Neurogenetics of Aggressive Behavior: Studies in Primates

Christina S. Barr and Carlos Driscoll

Abstract Aggressive behavior can have adaptive value in certain environmental contexts, but when extreme or executed inappropriately, can also lead to maladaptive outcomes. Neurogenetic studies performed in nonhuman primates have shown that genetic variation that impacts reward sensitivity, impulsivity, and anxiety can contribute to individual differences in aggressive behavior. Genetic polymorphisms in the coding or promoter regions of the Mu-Opioid Receptor (*OPRM1*), Corticotropin Releasing Hormone (*CRH*), Monoamine Oxidase A (*MAOA*), Dopamine D4 Receptor (*DRD4*), and Serotonin Transporter (*SLC6A4*) genes have been shown to be functionally similar in humans and rhesus macaques and have been demonstrated to contribute to individual differences in aggression. This body of literature suggests mechanisms by which genetic variation that promotes aggressivity could simultaneously increase evolutionary success while making modern humans more vulnerable to psychopathology.

Keywords primate · aggression · genetic · G x E · macaque

Contents

C. S. Barr (✉) · C. Driscoll
Section of Comparative Behavioral Genomics, Laboratory of Neurogenetics, NIH/NIAAA, Rockville, MD, USA
e-mail: cbarr@mail.nih.gov

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Aggression is a behavior that can have adaptive value in certain environmental contexts. However, when aggressive behaviors are extreme or if executed out of impulse or in inappropriate contexts, they can also lead to maladaptive outcomes. This chapter aims to present the study of aggressive behavior in nonhuman primates when considered in an evolutionary context, to present the current understanding of neurogenetic systems that contribute to high aggression phenotypes, to discuss G × E interactions, and to translate findings obtained in nonhuman primates to the human condition.

1 Animal Aggression

In many different species, aggression is important for the protection of self and offspring and in the defense and/or acquisition of rank, territory, or resources. It can also be exhibited in response to fear or pain, or in order to execute control over other individuals. Individual and species differences in aggression are observed in both wild and domesticated animals. While aggression in many wild animals, including primates such as the rhesus macaque, commonly plays an adaptive role, among domestic animals aggressive behavior correlates with "wildness" and behavioral problems. Still, even among relatively aggressive species of monkeys, such as rhesus macaques (pictured in Fig. 1), there is a high degree of variation in the expression of aggressive behavior, and these behaviors can be either advantageous or maladaptive, depending on the environmental context. Although human aggressive behavior may originally have been adaptive, excessive and inappropriate aggression is now a feature of many psychiatric disorders, such as borderline personality disorder, antisocial personality disorder, post-traumatic stress disorder, depression, and psychopathy.

In her book *Animals in Translation*, Temple Grandin (2005) describes the different types of aggression exhibited by animals. She argues that there are two types of aggression exhibited across species: predatory aggression and affective (emotional) aggression. Predatory aggression is reward based and involves hard-wired, fixed action patterns. All species of animals have these predatory brain circuits, but some don't engage them. Though the act of stalking and chasing prey engages the reward circuits in the brain, the behavior for the sake of reward rather

Fig. 1 Rhesus macaques *(Macaca mulatta)* in their social group on the island of Cayo Santiago. Rhesus macaques have been shown to be useful for the study of mother–infant behavior, stress reactivity, and, notably, the neurogenetics of behavior. These studies have had translational value for understanding the genetics of neuropsychiatric disorders and aggression. Photo taken by C. Barr

than for food must be inhibited among wild animals because the act of chasing can be energetically costly. Among domesticated animals, there is no need to inhibit the drive to engage in this type of rewarding behavior because they are generally provisioned; the cat can chase the laser pointer beam, and the dog can chase his own tail. Unlike predatory aggression, affective/emotional aggression is reactive rather than rewarding in nature. Examples of emotional aggression include assertive aggression, fear aggression, maternal aggression, irritable aggression, and inter-male aggression. When excessive or inappropriate, both predatory and affective aggression can potentially become pathological.

As stated above, Dr. Grandin describes predatory aggression as being a behavior that involves fixed action patterns that are hardwired. However, it is known that animals are also capable of learned aggression. The more complex the prefrontal cortices are among individuals of a given species, the more likely they are to exhibit learned aggressive behavior. In other words, more complex animals may be able to imitate aggressive behavior or learn that aggression can lead to a desired outcome in a given situation. While a lizard might only exhibit fixed action pattern-based aggression, animals such as canids, felids, and equids might be more capable of learned aggressive behavior, and may also show an increased incidence of planned or organized aggression. Adolescent male killer whales have been known to kill for sport, and dolphins will engage in gang-rapes and will mass murder porpoises despite the fact that they are nonthreatening and do not compete for resources. Goodall (1968) described what she referred to as “mini wars” among the chimpanzees she followed in the field. In effect, the more complex the brain, the more severe and organized aggressive behavior becomes. How this pertains to the human condition will be discussed in more detail at the end of this chapter.

2 Genetics of Aggression in Primates

Studies performed in rodents and primates have shown that a number of neurotransmitter systems are consistently involved in the expression of aggressive behavior. Among these are the serotonin, corticotropin-releasing hormone, oxytocin, neuropeptide Y, and endogenous opioid systems (Takahashi et al. 2012). Of relevance to the human condition, there may be functional genetic variations modulating these systems to promote aggression and violence. The aggression-related traits discussed in the previous section have been shown to be heritable in nature. Studies have shown that both anxious and impulsive behaviors are heritable in vervet monkeys (Fairbanks 2004), and others show anxiety to be heritable in rhesus monkeys (Williamson et al. 2003). Aggressive tendencies have also been shown to be both highly heritable and predictive of reproductive output in rhesus macaques, suggesting that the genetic factors that underlie aggression are likely to impact fitness (Brent 2013). Selection of genetic variants that predict aggression is likely to have had a role in human evolution as well.

Genetic factors that impact aggressivity in rhesus macaques and the mechanisms by which they may promote or moderate aggressive behavior may be predictive of the human condition. What follows is a discussion of some of the key neurogenetic studies that have been performed in the rhesus macaque, showing how genetic factors that may be adaptive in certain contexts can also render individuals more or less sensitive to particular environmental variables, ultimately driving potentially maladaptive responses such as excessive aggression. The chapter will close with a review of the literature presented in terms of how certain genetic variants could simultaneously promote evolutionary success while making modern humans more vulnerable to psychopathology. Interactions between genetic and environmental factors will also be discussed.

