Biology of Aggression

RANDY J. NELSON,
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Preface

The effects of aggression and violence on people can be seen in the news media every day. Whether the story is about the mauling of a woman by an aggressive dog, students attacking their colleagues in school, workers attacking their colleagues at work, or people detonating bombs in response to their ideological beliefs, unchecked aggression and violence exact a significant toll on society. For years, the roles of learning and environmental influences, both social and nonsocial factors, were prominent in discussions of the etiology of human aggression. Biological factors were not thought likely to be important candidates for dealing with human aggression or violence. With recent advances in pharmacology and genetic manipulation techniques, new interests in the biological mechanisms of human aggression have been pursued. Certainly, aggression is a complex social behavior with multiple causes, but pursuit of molecular biological causes may lead to interventions to prevent excess aggressive behaviors.

Aggression has been defined as overt behavior with the intention of inflicting physical damage upon another individual. The possibility for aggressive behavior exists whenever the interests of two or more individuals conflict. Conflicts are most likely to arise over limited resources, including territories, food, and mates. Indeed, the ubiquitous resident-intruder aggression test models rodent territorial aggression. In nature, the social interaction decides which animal gains access to the contested resource. In many cases, a submissive posture or gesture on the part of one animal avoids the necessity of actual combat over a resource. Animals may also participate in psychological intimidation by engaging in threat displays or ritualized combat in which dominance is determined, but no physical damage is inflicted.

Because most aggressive encounters among humans and nonhuman animals represent a male proclivity, studies using the most appropriate murine model (such as testosterone-dependent offensive intermale aggression, which is typically measured in resident-intruder or isolation-induced aggression tests) are discussed. In this book, various molecules that have been linked to aggression by pharmacological or the latest gene targeting techniques are emphasized as well. The evidence continues to point to androgens and serotonin (5-hydroxytryptamine, or 5-HT) as major hormonal and neurotransmitter factors in aggressive behavior, although recent work with gamma-aminobutyric acid (GABA), dopamine, vasopressin, and other factors, such as nitric oxide, has revealed significant interactions with the neural circuitry underlying aggression. The goal of this volume is to summarize and

synthesize the recent advances in the biological study of aggression.

Within the past decade a novel and compelling link has been formed between psychology and molecular biology. Molecular biologists have mapped large segments of the mouse genome as part of the ambitious Human Genome Project. As genes have been identified and sequenced, molecular biologists have begun the difficult task of identifying the function of these genes. An increasingly common genetic engineering technique used to discover the function of genes is targeted disruption ("knockout") of a single gene. By selectively disrupting the expression of a single gene, molecular biologists reason that the function of that targeted gene can be determined. In many cases, the phenotypic description of knockout mice includes alterations in aggressive behavior; this genetic approach provides complementary data to pharmacological studies. Another important technology in understanding the biology of aggression is brain imaging. Although advances in imaging, proteomics, gene microarrays, and RNA silencing are contributing directly to understanding the mechanisms of aggression, it is also critical to appreciate the adaptive and evolutionary forces that shape aggressive behavior. The chapters here were chosen to provide distinct perspectives and multiple levels of analysis of aggressive behavior, from genes to social behavior.

In the first chapter, Stephen C. Maxson and Andrew Canastar explore several contextual issues for developing more fully a comparative genetics of aggression in nonhuman animals. After describing the types of aggression in animals, aspects of the evolution and of the development of aggression are related to the study of its genetics; this is followed by a consideration of different species that are being or could be used to begin a comparative genetics of aggression. Each of these points is relevant to developing the genetics of aggression in animals as models for human aggression.

In chapter 2, Daniel M. Blonigen and Robert F. Krueger present an up-to-date review of human quantitative genetic studies of aggression and violence, including twin, adoption, and molecular genetic designs from both the child and adult literature. They begin their chapter by reviewing the behavioral genetic literature on aggression in childhood and early adolescence. Then they highlight systematic differences across studies based on the method of assessing aggression, as well as presenting evidence for both distinct and common etiologies that link aggression with other childhood behavioral problems. Next, Blonigen and Krueger review behavioral genetic investigations of aggression in adults. Molecular genetic studies of human aggression across a range of psychiatric and developmental disorders are introduced and briefly summarized in this chapter.

The vast majority of nonhuman animal aggression research is conducted on mice. Most laboratory strains of mice are not particularly aggressive, however, and other animal models may be appropriate to understand certain neurochemical and neuroanatomical circuits common in the regulation of aggressive behavior. In chapter 3, Donald H. Edwards and Jens Herberholz provide an extensive review of crustacean models of aggression. In addition to easily observed aggressive behavior patterns, crustaceans have readily accessible nervous systems that contain many large, identifiable neurons that play key roles in mediating these behaviors. Although this effort is only beginning, the role of specific neural circuits, such as those for escape, and specific neurohormones, including monoamines and peptides, in mediating aspects of aggressive behavior have been elucidated in crustaceans.

Stephen B. Manuck, Jay R. Kaplan, and Francis E. Lotrich evaluate the role of 5-HT in the aggressive behavior of humans and nonhuman primates in chapter 4. Because of its primary role in aggression, many chapters in this volume address some aspect of 5-HT signaling. Chapter 4 first provides a brief introduction to the neurobiology of 5-HT, including common methods of investigation and sources of 5-HT-associated genetic variation. Next, the authors briefly provide comparative conceptualizations of aggressive behavior in human and nonhuman primates, including the role of antagonistic interactions in primate social dominance and human psychopathology. Central nervous system (CNS) serotonergic activity as a correlate of aggressive disposition, as well as impulsivity (reported in studies employing neurochemical indices of serotonergic function), neuropharmacologic challenges, functional neuroimaging, and neurogenetic methodologies, are reviewed. Manuck and coauthors conclude the chapter by attempting to integrate observations derived from studies on humans and nonhuman primates to identify implications of these findings for models of serotonergic influences on aggression and speculate briefly regarding possible evolutionary origins of these associations.

Several classical neurotransmitters have been linked to aggression, but the effects of 5-HT are most prominent. In chapter 5, Klaus A. Miczek and Eric W. Fish

review the role of 5-HT, as well as norepinephrine and dopamine, on the mediation of aggressive behavior. These authors emphasize that aggression represents diverse behavioral patterns and functions, and that endogenous amino acids, steroids, and peptides may have very different effects on each kind of aggression. They highlight the importance of escalated forms of aggression in an effort to model the harmful acts of aggression and violence in humans. They also note the reciprocal relationship between monoamines and aggression, explaining that the effects of monoamines are likely due to their interactions with other neurotransmitters, such as GABA and glutamate, and neuropeptides, such as vasopressin and opioids.

The contribution of nitric oxide (NO), a signaling molecule in the brain, to aggression is reviewed in chapter 6 by Silvana Chiavegatto, Gregory E. Demas, and Randy J. Nelson. Male neuronal NO synthase knockout ($nNOS^{-/-}$) mice and wild-type (WT) mice in which nNOS is pharmacologically suppressed are highly aggressive. Castration and testosterone replacement studies in both $nNOS^{-/-}$ and WT mice exclude an activational role for gonadal steroids in the elevated aggression. NO also appears to affect aggressive behavior via 5-HT. The excessive aggressiveness and impulsiveness of nNOS knockout mice are caused by selective decrements in 5-HT turnover and deficient 5-HT_{1A} and 5-HT_{1B} receptor function in brain regions regulating emotion. Although precisely how NO interacts with the 5-HT system in vivo remains unspecified, these results indicate an important role for NO in normal brain 5-HT function and might have significant implications for the treatment of psychiatric disorders characterized by aggressiveness and impulsivity.

Craig F. Ferris details the role of neuropeptides on aggression in chapter 7. He and his colleagues have found that brain vasopressin facilitates aggression in Syrian hamsters. An interesting relationship among vasopressin, 5-HT, and aggression has been discovered; in an important series of experiments, Syrian hamsters treated with 5-HT agonists increased 5-HT, decreased vasopressin, and decreased aggression. Ferris reports a positive correlation between vasopressin and aggression, an inverse correlation between 5-HT responsiveness and aggression, and an inverse correlation between vasopressin and 5-HT responsiveness. Similar data were obtained from violent humans. Ferris's chapter not only serves as an example of how animal data inform human research, but also provides an excellent example of an interaction between two different neurochemical systems in the modulation of aggression in humans.

In chapter 8, John C. Wingfield, Ignacio T. Moore, Wolfgang Goymann, Douglas W. Wacker, and Todd Sperry review the biology of aggression from an evolutionary and ethological perspective. The goal of this chapter is to understand the stimuli and situational factors that underlie aggressive behaviors and to place aggressive behaviors in an ecological and evolutionary context. The different types of aggressive behaviors are defined and described, permitting a link from the ethological function and the laboratory assessments of aggression. This is among the first attempts to summarize how aggression is expressed *and* regulated in different contexts, with examples provided from natural settings. The authors initially address the types and contexts of vertebrate aggression and then discuss how it is controlled by the endocrine system. The second part of chapter 8 then addresses hormone-aggression interactions and their possible evolution.

Castration has been known to inhibit aggressive behavior for at least 2,500 years. We now know that the removal of the testes significantly reduces circulating androgens, primarily testosterone and its metabolites, and male-typical aggression is facilitated by androgens. Neal G. Simon and Shi-Fang Lu review the effects of androgens and aggression in chapter 9. Androgens are important mediators of aggression in several ways. During development, androgens guide the organization of the brain into a malelike pattern by inducing or preventing neural cell death. Early exposure to steroid hormones can also affect the distribution of serotonergic neurons, their connectivity, and the distribution and binding capacities of receptor subtypes. Masculinization and defeminization of the brain are often accomplished by estrogens, the aromatized products of androgens; the lack of androgens and estrogens during early development leads to female (feminized and demasculinized) brains and subsequent behavioral patterns. Later, postpubertal testosterone (or estrogenic by-products) stimulates neural circuits that were organized perinatally, presumably by making aggression-inducing stimuli more salient. Importantly, neurons in these aggression-mediating areas are rich in both steroid hormone receptors and 5-HT_{1A} and 5-HT_{1B} receptor subtypes. Taken together, the contribution of androgens to the regulation of aggression is through their actions as modulators of neurochemical function. The *neuromodulator hypothesis* allows the integration of data from endocrine, neurochemical, and peptide systems that

are currently recognized as critical factors in the regulation of conspecific aggression.

Estrogen, as an aromatized metabolite of testosterone, facilitates male aggressive behavior in mice. In chapter 10, Sonoko Ogawa, Masayoshi Nomura, Elena Choleris, and Donald Pfaff review the contribution of estrogen receptors in aggression. Their work focuses on the presence of two subtypes of estrogen receptors (ER), ER-α and ER-β, in the brain that bind estrogen. An individual gene can have opposite effects on aggressive behaviors in the two sexes. For example, ER-α knockout males are less aggressive than their control WT littermates, but ER-α knockout females are more aggressive than WT mice. The ER-β gene can show the opposite regulation of aggressive behaviors compared to the ER-α gene. For example, ER-β knockout male mice, tested as either an adolescent or young adult, are more aggressive, but the ER-α knockout males are less aggressive than WT control mice. In female mice, the ER-β gene can have opposite effects according to the type of aggression tested. For example, ER-β knockouts have quantitatively less testosterone-facilitated aggression, but are more sensitive in tests of maternal aggression postpartum. Finally, the interactions among estrogen receptors, 5-HT, and other neurotransmitters contributing to aggressive behavior are also discussed.

Mothers fiercely protect their young. The adaptive function of maternal aggression is to protect the young, which has direct fitness consequences. In chapter 11, Stephen C. Gammie and Joseph S. Lonstein review maternal aggression in the context of other maternal behavior and note that maternal aggression is different both in form and presumably in underlying brain mechanisms from other types of maternal care and from other types of aggression. They provide a review of what is currently known about the neural circuitry and endocrine processes underlying maternal aggression.

Stress can facilitate aggression. D. Caroline Blanchard and Robert J. Blanchard review the underlying mechanisms and environmental factors that interact with the effects of stress on aggression in chapter 12. Social stress is a common and enduring feature of life with important behavioral and physiological effects. Previous work with laboratory rodents indicates that acute stressors (e.g., exposure to a dominant male) can produce several potentially damaging changes, including increased defensive behavior and decreased social and sexual behaviors; higher circulating concentrations of stress hormones and impairment of brain mechanisms that normally limit stress hormone action; impairment of brain and peripheral mechanisms of male sex hormone production; and widespread changes in brain neurochemical systems. The authors review research using a visible burrow system that allows social interactions. Importantly, this system provides an ecologically valid assessment tool of aggressive behavior. They also document dominance relationships, as well as subordination relationships in response to exposure to various stressors. Chapter 12 also focuses on the analysis of the role of previous (early or recent) stressful experience in modulating or exacerbating the response to subordination.

