., 2008; Gonzalez et al., 2001; Kovan et al., 2009; Maestripieri, 2005; Maestripieri et al., 2007; Newcomb and Locke, 2001; Suomi, 1999; van IJzendoorn, 1992). Just how these behaviors are transmitted across generations is as yet unclear. Does the transmission stem from underlying similarities in genetic code, or are behaviors repeated because environments are similar? The short answer based on the evidence to date is: neither, and both.

Complex biological organisms function at the interface between their genetic programming and the environment in which they dwell. Myriad contextual or 'external' influences shape mothering, and much work has been done in this area. A smaller but growing number of studies have examined the heritable components of mothering and peered deeper at the molecular level of genetic variation to ask how DNA might shape parenting. Finally, we are beginning to understand the bridge between environmental and genetic influences: epigenetic changes. Epigenetic changes are more or less stable modifications of gene regulatory machinery occurring *outside* the level of DNA sequences. They might be the bridge or "physical point of connection" (Boyce and Kobor, 2015) between genes and environment that can account for some portion of the behavioral plasticity we see across an individual's development. For instance, early neglect and abuse tends to be repeated in the new generation, but not for everyone. Only about 30–40% of mothers who were abused as children go on to abuse their own children (Kaufman and Zigler, 1987; Sroufe et al., 2005), and the complex associations between early life abuse and later abuse toward one's own children might be in part owing to differential epigenetic changes. The epigenome represents a way to introduce plasticity in behavior, via plasticity in the expression of genetic products, despite the underlying stability of structural DNA.

The mammalian order presents species with vast differences in the types and quantities of parental care, from the simple licking and grooming behavior of the mother rat to the highly complex parenting behavior of humans. This review is aimed at the genetic underpinnings

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of *human* mothering, but we will provide multiple examples from other mammalian species used in parenting research (e.g., rats, sheep, voles, monkeys). Even though there are basic features in human parenting—including the provision of caretaking, ambulation, and feeding—we see much fine-tuning or variation according to cultural or environmental pressures (Bornstein, 1989; Bornstein et al., 1992, 2007; Harwood et al., 1999; Keller, 2004; Quinlan, 2007; Trehub et al., 1993). For instance, mothers around the globe engage in face-to-face communication, infant body contact/stimulation, and primary care (e.g. nursing) (Mesman et al., 2012; Mileva-Seitz and Fleming, 2011). Yet mothers can differ in their perception and processing of infant cues, and in their motivation to attend to them (Barrett and Fleming, 2011; Leavitt, 1998, 1999; Mileva-Seitz and Fleming, 2011; Mileva-Seitz et al., 2012a). When looking for genetic underpinnings of parental behavior it might be helpful to start at the systems that regulate these perceptual and motivational processes in the brain. In the present review, we will consider studies of three broad dimensions of 'parenting': (1) macro-analytic parental behaviors, such as the more global scales of *quality* of parental interactions (e.g., sensitivity and warmth); (2) micro-analytic parental behaviors, such as the *quantity* (duration, frequencies) of discrete parental behaviors (e.g. frequency of touch, orienting away from the infant); and (3) prenatal parenting effects, such as the nutritional and hormonal prenatal environment a fetus is exposed to. Before turning to specific genes of interest in parenting, we review the evidence for a heritable component of parenting.

The early evidence for heritability in parenting: Behavioral genetics

The original way to explore genetic effects on human behavior was through the use of 'behavioral genetics' studies, which employ multiple types of families including twins and adoptive vs. biological siblings. In twin studies, genetic contributions to behavior are inferred from quantification of behavioral differences between monozygotic (MZ) and dizygotic (DZ) twins. MZ and DZ twins differ in their genetic similarity. The environment is shared when it makes them more similar to one another, and unique or non-shared when it makes them more different. Behavioral genetics makes it possible to differentiate between the contribution of these three components—genetics, shared, and non-shared environment—to a behavior or trait. Examining the heritability of parenting, researchers have made use of twin studies that allow for comparison of parenting behavior between adult parent twin-pairs (parent-based in contrast to child-based designs, see Bakermans-Kranenburg and Van IJzendoorn, *in press*). Six parent-based behavioral genetic studies that addressed the heritability of different dimensions of parenting were meta-analyzed (Klahr and Burt, 2014). Non-shared influences (experiences that are unique for each sibling) including measurement error accounted for 63–90% of the variance in parenting. For parental control the combined genetic estimate was zero, whereas the combined genetic estimates for warmth and negativity were around 30% (Klahr and Burt, 2014). Twin studies however do not reveal the genetic mechanisms underlying variation in phenotypes. A second approach—the exploration of genetic variance at the molecular level of the DNA—is therefore a useful and timely complement to behavioral genetics efforts to gain a fuller understanding of genetic mechanisms in parenting.