2.1 Reward Sensitivity and OPRM1 Genotype: Responses to Both Natural and Artificial Rewards

The reward systems are critical to survival and reproduction because they are involved in driving ingestion of food, social interactions, and sexual activity, to name a few. When resources are scarce, these are particularly important, because they also relate to resource acquisition and control, as behaviors that can increase the likelihood of gaining access to limited resources (i.e., aggression) also involve the reward pathways.

One system that is activated in response to both natural and artificial rewards is the endogenous opioid system. In multiple primate species, there are nonsynonymous single-nucleotide polymorphisms (SNPs) in the first exon of the *OPRM1* gene that produce amino acid changes in the ligand-binding domain of the receptor (Miller et al. 2004; Bond et al. 1998). Among these are the A118G SNP in humans

and the C77G SNP in rhesus macaques; early in vitro work showed that both appeared to increase the affinity of the receptor for its endogenous ligand (ß-Endorphin) by approximately threefold. Studies examining intermediate phenotypes likely to be under the control of this receptor (for example, HPA axis activity) also suggest gain-of-function roles for these polymorphisms (Ray and Hutchison 2004; Chong et al. 2006; Barr et al. 2007; Schwandt et al. 2011).

The *OPRM1* SNPs present in humans and rhesus macaques not only predict responses to artificial rewards, such as alcohol, but to natural rewards as well. In rhesus, the 77G allele predicts increased attachment of an infant to its mother, and this is particularly true following repeated periods of maternal separation (Barr et al. 2008a). This finding has also been replicated in a study of human children aged 9–13, in which various measures of attachment to the caregiver were increased as a function of parental inconsistency or unavailability. *OPRM1* genotype predicts individual differences in aggressive behavior in rhesus macaques as well (Miller et al. 2004).

2.2 Impulsivity in a High-Risk Environment—CRH and MAOA

Impulsivity is a trait that is observed in many psychopathological conditions, from the personality disorders to attention deficit hyperactivity disorder (ADHD) to the addictions. It is a coping mechanism that, at certain life history stages and in certain environmental contexts, might be an adaptive one. The corticotropin-releasing hormone (CRH) system is critical to behavioral responses to stress, and studies in which CRH activity is experimentally manipulated suggest that naturally occurring *CRH* gene variation may mediate individual variability in the behavioral traits that determine an individual's coping style. One of the most consistent behavioral correlates of CRH system activity is the way in which an organism approaches novel stimuli and unfamiliar conspecifics (Kalin et al. 2000; Korte et al. 2005).

The *CRH* haplotype has been shown to predict behavioral inhibition in children (Smoller et al. 2003), and studies in rhesus macaques suggest that *CRH* variation in humans may moderate the risk of alcohol use disorders, perhaps through the pathway of behavioral inhibition. The presence of a rhesus polymorphism (−2232 C/G) that has similar in vitro functional effects to some *CRH* haplotypes reported in humans (Wagner et al. 2006) predicts decreased CSF levels of CRH, an intermediate phenotype found in individuals or strains characterized as being particularly extroverted, aggressive, or bold. Infant macaques carrying the G allele are characterized as being more exploratory and bold (Barr et al. 2008b), and, following adolescence, males that are G allele carriers exhibit a more bold and active response to an unfamiliar conspecific.

Variation at the monoamine oxidase A (*MAOA*) gene is also linked to impulsivity and impulsive aggression in both animal models and humans. Monoamine oxidase A degrades the monoamine transmitters (dopamine, norepinephrine, and serotonin), and, therefore can influence synaptic concentrations of these neurotransmitters. A variable number of tandem repeats (VNTR) polymorphism in the transcriptional control region for the human *MAOA* gene (MAOA-LPR) have been shown to produce differential transcriptional activity in vitro (Sabol et al. 1998). Rhesus and other primates also show variation at this locus (Gibbons 2004). This polymorphism is present across macaque species, but differs substantially in its frequency (Wendland et al. 2006). The low activity allele of rhMAOA-LPR contributes additively with peer rearing to increase impulsivity and aggression (Barr et al. 2004a; Newman et al. 2005). These studies in rhesus macaques support the hypothesis that *MAOA* gene promoter variation may specifically increase the risk for conduct or personality disorders characterized by impaired impulse control and aggressivity, particularly among those exposed to early stress or lack of parental influence. The effect of this genetic variant in human populations will be discussed at the end of this chapter.

2.3 Novelty Seeking: DRD4

Dopamine neurotransmission underlies many reward-dependent and reinforcing processes. Tandem repeats in the third exon of the dopamine receptor D4 gene (DRD4) exist across a variety of species, including humans, vervets, dogs, dolphins, bears, raccoons, horses, and chimpanzees (see Larsen et al. 2005). Some species, including rhesus, pigtail, and Tonkean macaques, exhibit variation in the number of repeats present, with various alleles differing in frequencies across species (Wendland et al. 2006; Livak et al. 1995). In humans, the DRD4 7-repeat allele (7R) reduces efficacy of the receptor and is linked with traits such as sensation seeking (Ptacek et al. 2011; Benjamin et al. 1996; Ebstein et al. 1996). A DRD4 length variant has also been associated with novelty seeking in vervet monkeys (Bailey 2007). In the dog, which has been subject to intense artificial selection, a repeat polymorphism predicts social impulsivity and activity-impulsivity endophenotypes (Hejjas et al. 2007a, b). We recently identified 4R, 5R, 6R, and 7R alleles in a colony of rhesus macaques. Compared to the ancestral allele (4R), the loss-of-function 7R allele predicted increased physical aggression toward an unknown age- and sex-matched conspecific (Fig. 2).