In chapter 13, Kim L. Huhman and Aaron M. Jasnow review the mechanisms underlying "conditioned defeat." Conditioned defeat is a long-lasting and profound behavioral response following a brief defeat in the home cage of a larger, more aggressive opponent. Following the initial defeat, hamsters fail to produce normal territorial aggression, but instead display only submissive and defensive behaviors even though they are now tested in their own home cages and a smaller, nonaggressive intruder is used as the opponent. Both glutamatergic and GABAergic neurotransmission in the amygdala can block the acquisition and expression of conditioned defeat. The role of anxietylike processes in conditioned defeat remains unspecified, but Huhman and Jasnow make this link, as well as a link to 5-HT mechanisms.

The development of aggression is discussed in chapter 14. Yvon Delville, Matt L. Newman, Joel C. Wommack, Kereshmeh Taravosh-Lahn, and M. Catalina Cervantes review the biological factors underlying the ontogeny of aggression using rodent, nonhuman primate, and human studies. For example, in male Syrian hamsters, the development of agonistic behavior during puberty is marked by a transition from play fighting to adult aggression. These behaviors are characterized by two components: the frequency and the type of attacks. First, attack frequency decreases during puberty. Second, the targets of attacks shift from the face to the lower belly and rump. In addition, the development of agonistic behavior is altered by repeated exposure to aggressive adults during puberty; subjugated hamsters develop adultlike attacks at earlier ages. Delville and coauthors also report new data showing how exposure of peripubertal hamsters to aggression or young people to bullying influences the development of aggressive behavior.

The neurobiology of aggression in children is reviewed in chapter 15 by R. James R. Blair, K. S. Peschardt, Salima Budhani, and Daniel S. Pine. They first consider

two general perspectives that have received considerable attention with respect to aggression in children: the frontal lobe and fear dysfunction positions. They then describe a fundamental difficulty with these two perspectives of a general account of aggression in children, namely, that they implicitly assume all aggression is mediated by the same neural mechanisms. Blair and coauthors argue that a distinction must be made between reactive and instrumental aggression. Finally, they delineate neurobiological risk factors for reactive and instrumental aggression.

The influence of drugs of abuse on aggressive behaviors is extensively reviewed by Jill M. Grimes, Lesley Ricci, Khampaseuth Rasakham, and Richard H. Melloni, Jr., in chapter 16. They present the effects of both common drugs of abuse and drugs classified as prescribed medications. Throughout the course of their review, they present studies in a systematic fashion beginning with age of drug exposure (i.e., adult, adolescent, gestational), using different experimental aggression paradigms for examining multiple aggression subtypes (i.e., resident/intruder tests for territorial aggression, neutral arena tests for intermale aggression, and maternal aggression tests, to name a few) in several different species and strains of animals.

The psychopharmacology of human aggression is reviewed in chapter 17 by Don R. Cherek, Oleg V. Tcheremissine, and Scott D. Lane. Epidemiological studies of the use of drugs of abuse, such as alcohol, benzodiazepines, CNS stimulants, and opiates, are reviewed, and all seem to increase aggressive behaviors in people. Several laboratory models of human aggression are described, including the authors' clever *point subtraction aggression paradigm*, which unlike other models (that involve electric shocks) allows subtraction of money as the aversive stimulus. The authors then review the effects of several drugs in these laboratory models of aggression.

Finally, psychophysiology and brain mechanisms of human antisocial behavior are reviewed by Angela Scarpa and Adrian Raine in chapter 18. Based on a wide range of approaches, including genetics, biochemistry, neuropsychology, brain imaging, and psychophysiology, it has been found that biological individual differences likely predispose people to antisocial behavior in response to environmental events. The authors review the major psychophysiological findings and theories regarding antisocial behavior, with a specific focus on skin conductance, heart rate, electroencephalogram, and startle blink research. Their goal is to provide evidence of psychophysiological relationships with antisocial behavior and overview theories regarding the meaning of these relationships.

All of the chapters emphasize future directions for research on aggression and reveal important domains that have received comparatively less attention in this literature. Taken together, these chapters provide up-to-date coverage of the biology of aggression by some of the leading authorities currently working in this field. There is much interest, both generally and among behavioral biologists, in the biological mechanisms of aggressive behavior, and during this past decade remarkable advances have been made using pharmacological and genetic approaches to understanding aggression and violence. It is my hope that this book provides both a comprehensive review of previous work in this field and a guide to future research on the biology of aggression.

—Randy J. Nelson
June 1, 2005

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PART I

GENES

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1

Genetic Aspects of Aggressions in Nonhuman Animals

Stephen C. Maxson & Andrew Canastar

This review could, but does not, consider what is known about the genetics of aggression in different animal species. Rather, it explores several contextual issues for developing more fully a comparative genetics of aggression in animals. After describing the kinds of aggression in animals, we relate aspects of the evolution and development of aggression to the study of its genetics. This is followed by a consideration of species that are being or could be used to begin a comparative genetics of aggression. A comparative genetics of aggression is most relevant to developing animal models for human aggression.

Types of Aggression in Animals

Here, we only consider the types of aggression known as agonistic behavior. Scott (1966) defined agonistic behavior as "behavior patterns having the common functions of adaptations to situations involving physical conflict between members of the same species." These include offensive, defensive, and parental aggression. Thus, this does not include Brain's (1979) categories of predatory aggression or reproductive termination (infanticide).

Blanchard and Blanchard (1984, 1988, and ch. 12 in this volume) have cogently argued that (a) across species, including humans, offensive and defensive motor patterns differ, (b) offense and defense serve different functions, and (c) defensive attack is more likely to cause serious injury than offensive attack. They suggest that defensive behaviors serve the functions of protecting one's self from injury by others and that offensive behaviors serve the functions of obtaining and retaining survival and reproductive resources. Furthermore, it has been proposed that each of these two broad classes of aggressive behavior (at least in mammals) has motivational systems with neural homologies across species (Adams, 1979, 1980; Blanchard & Blanchard, 1988). Parental aggression by female, male, or both parents serves the function of defending progeny from injury by conspecifics and predators. Where appropriate, the genetics of each type of agonistic behavior in both sexes should be, as discussed below, investigated in all animals used in studies of the genetics of aggression.

Evolution of Aggression

For a behavior to evolve by natural selection, its reproductive benefits must exceed its reproductive costs. The potential reproductive benefits of aggression have been discussed above. They are high. The potential reproductive costs are high, too—for many species, these include risk of injury and death. As a consequence, many species have evolved a sequence of interactions during one-on-one agonistic conflict, which can resolve the conflict without escalating to a fight, with the risk of injury and death (Archer, 1988).

For example, male red deer compete with one another during the rutting season for control of female herds (Clutton-Brock, Albon, Gibson, & Guinness, 1979). The male that controls the herd has exclusive mating rights. Agonistic encounters begin with roaring over and over up to 3,000 times a day. This can resolve the dispute, with one male leaving and the other controlling the female herd. If the conflict is not resolved in this way, then it escalates to the two males walking side by side, with each male making himself look as big as possible. If this does not resolve the dispute, then it escalates to a fight, with the males locking horns while pushing and shoving one another. There is a grave potential for injury and even death in this last stage, which will always resolve the conflict. Across species, it appears that two factors are involved in determining whether or not the conflict escalates. These are resource holding power (RHP) and resource value (RV). RHP is essentially fighting ability, and the male with the large RHP usually wins the conflict. Conflicts usually escalate when RHP or RV or both are the same for both contestants.

This has relevance to research on the genetics of aggression. Most of these studies in mice and other animals are concerned with the last phase of an agonistic conflict, the escalated fight (see Miczek, Fish, & DeBold, 2003, and Nyberg, Sandnabba, Schalkwyk, & Sluyter, 2004). We suggest that all phases of the agonistic conflict should be considered in genetic studies and that this should include an assessment of the genetics of RHP and RV and how each animal in the encounter evaluates these. There is one study with mice that incorporates this approach (Parmigiani, Ferrari, & Palanza, 1998). It was proposed that males with and without successful fighting experience differed in RHP and that males mating and cohabiting with females would have higher RV to defend than males that were singly housed.

Development of Aggression

A variety of environmental and experiential factors influence the development of agonistic behaviors. Evidence for these effects and their role in the development of agonistic behaviors across a range of species is discussed in Huntingford and Turner (1987) and in Delville, Newman, Wommack, Taravosh-Lahn, and Cervantes (ch. 14 in this volume). Such environmental factors appear to have more effects on the development of the occurrence and intensity of aggression than on its motor patterns. Regardless, they may have a critical role in adjusting the level of aggressive behavior to local environment conditions. In this context, it would be interesting to know whether they act on RHP, RV, or their assessment.

The effects of genetic variants on aggression are often dependent on environmental or experiential parameters, as has been shown repeatedly for mice. These include effects on aggression of genetic background, maternal environment, peer environment, early experience, sexual experience, wins and defeats, observational learning, type of opponent, and type of test (see reviews by Maxson, 1992, and Maxson & Canastar, 2003). For example, handling affects the aggressive behavior of male mice of the C57BL/10 strain, but has no effect on aggressive behavior of male mice from two other strains (Ginsburg & Allee, 1942; Ginsburg & Jummonville, 1967; Scott, 1942). The study by Ginsburg and Allee also showed that C57BL/10 males were aggressive in the presence but not in the absence of a female mouse. This may reflect a genetic sensitivity to the value of this reproductive resource. Additionally, mice of the aggressive BALB/c strain became pacific after a series of defeats, whereas mice of the C57BL/10 strain became aggressive after a series of wins. This may reflect learned changes in RHP of each strain. We suggest that such interactions of genes and environments may be ways to adjust aggression levels of genetic variants to the local circumstances and that they should be investigated across a range of species.

Comparative Genetics of Aggression

Elsewhere, Maxson (2003) has suggested that we should seek to develop a comparative genetics of adaptive behaviors, with the goal of finding general principles relating genes and environments across animal species. This can and should be done for aggressive behavior.

Such a comparative genetics has several advantages. It will identify (a) genes with effects on aggression across many species and those with effects restricted to a few or even one species, (b) neural mechanisms of aggression based on these genes involved in many species or limited to a few or even one species, (c) interactions of genes and environments that affect the development and expression of aggression across many species and ones that are restricted for a few or even one species, and (d) the role of these genetic and environmental interactions across species in the evolution of adaptive aggressive behaviors. This strategy will also provide a more substantial base for developing hypotheses about human aggression derived from animal models.

As a beginning of a comparative genetics of aggression, here we consider some aspects of the genetics and aggressive behaviors of a few invertebrates (fruit flies and honeybees) and vertebrates (fish [sticklebacks and zebra fish], birds [chickens], and mammals [rodents, carnivores, and primates]). These were chosen on the basis of their potential for genetic analyses and/or because of an existing literature on their aggression.

In general, three approaches are used in research that seeks to identify the genes with effects on one or more types of aggression in males and females of a species. One seeks to map genes with effects on one or more types of aggression in males or females to their chromosomal location. This detects the genetic variants with effects on a type of aggression in males or females that exist in the species. The other mutates a gene, and the variants in this gene are tested for effects on a type of aggression in males or females. Potentially, this can detect all of the genes that affect a type of aggression in males or females. Last, strain or phenotype differences in brain expression of many genes across development can (with gene chips) be assessed in relation to a type of aggression in males or females. This can detect both variant and nonvariant genes, as well as identify systems of interacting gene with effects on the development of aggression.

Invertebrates

It appears that aggressive behavior is widespread across the invertebrate phyla (Huntingford & Turner, 1987). It has been documented in Cnidierians, Annelids, Mollusks, Echinoderms, and Arthropods. But only the insects (an Arthropod class) have been the focus of genetic studies. Two of these are considered in more detail.

Fruit Flies

Recently, the aggressive behavior of fruit flies has been detailed (Chen, Lee, Bowens, Huber, & Kravitz, 2002). Here we briefly focus on several important aspects of this work.

First, the aggression test involves competition over resources. The agonistic encounters occur in the presence of food and a female. This should enable the manipulation of RV in these studies.

Second, there is a sequence of well-described interactions that progress from low-intensity behaviors to escalated fight with potential for injury. These steps allow the opponents to acquire information about each other's RHP. This should enable the detection of genetic and environmental effects on the full sequence of the agonistic encounter, not just the escalated fight.