Molecular genetics, candidate genes

Molecular genetic studies in humans examine particular DNA sequences that might be associated with traits of interest. Human maternal responsiveness might be influenced by large networks of interacting genes, in addition to the plethora of environmental influences. Given such complexity and the sheer volume of potential candidates for gene analysis, prior knowledge about function—of the genes, proteins, and associated biochemical networks resulting from the genes of interest—helps to narrow down the candidate genes. This is the 'hypothesis driven' or 'mechanistic' approach (Dalziel et al., 2009; Tabor et al., 2002). In accordance with this, genetic factors that regulate key brain systems related to perceptual and motivational processes are likely to also influence maternal behavior. The search for candidate genes associated with human parenting has centered on three key neurotransmitter systems (Bakermans-Kranenburg and van IJzendoorn, *in press*) to which we turn next: dopamine, oxytocin, and serotonin.

Dopamine

Dopamine has a crucial role in regulating maternal care in rats. This role can be better understood by considering the neural circuitry of the maternal rat. This circuit consists of several major regions: the medial preoptic area (MPOA), the ventral bed nucleus of the stria terminalis (vBST), the nucleus accumbens (NA) and the medial and cortical amygdala (MCA) (Numan, 2015). These regions either directly receive dopaminergic innervation, or interact with other regions of the brain that are under dopaminergic control. For instance, the MPOA stimulates dopaminergic neurons via the ventral tegmental area to the NA, which increases maternal responsiveness to pup stimuli (Numan, 2006). In virgin rats, electrical or hormonal stimulation of the MPOA/vBST induces maternal behavior (Numan et al., 2006), as does the application of dopamine receptor agonists into the NA (Numan et al., 2005). Conversely, lesions or the administration of dopamine receptor antagonists either systemically or in the MPOA, VTA, and NA *reduce* the naturally rewarding properties of pups in maternal rats (Lee et al., 2000), disrupt normal maternal behaviors (e.g. pup approach and pup retrieval) (Byrnes et al., 2002; Hansen et al., 1991; Keer and Stern, 1999; Li and Fleming, 2003a,b; Li et al., 2004, 2005; Numan et al., 2005; Parada et al., 2008), and block the consolidation of postpartum maternal experiences (Li and Fleming, 2003a,b).

There are also natural differences between rat dams in the levels of dopamine release into the NA: Those who are considered high-lickers and groomers have a greater dopamine release than those who have low levels of pup licking and grooming (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 et al., 1993). Pups are so rewarding that new rat mothers prefer pups to cocaine until about day 8 postpartum (Mattson et al., 2001). Even cycling (non-postpartum) females, for whom avoidance is the typical response to pups, show a dopamine increase when exposed to pups that is proportional to their prior pup exposure (Afonso et al., 2008). At the genetic level, early evidence suggests that expression of dopamine receptor genes D1 (DRD1) and D2 (DRD2) is upregulated during pregnancy in the rat (Mann, 2014). Furthermore, there is upregulated expression of dopamine receptor D4 (DRD4) and dopamine transporter DAT1 mRNA in the MPOA following pup exposure, regardless of maternal parity (Akbari et al., 2013). Taken together, this evidence suggests a strong role of dopamine in rat maternal regulation. As Rosenblatt (1967) already shown, pups may be partially responsible for the onset and ongoing maintenance of maternal behavior, and the mechanism might be the stimulation of gene expression in the mother. Natural bursts of dopamine firing neurons in the mammalian striatum are said to be crucial for the pup-regulated aspects of maternal care (i.e. maternal care in response to pup-cues) (Robinson et al., 2011). However, individual differences in dopamine gene function unrelated to pup cues (e.g., from early rearing effects or underlying genetic variation) might predict individual differences in maternal behavior. Other rodent models have provided evidence for the dopamine-mothering link. For instance, an interesting study of hypodopaminergic mice (mice genetically engineered to express less dopamine) indicated that striatal dopamine is crucial for 'active' maternal behaviors such as pup-retrieval and liking/grooming of pups, and not for 'passive' behaviors such as nursing (Henschen et al., 2013). In voles, the effects of a dopamine antagonist (haloperidol) had similar effects on parenting behavior as are found in rats, generally reducing 'active' components of maternal

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