2.4 Anxiety, Reactivity, and the Serotonin Transporter Gene

Perhaps the most extensively studied genetic variant in primate behavioral genetics and human psychiatric genetics is a polymorphism located upstream from the serotonin transporter gene (*SLC6A4*). In humans, this common polymorphism

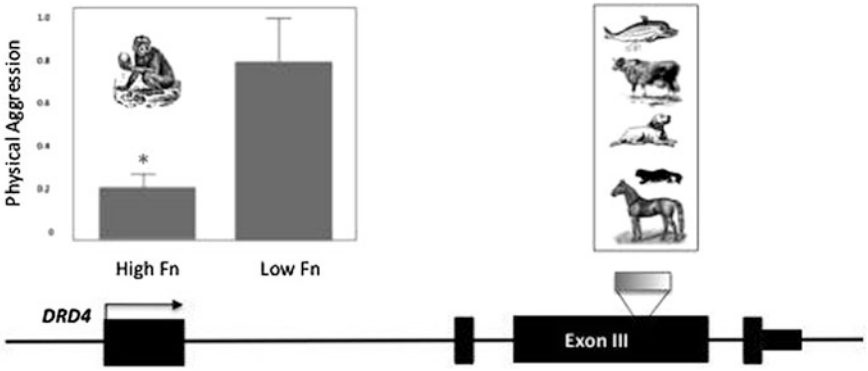

Fig. 2 DRD4 gene is present across species and predicts aggression in rhesus macaques. Tandem repeats present in the third exon of the DRD4 gene are present in a variety of species, including domestic animals. In macaques, variation at this locus predicts individual differences in aggressive responses to an unfamiliar conspecific

reduces expression of the serotonin transporter gene, and variation of this serotonin-transporter-linked polymorphic region predicts certain temperament traits related to anxiety, depression, and aggression, such as neuroticism, harm avoidance, and disagreeableness (Mazzanti et al. 1998). There is variation in the serotonin transporter gene regulatory region in many nonhuman primate species as well (Wendland et al. 2005; Lesch et al. 1997). In rhesus, a similar polymorphism has been shown to alter transcriptional efficiency (Bennett et al. 2002), resulting in decreased serotonin transporter mRNA levels in the brains of animals carrying the variant allele (Lopez and Higley 2002), which may be further regulated by epigenetic mechanisms (Kinnally et al. 2010). Because it might predict alternative strategies, particularly in certain environmental contexts, the serotonin-transporter-linked polymorphic region (5-HTTLPR) polymorphism has been studied extensively in both rhesus and human gene by environment interaction studies (Barr et al. 2004a, b, c). Studies in multiple, independent laboratories demonstrate that the 5-HTTLPR s allele predicts anxiety and responses to stress in rhesus macaques (Bethea et al. 2004; Champoux et al. 2002) and that the 5-HTTLPR genotype can interact with controlled prenatal exposure to stress or alcohol or early life adversity, resulting in long-lasting differences in stress reactivity, sensation seeking, and aggression (Barr et al. 2004a, b, c, d; Kraemer et al. 2008; Schneider et al. 2010, 2011; Schwandt et al. 2010; Spinelli et al. 2007).

3 Environmental Effects on Aggression

Field and laboratory studies of nonhuman primates have demonstrated effects of environmental variables on aggressive behavior. Many of these effects are attributable to the drive to reproduce (Knapp and Innocent 2012). The Challenge

Hypothesis has been put forth as an argument for intra-individual variability in aggression among chimpanzees (Sobolewski et al. 2013). This hypothesis was originally developed in order to understand the biological underpinnings of the transient increases in aggression observed among seasonally breeding male birds (Wingfield et al. 1990). One factor that helps to explain such variability is variation in circulating levels of the reproductive steroid, testosterone. A role for testosterone in the facilitation of aggressive behavior is well established. In fact, in domestic animals, castration is routinely performed in dogs, goats, and horses, to name a few, in order to reduce aggression, particularly toward male conspecifics. There are likely a number of independent mechanisms by which testosterone exerts such effects. First, testosterone binds to nuclear receptors, and the testosterone-receptor complex can then act to modulate expression of testosterone-sensitive genes in both peripheral tissues and in brain. Whether through effects on gene expression or via membrane receptor-mediated alterations in neurotransmitter release, it has been shown that testosterone facilitates attention given to threatening social stimuli. In rhesus macaques studied in the lab, testosterone replacement in hypothalamic-pituitary-gonadal axis-suppressed males increased selective attention to negative social stimuli and interactions without affecting environmental exploration or attention toward novel stimuli (King et al. 2012). Testosterone decreases fear and anxiety and has been shown to act through the dopamine system to increase social reward. As such, the behavioral effects of testosterone, regardless of molecular mechanism, could be attributable to both decreased aversion for negative emotional stimuli and facilitation of approach to social stimuli.

In a number of species, serum levels of testosterone in males increase during the mating season and as a function of female conception cycles (Fichtel et al. 2007; Bales et al. 2006; Ostner et al. 2011). In some seasonally breeding species, testosterone levels correlate with the frequencies of aggressive displays (Higley et al. 1996a), while in chimpanzees, it is proposed that testosterone only facilitates aggressive behavior in certain environmental contexts (Sobolewski et al. 2013). Chimpanzees are nonseasonal breeders, and females only give birth approximately once in a 5-year period. Because of the vigorous competition that exists for females among breeding-aged males and because the external environment does not control the female reproductive cycle, there is variability in the intensity of competition among males over time, and such variability is also dependent on the female over which males are competing. Studies in free-ranging chimpanzees have demonstrated that individual testosterone levels increase with the number of males in a group, particularly so when competing for females who have previously given birth (Sobolewski et al. 2013). Increased circulating testosterone in male chimpanzees exposed to these variables may promote aggressive behavior toward other males and, therefore, make them compete more successfully for breeding females.

Another important factor driving aggressive behavior is environmental stress (discussed in Korte et al. 2005). In humans, there are known links between stress and a variety of psychiatric disorders, including depression, posttraumatic stress disorder, anxiety disorders, and substance abuse disorders (McEwen 2006;

Sapolsky 2001), all of which may be linked to aggressive behavior. Like testosterone, the stress hormone cortisol can bind to nuclear receptors and alter gene expression. It has been demonstrated that expression of many genes that influence behaviors involved in stress response are under the control of glucocorticoids through this mechanism. In some instances, it has been shown that common genetic variants that moderate responses to stressful stimuli alter the corticosteroid response of these genes by disrupting or adding these types of elements to regulatory regions. Genetic variants that influence stress reactivity could predict whether an individual is at risk for psychopathology (Caspi et al. 2002, 2003). This might be assessed by evaluating an individual's sensitivity to environmental stressors, the magnitude and/or duration of the stress response, or the types of responses (including aggression) exhibited following stress exposure. Genetic variations that determine whether individuals habituate or sensitize to repeated or chronic stress would also be expected to play a major role (Spinelli et al. 2012).