Third, Chan, Nilsen, and Kravitz (2003) have described the agonistic behavior of females. Thus, sex differences in the genetics and development of aggression can be studied.

Fourth, there are at least 471 species of Hawaiian *Drosophila,* and about 1,000 to 2,000 species worldwide. Much is known about the taxonomy, phylogeny, ecology, and behavior of these species (Parsons, 1973). As genes with effects on aggression are identified and characterized for *D. melanogaster,* their role in the aggression of other species can be studied with the goal of understanding the evolutionary genetics of *Drosophila* aggression.

Fifth, there are the well-known genetic advantages of *Drosophila* (Sokolowski, 2001). Its DNA (160 megabases or Mb, on 4 chromosome pairs) was sequenced in 2000. There are many techniques for mapping genes to *Drosophila* chromosomes, and there are many approaches to making and rescuing genetic mutants, as well as to tracing their developmental effects. All of this should lead to the identification of all of the genes that can cause variation in fruit fly aggression and to successfully tracing the gene effects from protein to behavior.

Honeybees

Honeybees are eusocial insects with haplodiplod sex determination. Females are diploid and males are haploid. Females but not males show agonistic behaviors. Aggression occurs in both the reproductive queen and nonreproductive workers. The DNA (200 Mb) of the 32 chromosome pairs of the honeybee is now being sequenced (http://hgsc.bcm.tmc.edu/projects/honeybee/).

Some workers (about 15% of them) specialize at about 15 days of age in guarding the nest from invasion by honeybees from other nests or by various predators and thieves, and some of these guard bees at about 19 days of age sting such intruders. In the act of stinging, they usually die. In crosses of Africanized and European colonies, three quantitative trait loci (QTLs) (chromosomal regions) with effects on stinging behavior have been detected (Aerchavaleta-Velasco, Gregg, & Emore, 2003; Guzman-Novoa, Hunt, Uribe, Smith, & Aerchavaleta-Velasco, 2002). These are Stings 1, 2, and 3. Sting 1 affects both guarding and stinging behaviors and Stings 2 and 3 affect only stinging behaviors. Also, it appears that the role of guard or stinging worker is at least in part genetically determined, as it depends on having appropriate alleles of Stings 1, 2, and 3.

In the spring, a colony usually divides (Gould & Gould, 1995). The old queen leaves with about half the colony. Before that, the workers have prepared several brood cells for raising new queens. When one of these emerges, she kills the others still in the cells and fights to the death any that have already emerged. This behavior may depend on genes expressed in queens and not in workers. This differential gene expression could be assessed with gene chips, as has already been done for the transformation from nurse to foraging worker. It has been shown that there is in foraging workers (as compared to nursing workers) an increase in brain expression of the period (Bloch, Toma, & Robinson, 2001) and the foraging (Ben-Shahar, Robichon, Sokolowski, & Robinson, 2002) genes, among many others (Whitfield, Cziko, & Robinson, 2003).

The high cost and lethal aggression of workers and queens raises some interesting issues about inclusive fitness, kin selection, and aggression (Hamilton, 1964). This is relevant when a gene decreases the fitness of the individual (as occurs in honeybee workers) but increases the fitness of one or more relatives (as occurs in their sister, the queen). In honeybees, the workers are sterile. Moreover, the guard stingers die in defending the nest and the queen. Here, the reproductive cost of aggression to the worker is balanced by benefits to the queen, her sister. In other species, the high cost to the individual of an escalated fight may also be compensated for by a reproductive benefit to relatives.

Inclusive fitness and kin selection theories suggest that fighting among relatives should be attenuated. But this does not happen among queens that share between 75 and 50% of their genes. It may be that when the RV is very high for both individuals, genetic similarity does not inhibit aggression among relatives. Here only the winner of the fight between queens will reproduce. This may also account for siblicide in some birds and mammals (Dugatkin, 2004). For example, there is siblicide in egrets where the resource is food and in spotted hyena females where the survivor can achieve the mother's clan status.

Aggression among new queens and nest guarding by workers occur in other eusocial hymenoptera, including ants (Holldobler & Wilson, 1994), Many species of ants attack and raid the nests of the same or different species of ants. There are 12,000 known species of eusocial insects, with 11 independent origins in the hymenoptera. As genes are identified with effects on aggression in honeybees, it will be possible to investigate the effects of these across the hymenoptera and other eusocial insects.

Vertebrates

Aggressive behavior is widespread across the vertebrate phyla (Huntingford & Turner, 1987) and has been documented in fish, amphibians, reptiles, birds, and mammals. But to our knowledge no genetic studies have been conducted with amphibians or reptiles.

Fish

Sticklebacks

Both male and female three-spined sticklebacks (*Gasterosteus aculeatus*) are highly aggressive as reproductive adults. Males fight with males for access to females and sometimes females fight with females for access to males. Nonreproductive adults, subadults, and juveniles also can be aggressive. One study has investigated whether the various types of aggression in these sticklebacks are genetically correlated, with some genes causing variation in more than one type of aggression (Baker, 1994).

A series of double or two-way selection studies have been conducted. Fish were selected over 3 generations for one type of aggression and tested each generation for that and another type of aggression. There was selection for high and low levels of juvenile aggressiveness of both sexes, for territorial aggression of adult males and females, and for dominance. A random control line was also maintained. The base population was

composed of wild sticklebacks from a stream in the Netherlands. For the aggression test, a same-sex, same-age opponent was placed in a glass tube or plastic chamber in the home tank, and the duration of bumping and biting was recorded for 5 min. Dominance was based on a round-robin paired test among 15 males.

Selection was successful for all but the high line of adult male territorial aggression. This indicates that even with adaptive traits, such as these types of aggression, genetic variability can remain in the population and contribute to individual differences in aggression. Also, there were significant genetic correlations between juvenile and adult aggression of each sex and between territorial aggression and dominance in males. These genetic correlations indicate that variation in two traits is due in part to variation in the same genes. This may constrain the evolution of each kind of aggression. Selective effects on one type of aggression should influence the other types. In other words, because of the genetic correlation among types of aggression, selective effects on one will cause generational changes in another.

We know little or nothing about genetic correlations for different kinds of aggression in other species. However, it is critical to understanding the effects of reproductive costs and benefits on species aggressive behaviors and the underlying genetics.

Zebra Fish

Although selective breeding studies, such as those with stickleback, can show that aggression is heritable in an animal species and that the same genes can affect more than one kind of aggression, it cannot identify the individual genes with effects on aggression. It has been suggested that zebra fish could be used for this purpose (Gerlai, 2003).

Zebra fish have been used to identify genes with effects on neural and brain development. These fish do well in captivity and a single spawning can yield hundreds of progeny. Single gene variants can be and have been produced with the chemical mutagen ethyl nitrosourea (Guo, 2004). Males are exposed to the mutagen. Dominant mutants can be detected in the F1 generation, and the recessive mutants can be identified in the F3 generations.

A test of territorial aggression has been proposed that could be used as a mutant screen. Several aggressive behaviors would be measures in response to seeing the subject's image in a mirror. These are fin erection display (erection of dorsal, caudal, pectoral, and anal fins), undulating body movements, slaps of the caudal fin, and attacks (short bouts of fast swimming directed at an opponent, sometimes accompanied by an open mouth and biting).

A mutagenesis approach can potentially detect all of the genes across the 25 chromosomes of the zebra fish that could affect variation in these measures of aggression. The cell and neural biology of the zebra fish are well developed, which should facilitate tracing the pathway from each gene to behavior.

Once genes are identified with effects on aggression in this teleost fish, the effects of their homologues on aggression in other fish could be studied.

Birds

Surprisingly, there is very little genetic research on aggression in birds. It would be interesting to compare the genetics of aggression in polygynous species with that in polyandrous species. In polygynous species, males fight one another for reproductive access to females, whereas in polyandrous species, females fight one another for reproductive access to males (Dugatkin, 2004). It would also be of interest to know whether the genes involved in song learning of monogamous birds were involved in their territorial aggression. The experience of hearing one's own species song, but not other species songs, increases the expression of genes for transcription factors in zebra finch and in canary brains (Mello, Vicario, & Clayton, 1992). The songs of such birds are the initial part of their sequences of agonistic behaviors toward intruders. But most of the research on the genetics of aggression in birds has been with domestic chickens. In these, there is aggression in males and females to achieve and maintain status in dominance hierarchies. Selective breeding and strain differences in chickens suggest that the aggressive behaviors of female and male chickens are heritable (for a review, see Craig & Muir, 1998). In one study, selection for male aggression and dominance had a correlated effect on female aggression and dominance, suggesting that some of the same genes affect these behaviors in male and female chickens (Craig, Ortman, & Gujl, 1965). Also, there have been some recent studies to map regions of chromosomes (QTLs) that affect variability in the pecking of one bird by another (Buitenhuis et al., 2003; Kjaer & Sorensen, 1997). The search for genes with effects on aggression in domestic chicken will be facilitated by having a

genetic map for this species (Burt & Cheng, 1998) and by the DNA sequencing (1,000 Mb across 39 chromosome pairs) of the red jungle fowl, which is the ancestor of the domestic chicken (Burt & Pourquie, 2003; http://www.nhgri.nih.gov/11510730). Once genes with effects on aggression are identified in chickens, effects of their homologues on aggression in other bird species could be studied.

Mammals

Rodents, carnivores, and primates are considered in this section. Some information on the genetics of aggression for horses, cattle, swine, and sheep can be found in Huntingford and Turner (1987) and in Grandin (1998).

Rodents

Mice Both male and female mice show offensive and defensive aggression. Aggression by males is primarily territorial; male mice exclude other males from the territory or deme and dominate males within a deme. Aggression by females is both territorial and parental. They guard food and protect progeny by attacking intruding males and females. In the deme, adult females are usually both lactating and pregnant, both of which conditions facilitate parental aggression against an intruder.

In the laboratory, two paradigms are widely used in genetics research on mouse aggression. These are the resident-intruder test, in which an intruder is placed into the resident's home cage, and the neutral cage test, in which both opponents are placed into a cage other than the home cage. These tests may model encounters in the deme or home territory and outside the deme, respectively. Studies on maternal aggression occur in the home cage with pups present. It is also usual to weight match opponents in these tests, which could facilitate escalation of encounters to fights.

The search for genes with effects on aggression in male and female mice has been and will be greatly facilitated by the sequencing of its DNA (2,600 Mb), a dense gene map of its 20 chromosome pairs, knockout and chemical mutagenesis, and transgenic rescue of mutants (Maxson, 2003).

Male Aggression. The first studies on male aggression of inbred strains of mice were published more than 60 years ago (Ginsburg & Allee, 1942; Scott, 1942). Since 1942, many studies of strain differences in murine aggression have been published. There have also been three selective breeding studies of male mouse aggression (for a review of the literature on inbred and selected strains, see Miczek, Maxson, Fish, & Faccidomo, 2001). Taken together, these studies provide initial evidence that some aspects of male mouse aggression are heritable, but do not identify the genes that can or do cause variation in male mouse aggression. However, 36 of the genes that contribute to murine aggression by males have been identified to date, mostly using knockout mice (see review by Maxson & Canastar, 2003). Research on several of these is described in detail elsewhere in the volume (see Chiavegatto, Demas, & Nelson, ch. 6 in this volume, and Simon & Lu, ch. 9 in this volume). Here we consider some other aspects of the genetics of mouse aggression, especially some conceptual and methodological issues.

(A) The Y Chromosome (Male-Specific Part or Non-Pseudoautosomal Region) and Aggression. The DBA/1 and C57BL/10 Y chromosomes (male-specific part or non-pseudoautosomal region) differ in effect on offensive aggression. The differential effect of these Y chromosomes depends, at least in part, on the genotype of the opponent. When the congenic strains, DBA/1 and DBA1.C57BL10-Y, are tested in a homogeneous set test, the strains differ in aggressive behavior, but when they are tested against a DBA/1 opponent, they do not differ in aggressive behavior (Maxson, Didier-Erickson, & Ogawa, 1989). Similar effects of the opponent have been reported for the CBA/H and NZB Y chromosome pair (Guillot, Carlier, Maxson, & Roubertoux, 1995). The DBA/1 and C57BL/10 Y chromosomes have differential effects on a urinary odor type. Mice can tell the difference between the urinary odor types of DBA/1 and DBA1.C57BL10-Y males (Monahan, Yamazaki, Beauchamp, & Maxson, 1993). This Y chromosomal effect on odor type is independent of adult testosterone (Schellinck, Monahan, Brown, & Maxson, 1993). Also, DBA/1 but not DBA1.C57BL10-Y males appear to show differential aggressive behavior to these urinary odor types (Monahan & Maxson, 1998). There are at least 12 genes on the mouse Y chromosome (Mitchell, 2000) and some of these are expressed in brain (Xu, Burgoyne, & Arnold, 2002). These are candidates for the Y effect on aggression and the differential response to Y odor types.