4 Gene x Environment Interactions

From an evolutionary perspective, the roots of psychopathology may lie in the different strategies that have evolved for coping with environmental challenges (Korte et al. 2005). Rhesus macaques provide an opportunity to examine genetic-environmental (G × E) interactions in a controlled, prospective manner (Barr et al. 2003b, 2004d; Barr and Goldman 2006). Not only can variables like diet, light–dark cycle, and other factors that are contributors to "noise" in human genetic studies be controlled, but environmental factors that might contribute to G × E interactions can also be applied in a controlled manner. Such factors commonly studied in behavioral research include alcohol exposure (prenatal, in adolescence, or in adulthood), acute challenges (for example, the presentation of an intruder, or separation from attachment sources), response to certain neuropsychopharmacological agents, or early life stress (variable foraging demand or peer/nursery rearing) (reviewed in Barr and Goldman 2006).

Peer rearing is probably the most extensively studied environmental factor in G × E experiments in rhesus macaques. As with other primate species, rhesus macaque mothers invest much of their energy into defending, comforting, and caring for their infants, and this maternal "buffering" appears to be critical to normal infant development (Suomi 1982). In the so-called peer rearing condition, subjects are removed from their parents at birth and reared with other age-matched infants, so that they develop in the absence of adult influence (Harlow and Suomi 1974; Chamove et al. 1973). When compared to their mother-reared counterparts, peer-reared subjects exhibit evidence of insecure attachment, higher levels of anxiety, and lower levels of exploration in novel settings (Suomi 1982). Because their peers do not necessarily punish inappropriate behavior, they also can have impaired development of the behavioral inhibition system, and, as in humans, macaques that have been exposed to early adversity (in the form of peer-rearing)

show long-lasting differences in brain function and aggressive behavior (Higley et al. 1991; Spinelli et al. 2012). Interactive effects between functional genetic loci and early rearing environment have been demonstrated for the serotonin transporter, Neuropeptide Y (*NPY*), *MAOA*, *CRH*, and *DRD1* genes in rhesus macaques (Barr et al. 2008; Newman et al. 2005, 2009; Lindell et al. 2010).

Because selective pressures differ between the sexes, males and females differ in their responses to environmental challenges (Eme et al. 2007; Wood and Eagly 2002). Variation in the serotonin transporter-linked polymorphism results in sexually dichotomous qualitative and quantitative G × E interactions, first demonstrated in rhesus studies. Even prior to pubertal development, the 5-HTTLPR s allele predicted increased stress response, but only among females with histories of early adversity (Barr et al. 2004b). Responding to social threat is one domain in which males and females are likely to adopt different adaptive solutions. In terms of allelic effects on aggressive behavior, it has been shown that male adolescents carrying the s allele who were exposed to early life stress are more likely to respond aggressively toward an unfamiliar conspecific (Schwandt et al. 2010). Females, in contrast, are more likely to exhibit redirected aggression toward other members of their group. Both types of aggression are "affective" in nature and likely due to the increased reactivity known to exist among carriers of the 5-HTTLPRs allele.

5 Adaptive Value of Aggressive Behavior and the Role of Selection

In evolutionary biology, a behavior is *adaptive* if it makes the organism more fit to survive and reproduce in comparison to other members of the same species. Aggressive behavior in animals is thought to be adaptive since it increases success in competition for resources and mates and ensures survival during agonistic encounters with both conspecifics and predators. In his writings, Charles Darwin noted that there often appeared to be a conflict of interest between traits that increased survivability and traits that could potentially increase reproductive output (Darwin 1896). In other words, many traits that give advantage in reproductive success have negative consequences for survival. He referred to this as sexual selection, of which there are two types. The first is intersexual selection, a case in which an individual of one sex can choose a mate on the basis of a given trait (e.g., plumage in peacocks). The second is referred to as intrasexual selection, and most frequently refers to male subjects competing over mating opportunities. For the latter, genetic variants that promoted aggression would be most likely to be under selection.

While Brent et al. (2013) found that aggressive behavior predicted reproductive success in rhesus macaques, they also showed that passive, affiliative, nonaggressive subjects were equally successful. It has been shown in other primate species (e.g., baboons and assamese macaques) that individuals with higher levels

of sociality have higher infant survival rates and produce more offspring. The fact that high and low aggression phenotypes in rhesus macaques predict increased reproductive output suggests a role for disruptive selection at genes involved in moderating aggressive behavior (Brent et al. 2013; Lande and Arnold 1983).

While the field of behavioral genetics is growing rapidly, most of its research is concerned with the identification of "disease alleles," or gene variation underlying what is considered pathological behavior. Its methods and findings, however, can be applied to a long-standing goal of evolutionary anthropology, namely to understand how changes in allele frequency can affect divergences in primate behavior. Several studies have identified associations between specific alleles and natural features of behavior and life history strategies. For example, the loss-of-function short(s) allele of the serotonin transporter gene promoter length polymorphism, which increases risk for developing depression in the face of adversity, has a functional equivalent in the rhesus macaque (see above). In macaques, this allele is associated with increased endocrine and behavioral stress reactivity as a function of stress exposure, often in a sexually dichotomous manner (Barr et al. 2004; Spinelli et al. 2007; Schwandt et al. 2010). Therefore, this variant appears to increase the risk of developing psychopathology, particularly in the context of stress. Despite this, these variants have been maintained in both humans and in rhesus, in addition to some other nonhuman primate species. Moreover, in human populations in which the s allele is rare, another loss-of-function variant on the L allele background (LA > LG) is present at a higher frequency (Hu et al. 2006). In humans, there is also a VNTR in the second intron, which appears to be functional (Fiskerstrand et al. 1999). This VNTR is present in a number of primate and nonprimate species and is polymorphic in a number of hominoid species (Soeby et al. 2005).

Although SNPs are not necessarily conserved across species, there are instances in which functionally similar SNPs occur in humans and rhesus macaques (Barr et al. 2008a, b; Vallender et al. 2008; Miller et al. 2004). The serotonin transporter gene regulatory region is tremendously variable within species, and it has been demonstrated that gain-of-function *SLC6A4* SNPs have arisen and been maintained in both rhesus and in humans, suggesting that both gain- and loss-of-function variants may be under selection in primates (Vallender et al. 2008). It is interesting that *SLC6A4* variation not only predicts individual differences in impulse control and stress reactivity (Barr et al. 2004; Bennett et al. 2002; Champoux et al. 2002; Schwandt et al. 2010), but that it is also associated with adaptive traits in free-ranging macaques, such as earlier male dispersal (Trefilov et al. 2000) and male reproductive timing (Krawczak et al. 2005). Whether allelic variation at *SLC6A4* predicts "adaptive" traits in humans has not been elucidated (Homberg and Lesch 2011).

An impulsive, aggressive individual that readily approaches novel objects or conspecifics may do well in certain social situations, but may face higher risk of predation or attack than a more cautious, harm-avoidant individual. Such behaviors might, therefore, be predicted to confer selective advantage at particular developmental or life history stages and in certain environmental contexts.

Moreover, because of differences in their behavioral and physiologic responses to stress, the types of stress-related pathology to which bold, proactive individuals and harm-avoidant, reactive individuals are vulnerable are quite different. Whereas the latter are at risk for internalizing disorders, such as depression and anxiety, the former are more likely to develop externalizing conditions, primarily characterized by impaired impulse control and aggression (Korte et al. 2005).

Variation at the *CRH* locus would be expected to increase stress adaptation or modify behavior in a manner that is adaptive, but which may also moderate the risk of stress-related disorders in modern humans. In other words, though genetic variation that increases stress reactivity could assist in the adaptation to stress in the short term, with chronic, repeated or severe stressors it could also make individuals more prone to developing psychopathology. In macaques, the two most common haplotypes are yin-yang, or alternative, haplotypes (Barr et al. 2008b). The persistence of these divergent haplotypes over time suggests that at least one of the alleles on each background is being selected—possibly in a particular environmental context—while the rest are hitchhiking. Several studies in humans (Baerwald et al. 2000; Shimmin et al. 2007) have found evidence for selection at the *CRH* locus, in which alternative, yin-yang haplotype clades are observed. As in the rhesus macaque, the major human *CRH* haplotypes have been shown to vary in terms of their in vitro promoter activity, including differences in glucocorticoid sensitivity (Wagner et al. 2006). In rhesus macaques, carriers of a *CRH*−2232 G allele engage in risky behaviors (Barr et al. 2008b) and exhibit lower levels of the serotonin metabolite 5-HIAA, a neurochemical endophenotype observed both in macaques exposed to early life stress and in humans with antisocial personality disorder (Higley et al. 1991, 1996a). It may be that in humans genetic variations that alter CRH system function could influence multiple behavioral dimensions (i.e., both neuroticism and extraversion), and variants that place an individual at the extremes of these spectra (i.e., inhibited and anxious/stress reactive vs. bold/impulsive and novelty seeking) might increase the risk for psychopathology. Of note, based on its extended haplotype structure, studies that examine effects of the CRH receptor gene (*CRHR1)* haplotype demonstrate molecular evidence for selection (Nelson et al. 2010).

As another example, in both rhesus and in humans, there are nonsynonymous SNPs in the portion of the *OPRM1* gene that encodes the N-terminal domain of the receptor (C77G in rhesus macaque and A118G in human, as discussed above), and these SNPs perform similar functions in vivo (Barr et al. 2007; Chong et al. 2006). In humans, the 118G allele is suspected to increase the likelihood of alcohol abuse because it increases alcohol-induced dopamine release and subjective euphoria (Ramchandani et al. 2011; Ray and Hutchison 2004). We have shown that rhesus carrying the 77G allele exhibit increased alcohol-induced stimulation (a marker for the euphorogenic effects of alcohol) and that G allele carriers also consume more alcohol in the laboratory (Barr et al. 2007). It would stand to reason that *OPRM1* variation might also predict sensitivity to natural rewards, including aggressive or agonistic behavior, which, as stated earlier, can be rewarding. Since these two variants confer similar functional effects and are both observed at relatively high

frequencies, and since there is an extended region of LD with the A118G allele in humans (Luo et al. 2008; Zhang et al. 2006; Pang et al. 2009) it might be hypothesized that they have evolved as result of similar selective pressures in the two species, but data to directly address this hypothesis are not yet available. However, studies performed in the macaque demonstrate that this variant predicts behaviors that could theoretically be under selection, including aggressive behavior (Miller et al. 2004), and G allele carriers form stronger attachment bonds with their mothers during infancy (Barr et al. 2008; Higham et al. 2011), especially as a function of repeated maternal separation. It is interesting that the effects of repeated episodes of maternal separation and reunion are similar to those that might be observed during periods of alcohol intake and withdrawal. Similar effects of *OPRM1* genotype on social attachment have recently been demonstrated in human children, showing increased quality of parent–child relations as a function of parental unavailability or inconsistency. These types of studies highlight how traits that could have conferred selective advantage at some point in the evolutionary history of humans can increase the risk of psychopathology in modern society.

6 New Molecular Approaches: The Serotonin Transporter Gene and Genetic Selection

A high-profile meta-analysis performed in 2009 called into question the validity of all of the 5-HTTLPR x stress findings that had been reported in the human literature (Risch et al. 2009). Risch et al. and others who subsequently came out against candidate gene-based and G × E studies claimed that the field needed to look toward whole-genome linkage as a tool. Those who defended the validity of G × E interaction studies argued not only that whole-genome studies are substantially less powerful, but also cited many of the animal studies, including those performed in nonhuman primates (Caspi et al. 2010). This debate is ongoing and calls out for studies to verify the validity of G × E interaction results by elucidating mechanisms through which they might occur. New technologies and approaches in genomics and cell biology may make it possible to identify the mechanisms that underlie G × E interactions. Such studies may also inform us of genetic variation that promotes stress sensitivity or resilience, permitting the identification of candidate loci for the performance of future G × E interaction studies.

Epigenetic mechanisms are one mechanism by which stress could interact with genotype. The emergence of next generation DNA sequencing technologies has increased the potential for discovery of epigenetic effects. Several companies offer platforms that permit high-throughput sequencing, and by combining immunoprecipitation with these approaches, the effects of stress on levels of histone binding or sites of DNA modification (two forms of epigenetic regulation) can be

elucidated, and genetic factors that directly promote or inhibit these processes might be identified. Variation within regulatory or coding regions of genes encoding stress-responsive signaling molecules, which may contribute to environmental sensitivity and stress vulnerability, is of particular interest for the study of G × E interactions.