These findings on opponent effects raise two general issues: (a) the investigation of the mechanisms and functions of this and other opponent effects and (b) the recognition that effects of other genetic variants on

aggression in mice and other species might depend on the type of opponent.

The differential effect of the DBA/1 and C57BL/10 Y chromosomes also depends on strain background. This occurs on a 100 or 50% DBA/1 background but not on a C57BL/10 background (Maxson et al., 1989; Maxson, Ginsburg, & Trattner, 1979). For example, the congenic pair DBA/1 and DBA1.C57BL10-Y differ in aggressive behaviors, but the congenic pair C57BL/10 and C57BL10.DBA1-Y do not. Similar effects of background on aggression are seen for the CBA/H and NZB (Guillot et al., 1995), the CBA/Fa and C57BL/6 (Stewart, Manning, & Batty, 1980), and the SAL and LAL (Sluyter, van Oortmerssen, & Koolhouse, 1994) pairs of Y chromosomes. These findings raise three general issues for research on the genetics of aggression in mice and other species. First, how common are these epistatic interactions? Second, what are the mechanisms of these epistatic interactions? Third, what effects of other genetic variants on aggression in mice and other species might depend on the genetic background?

(B) The Y Chromosome (Recombining or Pseudoautosomal Region) and Aggression. Two groups have shown that there is an effect of the recombining or pseudoautosomal region of the Y chromosome on aggression (Roubertoux et al., 1994; Sluyter, van Oortmerssen, et al., 1994). There is a single gene in this region of the murine Y chromosome, and it codes for the enzyme steroid sulfatase. It is expressed in brain, and it may regulate neurosteroids. For the CBA/H versus NZB Y chromosome, the effect of this region occurs with nonisolated males paired with an A/J opponent in a neutral cage (Le Roy et al., 1999; Roubertoux & Carlier, 2003). There is no effect of variants in this region of the Y chromosome when the mice are isolated before testing, in a resident-intruder test, and the opponent is not an A/J male.

There are similar findings for the strain correlations between the size of the hippocampal mossy fibers and the proportion of attacking males across several strains. The strain correlation is $r = -0.86$ when the test is in the resident's cage, when the resident has been isolated for 13 days, and when the opponent is an A/J male (Guillot, Roubertoux, & Crusio, 1994). This strain correlation becomes zero when the test is in a neutral cage, or when the tested mouse is not isolated or isolated for a day, or when the tested mouse and its opponent are the same strain (Roubertoux, Le Roy, Mortaud, Perez-Diaz, & Tordjman, 1999). Also, in this study, a general factor for initiating attack was not revealed across 11 inbred strains for four groups that differed in one or more of the following: (a) isolated versus nonisolated test males, (b) resident-intruder test versus neutral cage test, and (c) an opponent of the same versus a different strain as the tested male. Also, for the four groups, there were unique strain correlations with measures of neurotransmitters or of gonadal hormones.

These findings raise several general issues. First, genetic effects on aggression in mice and other species depend on several nongenetic parameters. Second, this implies that a gene variant may not have the same effects across these nongenetic parameters. Third, how do genetic effects in laboratory tests for mice or other species relate to genetic effects on aggression in feral conditions, where the nongenetic parameters may differ between the laboratory and the wild?

(C) Short and Long Attack Latency Mice. About 1971, feral *Mus domesticus* were trapped in a mansion near Groningen, the Netherlands. Mice descended from these were the foundation stock for selective breeding for short and long attack latencies (van Oortmerssen & Baker, 1981). After 30 generations of selection, male mice of the long attack latency line (LAL) rarely attacked and male mice of the short attack latency line (SAL) consistently attacked. The opponent was a male of the Mas-Gro strain. The encounters occurred on a familiar, but not the home, part of the test cage. The successful selection for attack latency indicates that, at least in male mice, it is heritable, and that there was genetic variability with effects on attack latency in the wild population.

Studies of feral mice indicated that these occurred in two behavioral morphs, short and long attack latency males (van Oortmerssen & Busser, 1989). It was suggested that this was the result of each morph being adaptive in different phases of the population cycle in wild mice. Within a settled population or deme, selection favors for a while short attack latencies. Males with short attack latencies are more likely to dominate the deme and breed. But as the attack latencies get very short, these males attack not only intruding males but also females and progeny; this results in the collapse of the deme and the dispersion of its members. Now long attack latencies are favored in establishing new demes. Thus, extreme aggression is constrained by its effect on population dynamics, with shifting selective advantage for extreme aggression or extreme pacificity.

It would be of interest to know how many and which genes are involved in this dimorphism, as well as the

mechanism of their effect. There is a minor contribution of the two regions of the Y chromosome (Sluyter, van Oortmerssen, et al., 1994). Recent studies using gene chips have found differential expression of 191 genes in the hippocampus of SAL and LAL mice (Feldker, Datson, Veenema, Meulmeester, et al., 2003; Feldker, Datson, Veenema, Proutski, et al., 2003). Some but not all of these genes may be involved in the difference in size of the hippocampal mossy fibers of SALs and LALs (Sluyter, Jamot, van Oortmerssen, & Crusio, 1994). However, artificial selection was too rapid and heritability too modest for variants of all 191 genes to be involved in the difference between SAL and LAL mice in behavior and biology.

There are some general issues raised by these studies. First, whether aggression is adaptive depends on the level of aggression. Second, the same genes can affect both adaptive and nonadaptive aggression.

(D) Competitive Aggression. Most recent studies of the genetics of aggression in males take place in the resident's cage or a neutral cage in the absence of a resource such as food or a female. But earlier, there was research on strain differences for what was called competitive aggression. In these studies, mice were food deprived and a standard pellet of food was placed in the cage. Both male and female mice displayed competitive aggression, and within a strain, there were no sex differences in competitive aggression. This suggests that the same genes can cause variation in this type of offensive aggression for both males and females. In one study the rank order of offensive aggression was compared in a neutral cage test and a competitive test (Hahn, 1983). It was not the same, suggesting that some of the genes causing variation in offense have effects in one test but not in the other. Also, Adams (1980) proposed that the olfactory system is involved in sex recognition-mediated resident-intruder or neutral cage offense by males, but that it has no role in competitive aggression of males and females. This may account for different genetic effects on territorial and competitive aggression in males and for the same genetic effects on competitive aggression of males and females.

To date, the competitive test has not been used with gene knockout mutants. We suggest that it should be, for a more rounded understanding of the genetics of mouse aggression. We also suggest that the competitive test may be of use in studying the role of RV in the escalation of encounters.

(E) Sexual Aggression. Male mice are often characterized as nonaggressive toward females (Mackintosh, 1970; Maxson, 1999; Miczek et al., 2001). However, there are a few reports indicating that female mice can be the targets of male aggression. Male mice of various inbred strains, two sets of lines selected for male aggression, and laboratory-bred wild mice exhibit this behavior that is genotype dependent and can be modified by sexual and aggressive experiences (Benus, Den Daas, Koolhaas, & van Oortmerssen, 1990; Canastar & Maxson, 2003; Mugford & Nowell, 1971; Rowe & Redfern, 1969; Sandnabba & Korpela, 1994). To have a more complete picture of the genetics of aggression in mice, there should be a search for genes with effects on this type in comparison to other types of mouse aggression.

(F) Defensive Aggression. Defensive aggression has the adaptive function of protecting not only against attacks by conspecifics but also from predators. On this basis a Mouse Defense Test Battery was developed (Blanchard, Griebel, & Blanchard, 2001; see also Blanchard & Blanchard, ch. 12). When exposed to a potentially threatening stimulus, such as an anesthetized rat, mice can show risk assessment, defensive threat and attack, freezing, and flight. This battery has been used to study the effects of drugs on defense, but it has not been used in genetic studies to date. We suggest that it should be.

There have been a few studies of the genetics of defense in conspecific encounters. Potentially, one of these is a study of different aggression tests in the Turku Aggressive (TA) and Turku Nonaggressive (TNA) selected lines (Nyberg et al., 2004). As residents or as intruders, the TNA males are more aggressive than TA males in a resident-intruder paradigm. If the attacks by intruders were defensive, then this finding would suggest that some genetic variants enhance both offense and defense. However, knockout mutants of two genes appear to increase offense and decrease defense. These are knockouts of the genes coding for α-calcium calmodulin kinase II (Chen, Rainne, Greene, & Tonegawa, 1994) and Fyn tyrosine kinase (Miyakawa, Yagi, Takao, & Niki, 2001).

Because defense is a significant part of agonistic behavior in mice and other species, we strongly recommend that tests for this be included in chemical and knockout mutagenesis screens.

Female Aggression. Once upon a time it was thought that female mice were not aggressive. But it was subsequently shown that female laboratory mice could be aggressive when pregnant or lactating (see Gammie & Lonstein, ch. 11 in this volume). There are strain dif-

ferences in maternal aggression, which are mediated by ovarian hormones (Svare, 1989). Additionally, some inbred strain females (Ogawa & Makino, 1981) and some wild female mice (Ebert, 1983) are aggressive against males in resident-intruder tests when the females are neither pregnant nor lactating. Wild mice were a base population for the successful selective breeding of high and low female aggression lines, indicating that there was genetic variation in the wild population for this trait in female mice. There was also a correlated effect of this selective breeding on maternal aggression during lactation against an intruder female (Ebert, 1983). This suggests that some of the same genetic variants affect both kinds of female aggression. Regardless, it has been suggested that maternal aggression in mice is offensive or defensive depending on how likely an intruder is to kill pups (Parmigiani, Palanza, Rodgers, & Ferrari, 1999).

There has been a lively discussion as to whether the same genes cause variation in the territorial aggression of males and females. Two selection studies suggest that they do (Hood & Cairns, 1988; Lagerspetz & Lagerspetz, 1983) and two selection studies suggest that they do not (Ebert, 1983; van Oortmerssen & Baker, 1981). Some knockout mutants cause only male aggression to vary, some cause both to vary in the same direction, and some cause an increase in one and a decrease in the other (see Maxson, 1999, for a review). These suggest that the correlation depends on the gene involved and its variants. Also, it may depend on the opponent. Regardless, it appears, as discussed above, that the same genes cause competitive aggression to vary in male and female mice.

Many of the issues raised for the genetics of male aggression are also relevant to the genetics of female aggression, and the genetics of aggression in females should be as intensively and extensively studied as that in males.

Rats Both male and female rats show offensive and defensive aggression. Within the colony, there are male and female dominance hierarchies and status is determined by wins and loses in within sex agonistic encounters. Alpha males attack and exclude intruders. Aggression by females is also parental; they protect progeny by attacking intruding males and females. In the colony, adult females are usually both lactating and pregnant. These physiological conditions facilitate maternal aggression against an intruder.

There are two main paradigms for offense and one for defense in rats. For offense, these are the resident-intruder test and the colony model (Wall, Blanchard, & Blanchard, 2003). The resident-intruder test for rats is similar to that for mice. The colony model has both males and females present, and it consists of the burrow and other spaces. One of these is the visible burrow system (see Blanchard & Blanchard, ch. 12). Offense is shown by the resident in the resident-intruder test and by the alpha male in the colony model. Defense in males and females is often studied in the Rat Defense Test Battery. Frequently a cat or cat odor is used as the stimulus (Shepherd, Flores, Rodgers, Blanchard, & Blanchard, 1992). Rats also display risk assessment, defensive threat and attack, freezing, and flight in response to such potentially threatening stimuli.

The physiology, pharmacology, and endocrinology of rat offense and defense have been well studied and characterized (see Miczek & Fish, ch. 5 in this volume, and Blanchard & Blanchard, ch. 12). Except for some strain comparisons, there have been few genetic studies of aggression in rats (see, for example, Berton, Ramos, Chaouloff, & Mormde, 1997; Fujita, Annen, & Kitaoka, 1994; Hendley, Ohlsson, & Musty, 1992). This may be about to change, as the DNA (2,750 Mb across 21 chromosome pairs) of the rat is being sequenced (Gibbs et al., 2004; http://www.hgsc.bcm.tmc.edu; Pennisi, 2004). This and a genetic map of the rat chromosomes (Levan, Stah, Klinga-Levan, Szpirer, & Szpirer, 1998) will facilitate mapping of QTLs with effects on offense and defense. It may also assist in identifying chemically induced mutants with effects on rat agonistic behavior. These genetic research programs should be modeled on those in mice. Regardless, studies could now be conducted to determine whether any of the genes with effects on mouse offense are varying in rat populations and if any of these have effects on rat offense. Also, known physiological, hormonal, and pharmacological effects on rat offense and defense may suggest genes to consider for association analysis (see Blonigen & Krueger, ch. 2 in this volume, for a discussion of this genetic method).

Voles Prairie (*Microtus ochrogaster*) and pine (*M. pinetorum)* voles are socially monogamous and both males and females exhibit strong partner preference, joint parental care, and selective aggression toward unfamiliar intruders (Curtis & Wang, 2003). Meadow (*M. pennsylvanicus*) and montane (*M. montanus*) voles are socially promiscuous and neither males nor females exhibit much, if any, joint parental care or selective aggression. After mating, pair bonds are formed in

prairie and pine voles, as well as establishment of partner preference, parental care, and selective aggression by the male. This can also be induced in male prairie voles by intracerebral ventricular infusion of arginine vasopressin (AVP) and can be blocked by a specific antagonist of the AVP receptor (Young, Wang, & Insel, 1998). The infusion of AVP has no effect on these behaviors in montane voles. Prairie and montane voles differ in the gene for the AVP receptor; there is a 428-bp insert in the promoter of the AVP gene of prairie voles but not montane voles. This insert is also present in the AVP promoter of the monogamous pine but not the promiscuous meadow vole. The insert appears to have a role in directing the distribution of the neuropeptide receptor V1a in the brain. It has been proposed that male prairie voles become, after mating, socially monogamous, parental, and selectively aggressive toward intruders because of the brain regional sensitivity to AVP. Oxytocin and its receptor appear to have a similar role in the social monogamy, parenting, and selective aggression of female prairie voles. The dopamine systems and stress hormones, such as corticosterone, also appear to have a role in the development of these behaviors in prairie voles.

It is of interest that similar neurotransmitter and behavior correlations have been observed in deer mice. *Peromycus californicus* are monogamous and *P. leucopus* are polygamous. The former have lower latencies to attack opponents in resident-intruder and neutral cage tests. But although there are species differences in distribution of AVP receptors between the monogamous and polygamous deer mice, they are not the same as those for the monogamous and promiscuous voles (Bester-Meredith, Young, & Marler, 1999).

These studies raise several issues. First, it is possible to do genetic analysis at the molecular level by species comparisons. Second, it is possible to relate mating systems to aggressive behavior and their genetics by species comparisons. Third, some aspects of behavioral evolution may be primarily due to effects of a single gene. Fourth, it is unfortunate that the vole genome is not being sequenced. This would facilitate genetic analysis within the species. However, there are genetic maps of the chromosomes of some vole species (Nesterova, Mazurok, Rubtsova, Isaenko, & Zakian, 1998). Regardless, studies could now be conducted to determine whether any of the genes with effects on mouse offense are varying in vole populations and if any of these have effects on offense in male or female voles.

Carnivores There are two large taxonomic groups of carnivores—canids and the felids. Canids tend to be socially monogamous and many, but not all, live in groups. Felids tend to be socially polygamous or promiscuous and territorial, and most are solitary. For each, there is a domestic species in which the genetics of aggression could potentially be studied. The DNA of dogs (about 2,500 Mb across 39 chromosome pairs) is being sequenced (Kirkness et al., 2003). Also, linkage maps are being developed for dogs (Binns, Holmes, & Breen, 1998) and cats (Menotti-Raymond et al., 1999; O'Brien, 1993).

Dogs. Dogs are descended from wolves (Scott & Fuller, 1965), and they were domesticated about 14,000 years ago (Budiansky, 2000). Wolves live in packs with a dominance hierarchy for males and for females. Aggression occurs within sex to obtain and retain status. The alpha male also uses aggression to restrict mating of other males, and the alpha female uses aggression to restrict mating of other females. Much, but not all, of this aggressive behavior involves threat displays rather than physical attacks with bites. However, it has been reported that intraspecific fighting accounts for 35 to 65% of adult mortality (Mech, Adams, Meir, Burch, & Dale, 1998). Since their initial domestication, dogs have been selectively bred to develop the many breeds with differing characteristics, including behavior. There are effects on their social behavior, including aggression. Some dogs were selectively bred to fight other dogs as a sport. Two aspects of the genetics of dog aggression have been studied to at least some degree: (a) the aggressive interactions of dogs mainly as pups or juveniles and (b) attacks against humans.

From 1952 to 1965, a large study was conducted at the Jackson Laboratory on the genetics of dog behavior (Scott & Fuller, 1965). The behaviors of five dog breeds and their F1s and derived generations were studied. The breeds were beagles, cocker spaniels, fox terriers, Shetland sheepdogs, and basenji. Aggression and dominance were mostly investigated in puppy-puppy relationships across development.

In one test, pairs of puppies of the same litter competed for food in the bone-in-pen test from 2 weeks of age. Each puppy was tested with each littermate for control of the bone. Puppies and adults often growl and bark when given a meat-covered bone in the presence of another dog. For all breeds, little dominance had developed at 5 weeks of age; by 11 weeks of age, all breeds had shown an increase in the proportion of fully dominant individuals. After that, there was an increase

in the proportion of dominants in the fox terriers, but not in the other breeds. Actual fights, mostly with noise and struggle but no bites, occurred in many of these dominance tests. During the dominance tests, there were very few fights or attacks in fox terriers, Shelties' fighting decreased with age, and basenjis' fighting increased with age. However, outside these tests, the fox terriers were so aggressive by 5 weeks of age that litters had to be separated. This finding suggests that the genetics of aggression in dogs may be different in food competition situations and in social situations. Taken together, these data indicate that situation-specific aggression in dogs is heritable. No genes with effects on this in dogs have been identified.

Dog attacks on humans are a serious problem with legal consequences (Budiansky, 2000). About 5 million people are bitten by dogs in the United States every year, and about 500,000 to 1 million of these bites are serious enough to need medical attention. Some have suggested that there may be breed differences in dogs that attack people. However, there does not exist clear evidence that breed is a reliable predictor of whether a dog will bite a human (Hahn & Wright, 1998). They also discuss the statistical and methodological issues in determining this one way or another. The environmental contributions to dog attacks and bites have recently been reviewed for golden retrievers by van den Berg, Schilder, and Knol (2003).

Much progress has been made in the study of the genetics of the dog. Recently, molecular genetics has been used to classify dog breeds and their genetic distance (Parker et al., 2004). Also, the dog genome is being sequenced (Kirkness et al., 2003). But the study of its aggressive behavior lags. If not already characterized, the offensive and defensive motor patterns of dogs need to be described in the same detail as those for the domestic cat, and the environmental and experiential causes of dog offense and defense need to be analyzed. It then may be possible to identify the contributions of individual genes. These can then be related to these behaviors in other canid species.

Cats. Domestic cats are promiscuous and solitary. Both male and female cats are territorial. The territories of male cats are larger than those of female cats, and the territory of a male cat overlaps that of several female cats; this is known as a sublease territory. (Tigers have this type of territory, too.) Both male and female cats are aggressive in defending their territories against same-sex intruders. Most territorial encounters are avoided by marking the territory with scent from chin glands, food pad glands, and unburied scats and by spraying urine (males), and the use of claw marks. Male cats fight over access to estrous females. There is also maternal aggression: Female cats defend their progeny from lethal attacks by males.

There are distinct motor patterns for offense and defense in cats (Budiansky, 2002; Tabor, 2003). These include ear positions, pupillary size, vocalizations, body posture, hair fluffing or not, and tail position. In territorial disputes, intruders frequently show defensive patterns and the resident offensive patterns. Although territorial disputes are usually settled without a fight, such disputes can escalate to full fights. This usually occurs when both cats show offense patterns and when they are equally matched. Both cats will roll on the ground trying to get a good grasp on the other's chest, while kicking with their hind legs into the belly of the opponent. During courtship, a female may incite her many suitors to fight, and victorious males mate guard the estrous female.

There appears to be very little research on the biology of offense in cats. But there is substantial research on the brain systems and neurotransmitters involved in defense (Gregg, 2003). Most data are consistent with the dorsal rostral periaqueductal gray (PAG) of the midbrain as being the center that organizes, integrates, and controls all of the defensive behaviors. Neurons from the PAG project to brain stem areas involved in each of the motor patterns of defense. Also, the PAG receives input from hypothalamic, limbic, and cortical areas that modulate the intensity of the defensive behaviors. Neurotransmitters thought to be involved in these systems include serotonin (also known as 5-HT), acetylcholine, gamma-aminobutyric acid (GABA), and neurokinin (Siegel, Roeling, Gregg, & Kruk, 1999). This would appear to be an excellent system for studies to find genes with effects on defense. The effects of these genes could be readily related to the known neurobiology of defense in cats and perhaps in other vertebrates. Regrettably, the cat genome (about 2,900 Mb on 19 chromosomes) appears not to be undergoing sequencing at this time. We recommend that it should be, as was done for the dog genome. However, a genetic map of the domestic cat's chromosomes is being developed (Menotti-Raymond et al., 1999; O'Brien, 1993).

Primates There are four main groups of primates. These are the prosimians, the Old World monkeys, the New World monkeys, and the apes. Although aggressive

behavior has been studied and documented in all of these four groups, both in the wild and in captivity (deWaal, 1989; Holloway, 1974), most of the genetics research on primate aggression has been on the rhesus macaque. These macaques appear to have very frequent aggressive encounters; in two captive populations, the average aggression rate was 18 acts per monkey per 10 hr of observation (deWaal, 1989). These are social monkeys, with male dispersal and female matrilocality (Strier, 2003). This has a role in the aggression of males and females. In these matrilineal societies, there is a strict female dominance hierarchy, with daughters inheriting their status from their mothers. High-ranking mothers help their juvenile daughters assert and achieve their status in agonistic encounters with other females, and when their daughters reach adult size, they can maintain their place by aggressive displays and attacks. Males usually disperse before they are capable of winning fights. Young males dispersing for the first time are usually at the bottom of the male hierarchy of the joined group. There is often a secondary dispersal when the male has reached physical maturity and can hold his own in a fight, as well as having acquired social skills that attract females. Within-group competition among males for mates inevitably leads to fights. Success in these depends not only on the individual's fighting ability but also on his coalitions with other males. Higher ranking males have larger, stronger coalitions. In the birth season, females also defend infants. The agonistic encounters between females or between males often involve both offensive and defensive displays and threats, such as wide open mouth and staring, usually by dominants, or one with ears flat and chin thrust forward with grunting, usually by subordinates. But they can and do escalate to fights with potential for injury and death. In the wild, many show signs of injury, such as scars, frayed ears, and stumpy fingers (deWaal, 1989). Also, most of the deaths of males on Cayo Santiago Island, Puerto Rico, occur from fights during the breeding season (Wilson & Boelkins, 1970).

Genetic analysis of rhesus aggressive behavior will be facilitated by the development of the genetic map of its 21 chromosome pairs (Rogers & Vandenberg, 1998; http://www.shsu.edu/~org_tgs/abstracts%202004/johnson%20abstract.htm) and by characterization of its DNA (about 3,590 Mb) sequence (http://hgsc.bcm.tmc.edu/projects/ rmacaque/).

Most genetic studies to date on the agonistic behavior of male and female rhesus macaque have focused on the role of serotonin as follows (also see Manuck, Kaplan, & Lotrich, ch. 4 in this volume). (a) Levels of 5-HIAA in cerebrospinal fluid (CSF) are a measure of serotonin turnover. 5-HIAA levels are inversely correlated with individual differences in escalated aggression of male rhesus macaques (Higley, Suomi, & Linnoila, 1996). (b) Female pigtail macaques have higher levels of 5-HIAA in CSF and lower levels of escalated attacks than female rhesus macaques (Westergaard, Suomi, Higley, & Mehlman, 1999). (c) There is a polymorphism in the gene for the serotonin transporter in rhesus macaques (Lesch, 2003). This is a 21-bp repeat polymorphism in its promoter. A long (l) and a short (s) allele of this gene differ in the numbers of this repeat. In mother-reared monkeys, there is no effect of this polymorphism on 5-HIAA concentration in CSF. In peer-raised monkeys, those with the s allele had lower 5-HIAA levels than those with the l/l genotype. (d) There are behavioral effects of this genotype interacting with the environment. Mother-reared monkeys were more likely than peer-reared ones to engage in aggression. However, peer- but not mother-reared monkeys with the s allele were more aggressive than those with the l/l genotype (Barr et al., 2003). There are many other environmental contexts that influence the aggression of primates, including rhesus macaques (Wilson, 2003). It would be of interest to know how these environmental influences interact with genotype.