We recently performed a serotonin-transporter focused study using chromatin immunoprecipitation sequencing (ChIP-SEQ) in order to determine epigenetic stress effects at *SLC6A4* in archived brain tissue from male macaques (Lindell et al. 2012). We found that binding of H3K4me3, a histone protein that marks active promoters, at the serotonin transporter gene was affected by early life stress as a function of 5-HTTLPR genotype and that it varied across adolescent development. These findings support the idea that genetic effects may vary as a function of various environmental factors and that these may act, in part, through epigenetic mechanisms. The ChIP-SEQ methodology employed in this study involved antibody-based isolation of H3K4me3, after which levels of H3K4me3 binding were assessed by sequencing the histone-associated DNA, such that the number of reads for a region are the index for the relative degree of H3K4me3 binding and, therefore, epigenetic regulation via this mechanism. One by-product of approach is that genetic variation can also be identified. We identified 11 SNPs within the serotonin transporter gene and its regulatory region, 3 of which were present in the region of H3K4me3 binding, overlapping with a CpG island—a region that can act as a substrate for a more commonly studied epigenetic regulation, DNA methylation (Kinnally et al. 2010)—and within 100 nucleotides of the transcription start site. Interestingly, there are 3 SNPs present in the corresponding region in humans as well (rs55753714, rs25533, and rs61274396).

As stated earlier, genetic variation in the serotonin-transporter-linked polymorphic region may confer selective advantage in a variety of species. Our identification of abundant, putatively functional polymorphisms in rhesus in this study and the SNP density observed in the corresponding region for humans (http://genome.ucsc.edu/) is relevant to studies examining how variation at or around the *SLC6A4* gene relates to individual differences in environmental reactivity and behavior. Because the region 5′ of the gene includes the promoter and important transcription factor binding sites, these regions are typically under selection. The result is that, relative to intergenic regions, there is both increased conservation of sequence across species and lower levels of intraspecific polymorphism within these regions. We have previously shown that, in both human and macaque, the average SNP density for the region 5 kB upstream of transcription start sites is low relative to intergenic regions, and that it is more similar to that observed in other important regulatory sequences, such as intronic or untranslated regions (which, like the promoter regions, are also under selection) (Yuan et al. 2012). In our 5-HTTLPR epigenetic study, not only did we identify 3 SNPs within the core promoter for the rhesus *SLC6A4* gene (despite sampling a limited number of subjects), but there also appears to be increased diversity in this region in humans, with 25 SNPs within the 1 KB 5′ of the *SLC6A4* transcription

start site. This was approximately 10× higher than we had previously reported for variation in human intergenic regions (Yuan et al. 2012).

These findings demonstrate how genetic and environmental effects may interact and how genetic variability could be driven by disruptive and/or balancing selection at genes known to moderate aggressive behavior. It may be that certain genetic variants are only "functional" under certain environmental conditions or during certain developmental phases. It is possible that within-species variation at genes that influence behavior and stress response is favored because these genes promote alternative strategies, particularly at critical developmental time points or under specific environmental conditions.

7 Genetic Selection in Primates: Understanding the Origins of Human Aggression and Psychopathology

Several decades ago, Maynard Smith applied "Game Theory" to animal behavior and found that aggression and fearfulness are traits that tend to balance each other in any social population (Smith and Price 1973). He described the "Hawk-Dove game" in which "Hawks" (aggressive individuals, who were proactive and exhibited a fight-or-flight response to stress) and "Doves" (who were fearful, cooperative and adopted a freeze-and-hide stress response) were likely to co-occur in the same species. He determined that both "Hawk" and "Dove" strategies could potentially be adaptive, perhaps especially so in certain environmental contexts. While "Hawks" would do better when food was abundant and population density high, since they are better at fighting for access to mates than foraging), "Doves" would likely outcompete "Hawks" when the opposite were true since they would excel at getting food during periods of scarcity and avoiding danger during times of increased conflict. The two temperaments must be balanced in any given population; in a population comprised completely of "Hawks," excessive aggression would reduce the chances of an individual surviving to successfully reproduce, while an all "Dove" population would quickly be killed off by some other, more aggressive species. In other words, the presence of both behavioral types may be critical to the survival of the species, while at the same time, there will be selective pressure at the individual level, depending on life history, sex, and environmental context. It then stands to reason that the genetic factors that underlie these two alternative strategies would be likely to be subject to balancing selection and that, as a result, both types of traits or strategies will be observed among individuals of any social species.

There are a number of research groups that have been investigating genetic variations in the rhesus macaque that contribute to the expression of traits that have been linked with human personality and psychiatric disorders, all of which may map well onto the Hawk versus Dove model (i.e., stress reactivity, behavioral dyscontrol, aggression, and reward seeking/sensitivity) (reviewed in Barr 2013).

Many of the variants that have been identified and studied in macaques are functionally similar to those present in humans, and some findings suggest convergent evolution, with the variants maintained by selection in both species (Barr et al. 2008a, b; Vallender et al. 2008). The macaque model has proven useful for learning how relatively common genetic variants, which are associated with traits that may be adaptive in certain environmental contexts, can also increase vulnerability to behavioral pathology.

As stated earlier in this chapter, the more complex the brain of a species, the more severe and organized the aggressive behaviors exhibited among its members becomes. Humans are a highly aggressive species in comparison to other animals, probably as a result of an unusually high benefit-to-cost ratio for intraspecific aggression (Georgiev et al. 2013). Humans are also unique in their capacity for planned murders, and they are the only primate species among which mothers exhibit infanticidal behavior toward their own young (Raine 2013; Hrdy 1999). Several of the genetic variants that have been found across primate species have been linked to human aggression. One of the first genetic variants to be linked with severely aggressive behavior was a coding SNP in the *MAOA* gene, discovered by Han Brunner when he was approached by a woman who wanted genetic counseling because her 10-year-old son was showing signs of aggression (Brunner et al. 1993, discussed in Raine 2013). She reported that many of her male relatives had significant behavior problems, and she described them as being "frightening and aggressive." Brunner et al. tracked down members of the extended family, found 14 male relatives who had a history of violence and impulsive aggression, and were able to identify the variant that had arisen de novo in this familial line. Since the MAOA gene is on the X chromosome, males who were hemizygous for this functional coding variant were unprotected by a "normal" copy of the gene and, thus, all male individuals were affected.