These studies raise two general issues. First, the effect of the 5-HTT variant depends on the environment. Similarly, genotype-environment interactions were reported recently for human behaviors. The effect of monoamine oxidase A variants on adult antisocial behavior depends on childhood maltreatment (Caspi et al., 2002), and that of serotonin transporter variants on adult depression depends on childhood maltreatment or stressful events (Caspi et al., 2003). Such genotype and environment interactions should be studied for agonistic behaviors across species (see Edwards & Herberholz, ch. 3 in this volume). Second, everything discussed so far on the genetics of aggression fits the individual model (deWaal, 2000) in which factors such as genes act on the individual and thus facilitate or inhibit the probability of aggression. But at least for primates, there is a well-developed social context for aggressive acts, and agonistic encounters are often followed by acts of reconciliation, such a mutual grooming. For this reason, deWaal (2000) suggested a relationship model for aggression in which aggressive behavior is one of several ways of settling conflicts of

interest. This model also proposes that after an agonistic encounter, reconciliation restores cooperation among individuals with competing interests. So far, those working in the genetics of aggression have not considered this model, But we suggest that it should be.

Conclusions and Future Directions

We have already discussed the implications and goals of a comparative genetics of aggression in the context of evolution and development. What is needed for now are intensive genetic studies of the species indicated above. Eventually, this should be broadened to other species, both closely and distantly related. Only then will we have a genetics of aggression with general principles across species that would be a firm basis for understanding the evolution, development, and mechanisms of aggression.

However, most genetics studies on aggression in animals are currently directed toward developing and studying genetic variants in animals as models of escalated aggression in humans (Miczek et al., 2003; Nyberg et al., 2004). We suggest that the following be considered in developing and using such models. First, any animal behavior will be, at best, both similar to and different than that of humans. For this reason, Scott (1984, 1989) suggested that no animal species could serve as an exact model for human aggression. Consequently, he proposed that information should be accumulated on the various types of aggression in a wide range of animal species. This is a comparative approach to aggressive behavior in animals as models, an approach that we also recommend for genetic models of human aggression. A comparative approach can identify genes, mechanisms, gene-environment interactions, and contexts with effects across many species. It seems to us that these are more likely to have a role in human aggression than ones limited to one or a few species. Second, what is discovered about the genetics of aggression in an animal should be viewed as generating hypotheses about human aggression. These hypotheses would be about what genes are involved, how these genes have their effect, the interactions of one gene with others, the interactions of genes and the environment, such as nonsocial and social context, the gene-based physiological or hormonal mechanisms, and much more. Such hypotheses need in some way to be tested in humans. One cannot simply assume that what is found in another species will generalize fully to humans. The generation and testing of these hypotheses will necessitate considerate and knowledgeable interactions among those working on animal and human aggression (Blanchard, Wall, & Blanchard, 2003).

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2

Human Quantitative Genetics of Aggression

Daniel M. Blonigen & Robert F. Krueger

For some time, psychological science has sought to understand the underlying biological and etiological processes involved in human aggression and violence. Primarily in the latter half of the 20th century, behavioral genetic methodology has contributed substantially to this body of knowledge by providing a means of systematically estimating the relative influence of genes and environments on aggressive traits and behaviors. Quantitative genetic studies of twins and adoptees, as implemented in behavior genetic investigations, present a distinct advantage over other methods because they are able to disentangle the inherently confounded influences of nature and nurture. In this way, behavioral genetic designs provide an important step toward identifying genetic and environmental risk factors for aggression and violence.

In this chapter we present an overview of human quantitative genetic studies of aggression and violence, including twin, adoption, and molecular genetic designs from both the child and adult literature. Our review begins with the behavioral genetic literature on aggression in childhood and early adolescence. We highlight systematic differences across studies based on the method of assessing aggression, as well as present evidence for both distinct and common etiologies that link aggression with other childhood behavioral problems. Next, we review relevant behavioral genetic investigations of aggression in adulthood; in particular, we note results from studies using official statistics and self-report questionnaires, as well as highlight the absence of a consistent operational definition of aggression in this literature. From there, we discuss predominant theories and empirical findings from longitudinal studies of aggression in both childhood and adulthood, as well as highlight various moderating effects on the etiology of these behaviors (i.e., gender differences and gene-environment interactions). Subsequently, we introduce and briefly summarize molecular genetic studies of human aggression across a range of psychiatric and developmental disorders. Last, we discuss future directions for behavioral genetic research on aggression and underscore important domains that have received comparatively less attention in this literature.

Before proceeding, it should be noted that aggression is a heterogeneous phenotype that pervades numerous forms of psychopathology. Importantly, aggression is a criterion in several diagnostic categories, such as conduct disorder and antisocial and borderline personality disorders. In addition, it is common among individu-

als suffering from mood disorders, psychosis, or dementia. The present review, however, primarily focuses on individual differences in aggressive traits and behaviors rather than these aforementioned diagnostic categories. Such an approach should minimize issues of phenotypic and genotypic heterogeneity that can arise when dealing with heterogeneous diagnostic categories (Alsobrook & Pauls, 2000; Plomin, Nitz, & Rowe, 1990).[1] Nevertheless, when applicable, the degree to which aggressive traits or behaviors are related to these disorders on a genetic level is explored to determine whether there are broader etiologies or vulnerabilities underlying the comorbidity of aggression with specific forms of psychopathology.

Behavioral Genetic Methodology

Prior to reviewing the literature, it is important to discuss some key concepts, assumptions, and limitations in behavioral genetic research. Two models of inheritance are especially relevant. *Monogenic* models assume that a single gene is both necessary and sufficient for the expression of a phenotype. Monogenic models are best suited to explain the inheritance of discontinuous or dichotomous traits. However, with exceptions such as the discovery of a single autosomal dominant gene on Chromosome 4 resulting in the development of Huntington's disease (Gusella et al., 1983), single gene findings in psychopathology research are the exception rather than the norm. Nevertheless, the aggression literature does include a study showing increased rates of antisocial behavior among individuals with an extra Y chromosome (Jacobs, Brunton, Melville, Brittain, & McClement, 1965) and another investigation linking a point mutation in the structural gene for the monoamine oxidase (MAO) enzyme to impulsive aggression in a Dutch pedigree (Brunner, Nelen, Breakefield, Ropers, & van Oost, 1993). The former finding, however, has since been discounted, given that most criminals do not possess the XYY sex chromosome genotype and the vast majority of XYY individuals are not criminal. The latter finding regarding MAO represents a unique intrafamilial mutation that may not necessarily generalize to the larger population. This last point is discussed further in the section on molecular genetic findings.

In contrast to monogenic models, most individual difference traits and forms of psychopathology follow a quantitative, or *polygenic*, pattern of inheritance (Fisher, 1918; Wright, 1921). In this model, several genetic loci as well as various environmental factors combine in either an additive or nonadditive fashion to form continuously distributed traits. As the number of loci contributing to a trait or disorder increases, the overall distribution of phenotypes begins to approach normality. Aggression is typically conceptualized as a quantitative, normally distributed trait that is dimensional in nature rather than a dichotomous, "either-or" category of pathology. Moreover, pathological expression of quantitative traits is thought to occur at the extreme end points of the trait's distribution. Therefore, unless it is demonstrated that the etiology of the extremes differ from the rest of the distribution, aggressive traits and behaviors lend themselves most readily to quantitative genetic analyses (Plomin et al., 1990).

Though it is seemingly contradictory, single-gene inheritance forms the basis for the transmission of polygenic traits. According to Mendel's law of segregation, each gene in the offspring is inherited as a combination of two alleles. In a Mendelian model, certain alleles are dominant and recessive and, therefore, limit the number of phenotypic outcomes which may occur. For traits that are inherently quantitative or polygenic, alleles are not simply dominant or recessive with respect to the phenotype, but operate in synchrony across multiple loci, with each allele contributing some small effect to the phenotype. In other words, quantitative phenotypes are expressed through the cumulative effect of several genetic loci, each of which is inherited according to Mendelian laws of segregation (Evans, Gillespie, & Martin, 2002; Plomin, DeFries, McClearn, & Rutter, 1997).

Twin Studies

Twin studies offer a powerful means of estimating the degree to which genetic and environmental influences contribute to the etiology of human quantitative traits. Twin designs rely on the difference in genetic relatedness between monozygotic (MZ) and dizygotic (DZ) twin pairs to estimate the degree to which these traits are influenced by genetic as well as environmental factors. Genetic effects are of two sorts: *additive* and *nonadditive*. Additive genetic effects involve the summation of individual alleles across several loci in which each allele in the genotype has a cumulative impact. Given that MZ twins share all of their genes, whereas DZ twins share half on average, additive genetic effects are inferred when MZ twin correlations are roughly

twice the magnitude of the DZ twin correlations. Shown below, twice the difference between the identical twin correlation (r_{MZ}) and the fraternal twin correlation (r_{DZ}) can be used to compute additive genetic heritability estimates: $h^2 = 2(r_{MZ} - r_{DZ})$.[2] Some genetic effects do not involve a simple linear summation of genes across loci but rather result from nonadditive genetic mechanisms such as *dominance* and *epistasis* (Plomin et al., 1997). Dominance involves an interaction rather than linear combination of two alleles at a given locus, whereas epistasis results from the interaction of alleles across several genetic loci. Given that MZ twins are genetically identical, they will share all of their genetic effects, including nonadditive influences. However, because these genetic mechanisms deviate from the typical linear pattern seen in additive genetics, DZ twins will share less than half of their nonadditive genetic effects. Specifically, when dominance is relevant to the etiology of a phenotype, DZ twin correlations will be one quarter of the MZ twin correlation, on average. Epistatic effects, on the other hand, are no more likely to occur in fraternal twins than in individuals randomly chosen from the population and, therefore, result in DZ twin correlations of roughly zero.

Twin designs also allow for the quantification of two sorts of environmental effects: *shared* and *nonshared* environmental effects. The shared environment (c^2) consists of factors which both members of a twin pair have in common that serve to increase resemblance between them (e.g., early family environment). Such effects are inferred when MZ and DZ correlations are similar in magnitude. Shared environmental estimates may be computed according to the formula $c^2 = 2(r_{DZ}) - r_{MZ}$. Nonshared environmental effects (e^2) are environmental factors unique and specific to each member of a twin pair (e.g., random accidents) that tend to decrease resemblance between them. To the extent that MZ twins share all of their genetic effects and none of their nonshared environmental effects, e^2 may be computed by subtracting the MZ twin correlation from one: $e^2 = 1 - r_{MZ}$.

Despite their utility, some limitations and assumptions regarding the twin method must be considered. First, this method has been criticized on the grounds that identical and fraternal twins are not representative of the general population and differ from nontwins in important and systematic ways. Though being a twin is certainly a unique experience, findings from the literature suggest that with respect to psychiatric symptoms (Kendler, Martin, Heath, & Eaves, 1995), as well as normal range personality traits (Johnson, Krueger, Bouchard, & McGue, 2002), twins are not systematically or appreciably different than nontwins in the population. Second, the equal environments assumption, or the equal "trait-relevant" environments assumption (cf. Krueger & Markon, 2002), is also crucial to the twin design. This assumption holds that any imposed environmental differences in terms of how MZ twins are treated compared to DZ twins are not relevant to the etiology of the phenotype under investigation.[3] Although environmental differences may exist between MZ and DZ twins (e.g., mothers may dress identical twins more alike than fraternal twins), these differences have not been shown to be relevant to psychological variables, such as personality (Loehlin & Nichols, 1976) or psychopathology (Kendler, Neale, Kessler, Heath, & Eaves, 1994). A third assumption, assortative mating, holds that individuals mate randomly and not based on their degree of similarity for a specific trait. If nonrandom mating does occur based on the trait in question, DZ twins may share more genes for that trait than expected by chance. DZ twins will be more genotypically similar than they would be given random mating, resulting in an overestimate of shared environmental effects and an underestimate of heritability (see, e.g., Krueger, Moffitt, Caspi, Bleske, & Silva, 1998).

Adoption Studies

Adoption studies provide another powerful method of disentangling confounding causes of familial resemblance. In this method, the correlation between adoptees and their adoptive relatives is compared to the correlation between adoptees and their biological relatives. If a trait is primarily genetic in nature, adopted children should resemble their biological relatives to a greater degree than their adoptive relatives. In turn, any resemblance between individuals and their adoptive relatives is, in theory, due to the family environment. An important assumption in adoption designs is that selective placement has not occurred in the adoption process. That is, adopted-away children are not placed with adoptive families that are systematically related to the biological families on the trait in question. However, if a correlation does exist between these groups, that correlation can be modeled and included in the analyses in order to determine its impact on the findings. Notably, a meta-analytic review of twin and adoption studies of aggression tested the relative fit of models which assumed both perfect selective placement and

heritability against the fit of models assuming only the influence of heritability (Miles & Carey, 1997). Though the models assuming perfect selective placement provided an adequate fit to the data, models containing only a heritability parameter provided the best fit across three separate measures of aggression. Furthermore, the heritability estimates from the models assuming perfect selective placement were not appreciably different from the heritabilities of any of the other models (for a more detailed review of the aforementioned behavioral genetic methods and their relevant assumptions and limitations, see Evans et al., 2002, or Plomin et al., 1997).

Genetic and Environmental Influences on Aggression in Childhood and Adolescence

Method of Assessment: Variability in Heritability

In general, findings from behavioral genetic studies in childhood and adolescence suggest that genetic factors play at least some role in the etiology of aggression (DiLalla, 2002). However, heritability estimates vary across these studies depending on the method that is utilized to index aggression. In studies of children, aggression has primarily been assessed via parental reports or independent observational ratings. In terms of parental ratings, the Childhood Behavior Checklist (CBCL; Achenbach & Edelbrock, 1984) is perhaps the most widely employed and validated measure to assess behavioral and psychiatric problems in childhood. The CBCL is a broad range measure consisting of several scales tapping both internalizing (e.g., anxious/depressed) and externalizing (aggression and delinquency) syndromes of childhood. Using this measure, several behavioral genetic studies have demonstrated large genetic contributions to variance in aggression. Ghodsian-Carpey and Baker (1987) obtained maternal ratings of aggression in 4- to 7-year-old twins on the CBCL and found that the vast majority of the variance in these behaviors (94%) could be explained by genetic factors. Also, two other twin studies using parental reports on the CBCL have noted substantial genetic contributions to aggressive behaviors despite using twins across a wide developmental span (ages 7–16; Edelbrock, Rende, Plomin, & Thompson, 1995; Eley, Lichtenstein, & Stevenson, 1999). Largely parallel findings have also emerged from adoption studies of aggression. Genetic effects accounted for 70% of the variance in the aggression scale of the CBCL among groups of adoptees consisting of either biologically related or unrelated sibling pairs (van den Oord, Boomsma, & Verhulst, 1994). In addition, results from a similar adoption design yielded a heritability estimate of .57 for CBCL aggression (van der Valk, Verhulst, Neale, & Boomsma, 1998).

Other investigations using parental ratings from different indices of childhood behaviors have obtained similar findings. O'Connor, Foch, Sherry, and Plomin (1980) used a revised version of the Connors Parental Symptom Rating form (PSR; Connors, 1970) to measure specific behavioral problems in twins averaging 7 years of age. On the Bullying scale (e.g., hits or kicks others, is mean, fights constantly, picks on other children), DZ twin correlations were roughly half the MZ twin correlations ($r_{MZ} = .72$, $r_{DZ} = .42$), suggesting that genetic influences also play an important role in the etiology of aggression as measured by the PSR. Similarly, a twin design by Scarr (1966) in which parents rated their children's aggression using an adjective checklist yielded a heritability estimate of .40 on this measure.

Although there is variability across these studies in terms of the magnitude of the heritability estimates, investigations using parental reports consistently reveal significant genetic contributions to aggression in childhood. On the other hand, observational studies of childhood aggression have been much less consistent, with some investigations yielding little or no evidence of heritability for these behaviors. In a study of 6- to 14-year-old twins using a projective measure in which subjects sorted a series of pictures into groups based on whether or not they looked "fun," a heritability estimate of .16 was obtained on an aggressivity scale, suggesting minimal evidence of genetic contributions (Owen & Sines, 1970). In a laboratory study, physical aggression was observed in twins who were encouraged to hit a Bobo the Clown doll, as demonstrated by the experimenter (Plomin, Foch, & Rowe, 1981). MZ correlations were not significantly greater than the DZ correlation, indicating that individual differences in this form of aggression in children are not genetically mediated. In addition, one twin design involving observational ratings of parent-adolescent interactions found a heritability estimate of .27 for adolescents' behavior toward fathers on a scale of transactional conflict (i.e., reciprocated anger/hostility; O'Connor,

Hetherington, Reiss, & Plomin, 1995). As a whole, results from observational designs generally demonstrate less evidence for the heritability of childhood aggression than studies using parental ratings. Consistent with this, Miles and Carey (1997) examined mode of assessment as a moderator in their meta-analysis of twin and adoption studies of aggression. Whereas genetic contributions explained a large amount of the variance in studies using parental and self-reports, observational ratings showed significantly less genetic contribution and a greater impact of the shared and nonshared environment.

Several explanations may be posited to explain why heritability estimates vary by mode of assessment. With respect to observational ratings, this method may be inherently less internally consistent than more psychometrically sound parent or self-report measures. If this is the case, measurement error, which is encompassed under the nonshared environmental parameter, will be inflated and, in turn, heritability estimates will be attenuated (DiLalla, 2002). In terms of parental ratings, some scholars have conjectured that contrast effects may explain the larger heritability estimates in these studies (Borkenau, Riemann, Spinath, & Angleitner, 2000; Plomin, 1981; Saudino, 2003; Simonoff et al., 1998). Contrast effects result from parents rating identical twins as more similar than fraternal twins on a certain trait based on the expectation that the former are more alike than the latter. Accordingly, parental reports may introduce some degree of bias in their measurement of childhood behaviors and, thus, may overestimate heritability relative to other informants.

Despite these limitations, specific "biases" from reports by different informants in some cases may actually reflect true differences observed in a child's behavior based on the relationship the informant has with that child. In such cases, differences across raters essentially reflect rater-specific contributions rather than rater biases per se. To account for both of these effects, behavioral genetic designs need to utilize multiple informants to clarify the relative influence of genes and environment in the etiology of childhood aggression. One study utilizing this approach involved a cross-sectional analysis of Dutch twins at ages 3, 7, and 10 years (Hudziak et al., 2003). The authors examined the genetic and environmental contributions to aggression as defined by the CBCL in a multi-informant design by obtaining paternal, maternal, and teacher ratings of each twin. Although mean differences did emerge across the ratings of aggression, the common variance across all informants was largely due to additive genetic effects (60–79%). Moreover, each informant also provided a small, albeit significant, amount of rater-specific variance that was also genetic in nature. That is, rater differences did not merely reflect measurement error or rater bias, but ultimately further informed the extent to which genes influence aggressive behavior. In effect, the results advocate for the use of multiple informants in behavioral genetic investigations of aggression in order to more reliably measure the genetic and environmental contributions to this construct (Hudziak et al., 2003; Loehlin, 1998).

Aggression and Other Childhood Behavioral Problems: Distinct or Common Etiologies?

There is some evidence to suggest that both distinct and common etiologies may link aggression with other childhood behavioral problems. For instance, some findings have noted that aggression is predominantly influenced by genetic factors, whereas delinquency (i.e., rule breaking) is more determined by the shared environment. Parental ratings of twins on the CBCL yielded significant genetic influences for both the aggression and delinquency subscales (Edelbrock et al., 1995). However, a larger proportion of the variance in aggression was due to heritable factors (60%) than for delinquency (35%), while shared environmental effects were significant for delinquency but not aggression. A similar pattern was reported in male twins (Eley et al., 1999). Heritability estimates were large and significant for aggression ($h^2 = .70$), but not for delinquency, and the shared environment was substantial for delinquency only ($c^2 = .54$). Moreover, in a sibling adoption study teacher ratings on the Teacher Report Form (TRF) of the CBCL were moderately heritable for the aggression scale, but not for delinquency (Deater-Deckard & Plomin, 1999).

Other investigations have noted a large degree of covariation between measures of aggression and delinquent behaviors in children (Achenbach & Ruffle, 2000; Deater-Deckard & Plomin, 1999; Verhulst & van der Ende, 1993; Yang, Chen, & Soong, 2001). Moreover, some scholars have posited that the comorbidity of these behaviors may arise from correlated risk factors that are either genetic or environmental in nature (Rutter, 1997). Although the studies are limited, there is some evidence to suggest that the co-occurrence of these behaviors is largely due to shared genetic effects.

For example, Eley (1997) presented data showing that a large amount of covariance between the aggression and delinquency scales of the CBCL was due to genetic factors. As well, a recent twin analysis specifically examined the etiology of the co-occurrence between CBCL aggression and delinquency and reported that roughly 80% of the covariance between these phenotypes was due to additive genetic contributions (Bartels et al., 2003).

These ostensibly incompatible findings regarding the etiology of childhood behavioral problems may be resolved under a hierarchical model (Achenbach & McConaughy, 1997). Such a model posits that the etiology of co-occurring behaviors is due to both a broad or common factor, which may be genetic or environmental in nature, and specific etiologic influences that are unique to each of the disorders in the model. Krueger et al. (2002) delineated such a model in their biometric analysis of externalizing psychopathology (i.e., covariation of child and adult antisocial behavior, substance abuse, and disinhibitory personality traits) in a sample of 17-year-old male twins. The authors demonstrated that although a common latent factor that was highly genetic accounted for a large amount of the covariance among externalizing symptoms, significant and unique genetic and environmental contributions were evident for each of the observed phenotypes. Based on the aforementioned findings, the etiology of aggression and delinquency may be similarly represented by a hierarchical model. As suggested by Eley (1997), "general" genes may confer a propensity to a broad spectrum of externalizing behaviors in childhood. In turn, other unique and specific genetic and environmental factors may determine how this broad vulnerability is ultimately expressed. Future behavioral genetic investigations may need to take this perspective into account and consider expanding the boundaries of the phenotypes they study in order to more precisely delineate the underlying etiology of aggression in childhood and adolescence.

Genetic and Environmental Influences on Aggression in Adulthood: Operational Inconsistency

Somewhat analogous to the childhood literature, behavioral genetic studies of aggression in adulthood have been plagued by inconsistent operational definitions of the construct (DiLalla, 2002). Early twin and adoption studies of criminality approached this issue using official statistics of violent crime. However, the findings from these classic studies are mixed. Cloninger and Gottesman (1987), in their reanalysis of twin data from Christiansen (1977), found both nonviolent and violent crimes to be highly heritable (h^2 = .78 and .50, respectively). Conversely, a large investigation of 14,427 adoptees from Denmark (Mednick, Gabrielli, & Hutchings, 1984) reported a significant relationship between adoptees and their biological parents for nonviolent, but not violent criminal convictions, suggesting that the latter are not due to the influence of genes. Similarly, petty, but not violent, crime was heritable in cases in which the adoptee and the biological parent were not alcoholic (Bohman, Cloninger, Sigvardsson, & von Knorring, 1982). Despite these inconsistencies, some caution is warranted in interpreting these findings. First, as previously emphasized (Coccaro & McNamee, 1998), violent crime is much less frequent than property crime and, therefore, is likely to be restricted in terms of its variance. In effect, there will be a limited amount of statistical power to detect a heritable signal for these particular crimes. Second, criminality is a fairly global and heterogeneous construct that relates to an assortment of personality styles and psychopathologies. Given this phenotypic heterogeneity, violent criminal convictions may not be the most appropriate means of operationalizing and investigating the etiology of aggression.

In an effort to overcome the problems of operationalizing aggression via violent crime statistics, other behavioral genetic researchers have turned toward the domain of personality as assessed via self-report to assess the etiologic contributions to the construct. Though self-report questionnaires are more amenable to use in epidemiological samples of twins and adoptees, the findings from these studies are ambiguous, given the variety of constructs and measures that have been employed to index aggression. For example, some investigators have examined the etiology of aggression using traits of hostility and have obtained mixed findings. Genetic and environmental influences on scores on the Cook and Medley Hostility (Ho) scale were examined in a small sample of male twins and significant genetic contributions for the Cynicism subscale, but not for the full Ho scale or the Paranoid Alienation subscale of this measure, were reported (Carmelli, Rosenman, & Swan, 1988). In a follow-up to this study using a larger sample of twins, similar findings were obtained, although there was some evidence of modest

heritability to the full Ho scale (Carmelli, Swan, & Rosenman, 1990). Overall though, environmental factors appear to play a greater role in the etiology of hostility as measured by the Cook and Medley Ho scale. Despite these findings, the validity of the Ho scale as an index of aggression appears questionable, as this measure may actually tap social desirability, suspiciousness, resentment, and mistrust rather than overtly aggressive behaviors (Carmelli et al., 1988; Smith & Frohm, 1985).