Less than a decade later, a common functional VNTR polymorphism was discovered in the transcriptional control region for the human *MAOA* gene (Sabol et al. 1998). The low activity allele for this variant was found to interact with early adversity to predict later antisocial and violent behavior in a large population of boys (Caspi et al. 2002). Since then, some of the neurocircuitry differences in individuals carrying this allele have been determined. The low activity MAOA-LPR allele predicts decreased prefrontocortical and increased amygdalar responses to emotional stimuli, suggesting impaired ability to control emotional responses during arousal (Meyer-Lindenberg et al. 2006). As stated above, this genetic variant interacts with environmental factors. Not only does early stress exposure moderate the effects of MAOA-LPR genotype, but there is interaction with testosterone levels as well (Sjoberg et al. 2008). This is relevant to the discussion of testosterone and cortisol effects on gene expression and behavior. It is possible that the *MAOA*/testosterone interaction may reflect the direct action of testosterone on the *MAOA* promoter. Testosterone and glucocorticoid hormone/receptor complexes bind with different effects or affinities to enhancer elements in the *MAOA* promoter and, as such, testosterone and cortisol may both alter *MAOA* transcription.

As discussed at the beginning of this chapter, Temple Grandin writes in her book (2005) that animals exhibit different types of aggression, predatory, and affective/emotional. The type of impulsive aggression described by Brunner (1993) and in other studies examining effects of MAOA-LPR variation is most likely affective aggression. In his book *The Anatomy of Violence*, Raine (2013) describes aggression predicted by the *MAOA* genotype as "hot-headed" aggression. What has been found with the 5-HTTLPR genetic variant is quite different. Earlier, we discussed the Hawk versus Dove model and the rhesus macaque 5-HTTLPR variant with regard for the potential for balancing or disruptive selection. What has now been demonstrated is that both the l and the s 5-HTTLPR alleles can predict aggressive behavior in humans, but that the types of aggression are quite different. Consistent with what was found with MAOA-LPR, the low activity 5-HTTLPR s allele was present in individuals who exhibited affective aggression. This is not surprising given that the s allele predicts increased anxiety, environmental sensitivity, and reactivity (Lesch et al. 1997; Caspi et al. 2003, 2010). However, it has also been shown that individuals homozygous for the l allele can also exhibit inappropriate aggression. These subjects are psychopathic individuals, who exhibit lower stress responses than carriers of the s allele and who are more likely to engage in cold-blooded, planned "predatory" aggression (Glenn 2011) (Fig. 3).

Variation in other genes discussed in this chapter has been shown to be under selection in humans and may predict aggressive behavior in this species of primate. Polymorphisms in the *DRD4* and *OPRM1* genes both appear to have been under recent positive selection, and both of these variants have been linked to reward-based behaviors (D'Souza and Craig 2008; Ding et al. 2002). The DRD4 7R allele predicts novelty seeking, impulsivity, thrill seeking, anger, and short temper, traits that may have been under selection. It is likely that various combinations of genetic variants contribute to human violence. Since polymorphisms that affect aggression appear to exist in parallel in humans and some nonhuman primates, these animals will be valuable for determining genetic effects on aggression, for elucidating how environmental factors interact with genetic variation and as potential models for treatment of pathologically aggressive behavior in humans.

8 Future Agendas

8.1 Looking to Other Model Organisms

We have just discussed how violent crimes in humans can be characterized as being hot headed or cold blooded (Raine et al. 2013). The hot-headed crimes are likely similar in etiology to the affective aggression observed in nonhuman primates, and, as such, studies examining impulsive/reactive aggression have been of

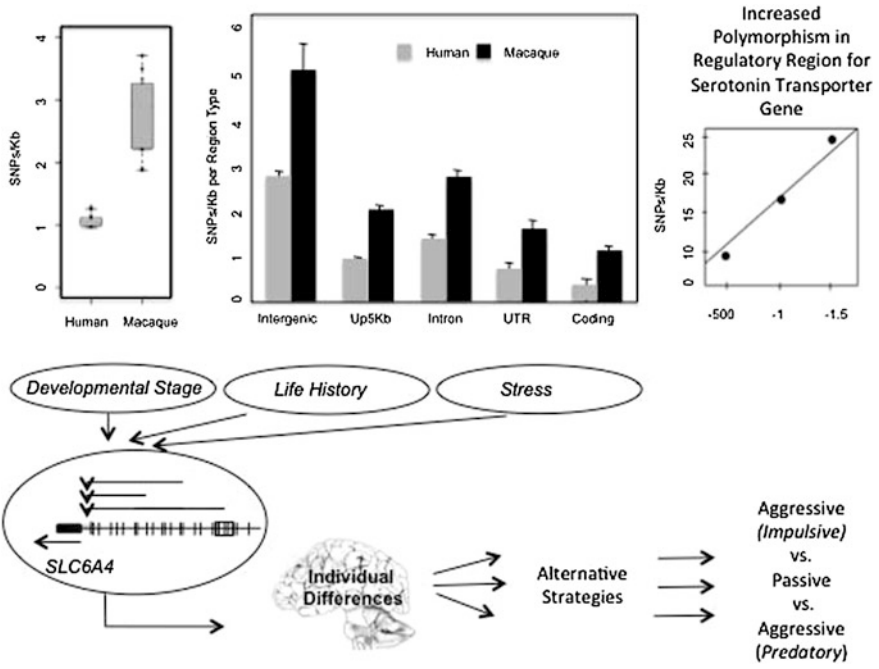

Fig. 3 Density of SNPs within the serotonin transporter regulatory region is higher than that observed for other regulatory regions genome-wide. Shown above are the average number of SNPs in each type of region across the genome as determined by ChIP and RNA-SEQ in comparison to the number of SNPs observed in the 5′ Flanking region for the serotonin transporter gene. Shown is an example of how factors such as developmental stage, life history variables, and stress exposure can differentially regulate genes expressed in brain in a genotype-dependent manner to promote diversity in behavioral strategies within a given population

interest to psychiatrists, evolutionary biologists, psychologists, and primatologists alike. However, other types of aggressive acts committed by humans are less easily modeled in a nonhuman primate. Above, we introduced the idea that, in humans, serotonin transporter genotype can be predictive of impulsive/affective aggression while the alternative genotype increases the risk of psychopathy (Glenn 2011). It could be that a predator species may be a better model for determining the genetic underpinnings of dysregulated predatory behavior and modeling psychopathic, cold-blooded, predatory aggression. This type of killing may have its basis in reward and, though most of us find the idea of harming or killing another aversive, those who do not and who cannot inhibit their prey drives may be at risk (see discussion above relating to prey drive inhibition in domestic animals).

Another area of interest is the aggressive behavior noted among individuals diagnosed with a developmental disorder. In recent years, the incidences of autism and autism spectrum disorders (ASD) have increased rather markedly. Aggression among ASD subjects is, in part, attributable to increased reactivity and impulsivity, both of which can be studied in nonhuman primates. However, other

features of the autism spectrum disorders are not easily modeled using nonhuman primates. As with psychopathic, cold-blooded killers, ASD subjects exhibit deficits in empathy and social cognition and some of these have been shown to be dependent on an individual's genotype (for example, 5-HTTLPR; Brune et al. 2006). Unlike the callousness observed among psychopathic individuals, however, ASD subjects have affective empathy that is intact (they can resonate with others' feelings), but they lack the ability to read others' emotions (Jones et al. 2010). Therefore, aggressive behavior observed with ASD is proposed to be aimed at eliciting a clear emotional reaction and, therefore, thought to be attributable to this deficit in social cognition and not aggressiveness per se. In other words, risk for aggression relates to deficits in social cognition among ASD subjects.

One approach that could be used to determine the genetic factors that underlie deficiencies in social cognition is the study of the genetics of domestication (for example, dogs, cats, and horses). At its most basic, domestication is a suite of heritable traits affecting behavior (Belyaev et al. 1981). There are intriguing phenotypic commonalities among domesticates. Most important among these traits, and the only one common to all domesticates, is the ability to coexist with humans. The systems that likely permitted early domestication range from those involving fear and impulse control to those involving reward and sociality. In general, domestic animals have lower levels of aggression than do their nondomesticated ancestors. This is shown not only with aggression toward humans, but with predatory aggression as well. When compared to coyotes, beagle-coyote hybrids exhibit less effective predatory behavior, partially attributable to decreased arousal and increased response threshold. There is also partial inhibition of killing bite in hybrids, and this is completely inhibited in the purebred beagle dog (Fox 1976). At some point in the domestication of some species of animals, there may have also been selection for social cognition, as many domestic animal species are good at looking to humans and for reading human emotions. For example, it has been shown that in studies of wolves, dogs, and hybrid animals, dogs are more likely to look to humans for cues in order to retrieve a reward. It has further been shown that genetic variation at the DRD4 gene contributes to phenotypic variation in this trait (Hori et al. 2013). Whether the latter relates to differences in reward sensitivity or to social cognition are not clear.

In some domestic species, there has been selection among breeds or lines for other desirable traits that have inadvertently resulted in some increased frequency of aggression related to fear, prey drive, territoriality, deference refusal, or impulse control (Overall 1997). These may serve as very powerful models for looking at effects of domestication and reversal of some of those effects through more recent artificial selection. There have been several instances, however, in which wild animals were experimentally domesticated. In Siberia in the late 1950s, Belayev and Trut began an experimental domestication of the silver fox a coat color variant of the red fox (*Vulpes vulpes*) raised industrially on commercial fur farms. Selective breeding began with 130 individuals, 100 females, and 30 males. Using a rather coarse test of mansuetude (see Kukekova 2008) they selected the top 5 % of males and 20 % of females for each successive generation while keeping the

population roughly the same size. In order to avoid conditioning the animals to human contact the foxes were never handled prior to phenotyping for the selection of suitable breeders for the next generation. Within a few generations demonstrable changes in behavior toward people were evident in the foxes' vocalizations, position in their cages on approach, the ear and tail positions, gaze toward and willingness to be touched by humans; within 10 generations they had succeeded in breeding a reasonably 'domestic' fox. It is significant that 'domestication' occurred in so few generations, as this is an indication that the number of genes involved in domestication cannot be exceedingly large, perhaps in the range of 10–20 genes of major effect, a conclusion supported by subsequent research which found that large behavioral differences result from limited changes in the transcriptome of genes expressed in the brain (Lindberg et al. 2007). The study of the genetics of domestication across species may, therefore, access a number of traits and underlying genetic variation that are highly relevant to the types of aggression observed in the human condition; not only those relating to fear/anxiety, impaired impulse control, and reward, but those involving individual differences in social cognition as well.

9 Molecular Mechanisms of G × E Interactions

While much has been learned with the use of molecular genetics to dissect behavior in primates, the molecular effects of environment factors are not as widely known. Increasing this knowledge base might aid in prevention and/or development of new pharmacotherapies for the treatment of severe aggression in both domestic animals and humans. One limitation to performing such studies in a nonhuman primate is that it requires the use of a brain sample, which presents ethical concerns to many primatologists and neuroscientists. We discussed in this manuscript the use of massively paralleled sequencing technologies in order to examine epigenetic effects and to discover genetic variation in primates. These techniques can be used to study environmental effects on levels of histone binding or sites of DNA modification (two forms of epigenetic regulation), the advantage being that the entire genome is queried, increasing the yield from a given brain sample. We are currently performing whole exome sequencing in macaques that exhibit extreme variation in aggressivity and have identified a number of candidate alleles using this method.

In this chapter, we also discussed the importance of stress and gonadal steroids as they relate to aggressive behavior in primates. Besides epigenetic modifications, one mechanism by which environmental factors might interact with genetic variation is via hormone receptor-induced regulation of gene expression. Cortisol and testosterone exert pleiotropic effects by altering gene expression in brain regions containing high concentrations of glucocorticoid or testosterone receptors, which can alone or in combination with other factors to influence expression of genes containing glucocorticoid, or androgen response elements (GRE/ARE). Of

interest, all of the gene variants presented in this chapter (5-HTTLPR, *CRH*, MAOA-LPR, and *OPRM1* C77G) have AREs or GREs in their regulatory regions, making them putatively responsive to these hormones, and in many of the cases in which we have identified gene by stress interactions in rhesus, glucocorticoid or androgen response is either enhanced or disrupted via polymorphism within AREs/GREs. Unlike histone proteins, transcription factors are not tightly associated with DNA. However, one might still be able to use next generation sequencing technologies to identify corticosteroid-sensitive genes. By performing X-ChIP-SEQ (with anti-glucocorticoid receptor antibodies) combined with mRNA-SEQ, there may be potential to identify genes that are sensitive to glucocorticoid receptor-mediated activation or repression and to determine if this regulation occurs in a genotype-dependent manner.

Various other nongenomic approaches can be used to assist in elucidating mechanisms through which G × E interactions might occur. The development of induced pluripotent stem cells (IPSCs) could be critically important in determining how G × E interactions occur in brain. These cells, if induced to develop into neurons, could be tremendously informative for examining hormone effects (both sex and stress steroids). The fact that cells can be derived from peripheral tissues affords the opportunity to examine effects of any or all of these variables that are specific to the individuals' genetic makeup and, therefore, can be used to examine individual differences.

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