In contrast to the Ho scale, other investigators have taken a multifaceted approach to exploring the etiology of hostility-related traits and behaviors. Coccaro, Bergeman, Kavoussi, and Seroczynski (1997) obtained scores on the Buss–Durkee Hostility Inventory (BDHI; Buss & Durkee, 1957) in a sample of male twins. The BDHI is composed of four subscales: Direct Assault (i.e., violence against others), Indirect Assault (i.e., covert or relational aggression), Verbal Assault (i.e., arguing, shouting, screaming), and Irritability. Genetic contributions were significant for each subscale of the BDHI (28–47%) and were primarily nonadditive in nature, with the exception of Direct Assault, which was due to additive genetic factors (47%). Contrary to this, in an examination of the heritability of the BDHI scales in a sample of female twins, only verbal and indirect forms of aggression were due to genetic factors, whereas physical aggression and direct assault demonstrated no evidence for genetic influence (Cates, Houston, Vavak, Crawford, & Uttley, 1993). The authors note, however, that socialization may serve to reduce the expression of overt, physical aggression in women, thereby restricting variance and limiting the power to detect a heritable effect for these more extreme behaviors in women (Cates et al., 1993).

Other behavioral genetic studies of aggression have explored slightly different yet related trait dimensions of the construct. For example, Pedersen and colleagues (1989), in a study of twins reared together and apart, found that the majority of the variance in Type A personality, a multidimensional construct characterized by such features as aggression, hostility, and time urgency, was due to nonshared environmental factors, whereas genetic factors accounted for less than 20% of the variance. Gustavsson, Pedersen, Åsberg, and Schalling (1996) examined the etiologic contributions to individual differences in the Aggression-Hostility-Anger dimension of personality (Spielberger et al., 1985) in a sample of male and female twins. The majority of the variance in these traits was due to nonshared environmental factors, with genetic contributions significant for only the Anger component of this dimension. Conversely, significant heritabilities were obtained for both an irritable impulsiveness and (lack of) aggression factor in a sample of male twins reared apart (Coccaro, Bergeman, & McClearn, 1993). However, the magnitude of these estimates varied considerably as irritable impulsiveness was due largely to nonadditive genetic effects (44%), whereas lack of aggression was primarily due to nonshared environmental contributions and only a small amount of additive genetic variance (17%).

By and large, these findings demonstrate the considerable variability across these studies in terms of the extent to which genetic factors play a role in the etiology of aggression. Although these differences may be due to small sample sizes or the inclusion of only one gender, the range of operational definitions and measures used to index aggression likely introduced considerable phenotypic heterogeneity across these investigations and, therefore, this makes it difficult to draw any firm conclusions. In contrast to these investigations, other behavioral genetic studies have utilized more explicit self-report indices of trait aggression to assess the relative genetic and environmental contributions to this construct. Rushton, Fulker, Neale, Nias, and Eysenck (1986) examined the heritability of individual differences in aggression in a sample of male and female twins using 23 items from the Interpersonal Behavior Survey (Mauger & Adkinson, 1980). Approximately 50% of the variance in self-reported aggression was due to genetic effects, with no evidence of shared environmental contributions. Other investigations have explored the etiology of aggression using the Multidimensional Personality Questionnaire (MPQ; Tellegen, in press), an omnibus measure of normal range personality variation. The MPQ is composed of 11 lower order primary trait scales that cohere into three higher order personality superfactors. The aggression scale is a primary scale relating to physical aggression and vindictiveness and loads onto the higher order superfactor of negative emotionality (Krueger, 2000; Tellegen, 1985). Using the MPQ, several investigations have also demonstrated substantial genetic effects and minimal influence from the shared environment to the etiology of trait aggression. In an investigation of the heritability of the MPQ subscales in a sample of twins reared together and apart, approximately half the variance in the aggression scale was due to genetic factors (Tellegen et al., 1988). Other twin studies also note significant and substantial genetic contributions to the aggression scale

of the MPQ (Finkel & McGue, 1997; McGue, Bacon, & Lykken, 1993). Furthermore, results from each of the aforementioned designs yielded MZ twin correlations more than twice the magnitude of the DZ twin correlations, suggesting that nonadditive genetic factors may be involved in the etiology of these traits.

Given the large amount of variability across twin and adoption studies of aggression in adulthood, it is difficult to assess the degree to which genes and environment actually contribute to expression of these traits and behaviors. Meta-analyses, however, provide a means of summarizing this literature (Miles & Carey, 1997; Rhee & Waldman, 2002). In general, these investigations reported aggression to be largely due to genetic factors in adulthood and to a lesser extent the shared environment. Miles and Carey (1997) reported that approximately 50% of the overall variance was due to genes, whereas Rhee and Waldman (2002) found that 44% of the variance in twin and adoption studies of antisocial behavior (operationalized in terms of aggression) was largely due to genetic contributions. In sum, despite problems in operationally defining aggression in the adult literature, there is sufficient evidence to assert that genetic factors play a significant role in the etiology of these behaviors.

Genes and Environment in the Stability of Aggression: Longitudinal Findings

In investigating the developmental course of aggression, several studies have noted that these traits are relatively stable from childhood to adulthood (Hofstra, van der Ende, & Verhulst, 2000; Koot, 1995; Loeber & Hay, 1997; Pulkkinen & Pitkaenen, 1993; Verhulst & van der Ende, 1995). With regard to this continuity, it is worth inquiring about the extent to which genetic and environmental influences contribute to the persistence of these traits across development. Moreover, what is the pattern of these etiologic effects? If this stability is largely genetic, then are the same genes exerting an influence on the expression of a phenotype throughout development or do new genes "turn on" at specific maturational points? Conversely, do environmental forces contribute to the persistence of these traits or are there critical periods in which environmental factors have their greatest impact and exert change in these behaviors? According to the meta-analyses highlighted earlier (Miles & Carey, 1997; Rhee & Waldman, 2002), the influence of the shared environment appears to decrease, whereas the relative influence of genes increases from childhood to adulthood, suggesting that genetic factors may represent an important component in the persistence of aggression over time. However, these studies are cross-sectional and cannot directly attest to the role of genes and environment in the stability or change of these behaviors. Instead, other studies have utilized longitudinal (prospective) designs with genetically informative data to answer these questions and elucidate the etiologic contributions to the stability of aggression.

In studies of children and adolescents, several prospective designs suggest that the stability of aggression is largely due to the influence of genetic factors. CBCL data were examined in twins using parental reports when the twins were 2 years old and then again at 7 years of age (Schmitz, Fulker, & Mrazek, 1995). Although the sample was small, all of the covariance in aggression scores across these two time periods was due to genetic effects. In a study of biologically related and unrelated adoptees (van der Valk et al., 1998), parental ratings on the CBCL were obtained when the adoptees were in either early or mid adolescence and again 3 years later. Genetic influences were substantial for aggression at both assessment points (61% and 52%, respectively), with 69% of the covariance in aggression across these time points due to genetic factors. Moreover, 37% of the genetic variance at the second assessment was due to the continuing influence of genes that were important at the first assessment, whereas 15% of the genetic variance at the second assessment was due to the expression of new genetic factors.

In a recent longitudinal twin design, the genetic and environmental contributions to the stability and change of parentally rated CBCL aggression were examined at 3, 5, 7, 10, and 12 years of age (van Beijsterveldt, Bartels, Hudziak, & Boomsma, 2003). To explore the mechanisms involved in both continuity and change in these behaviors, the authors tested the applicability of two developmental models: a *common factor* model and a *simplex* model. The common factor model implies that the same genetic or environmental factors contribute to the stability of a behavior or trait throughout a particular developmental period. In the simplex model, genetic and environmental factors may exert a continuous effect across a period of time but begin to wane as new age-specific genetic and environmental factors emerge. The results indicated that CBCL aggression was highly stable across these age ranges and largely accounted for by genetic influences that followed a

simplex model of inheritance. Although shared environmental contributions were fairly modest, these influences were best described by a common factor model, suggesting that the same shared environmental influences underlie the development of aggression from early childhood to the beginning of adolescence. In total, the stability of aggression in childhood and adolescence appears to be largely genetic and follows a dynamic pattern, with the continuous influence of some genes across this developmental epoch combining with the emergence of new genetic factors at specific ages.

Although few studies have explicitly assessed the etiologic contributions to the stability of aggression in adulthood, a few notable exceptions exist. One longitudinal twin design assessed the influence of genes and environment in the stability and change of personality from ages 20 to 30 (McGue et al., 1993). Using the MPQ as their measure of personality, the aggression scale was highly genetic at both time periods and consisted primarily of nonadditive genetic and nonshared environmental contributions. While changes in aggression were largely due to the nonshared environment, genetic factors exerted a substantial influence on the stability of these traits, as roughly 90% of the stable variance was genetic in nature. A recent investigation, however, suggests that the impact of genes on the stability of MPQ aggression may begin to wane in late adulthood (Johnson, McGue, & Krueger, 2005).

Overall, longitudinal findings from both the child and adult literatures suggest that the continuity of aggression across development is largely due to genetic factors. Notably, these findings align with several developmental taxonomies posited in the literature on antisocial behavior. Specifically, both Moffitt's (1993) *life course persistent* and DiLalla and Gottesman's (1989) *continuous antisocials* represent developmentally stable subtypes that are largely constitutional in nature and associated with higher levels of trait aggression (Elkins, Iacono, & Doyle, 1997) and violent criminal offenses (Moffitt, Caspi, Harrington, & Milne, 2002).

Moderating Effects in the Etiology of Aggression

In our review of the behavioral genetic literature thus far, it is apparent that genes play a significant role in the etiology of aggressive traits and behaviors across development. It would be misleading, however, to characterize this as an absolute finding or to suggest that genetic factors are impervious to the moderating influence of other variables. For example, some evidence suggests that gender differences, as well as gene-environment interactions, are significant moderators in the etiology of aggression and violence.

Gender Differences

A thoroughly investigated and fairly consistent finding from both the child and adult literature is that males exhibit higher mean levels of aggression than females (Hudziak et al., 2003; Maccoby & Jacklin, 1980; McGue et al., 1993; Rushton et al., 1986; Verhulst & Koot, 1992). There has been less empirical attention, however, investigating whether there are gender differences in the genetic and environmental contributions to aggressive behavior. Despite the inclusion of both male and female samples, most behavioral genetic studies of aggression have not fit sex-limitation models to the data which specifically test for gender differences in the genetic and environmental contributions to a phenotype. However, a few studies employing such models have noted gender differences in the etiologic contributions to these behaviors.

The relative fit of two sex-limitation models to CBCL data was assessed on 10- to 15-year-old adoptees (van den Oord et al., 1994). A *general* sex-limitation model assuming no differences in the magnitude of the genetic and environmental influences across males and females was compared to a *specific* sex-limitation model in which these estimates were assumed to vary by gender. The specific sex-limitation model fit best for the aggression scale, with significantly larger genetic and smaller shared environmental influences for males than females. Analogous findings were obtained in a longitudinal study of twins ages 3–12 (van Beijsterveldt et al., 2003). Gender differences in terms of the overall magnitude and stability of the genetic effects on CBCL aggression were evident after age 7, with greater genetic contributions for males and larger shared environmental contributions for females.

In a recent investigation of 11- to 12-year-old twins (Vierikko, Pulkkinen, Kaprio, Viken, & Rose, 2003), a different pattern of gender differences was observed. Using parent and teacher reports on a six-item scale of aggression derived from the Multidimensional Peer Nomination Inventory (Pulkkinen, Kaprio, & Rose, 1999), the authors examined two questions: (a) whether the same etiological factors contribute to aggression in

males and females (i.e., qualitative sex differences) and (b) whether the magnitude of these contributions differs across gender (i.e., quantitative sex differences). Qualitative sex differences varied by informant. Teacher reports suggested some sex-specific genetic and shared environmental effects, whereas parental reports yielded no such effects. Conversely, quantitative sex differences were evident for both teacher and parent reports, but yielded lower heritabilities and higher shared environmental contributions for males than females, a finding that contrasts with the aforementioned studies observing greater genetic and less shared environmental influences in males.

Contrary to these findings, other studies have failed to detect any significant gender differences in the etiologic contributions to aggression altogether. In two studies (Eley et al., 1999), no gender differences were noted for maternally rated aggression in either a Swedish sample of twins ages 7–9 or a British sample ages 8–16. As well, results from a twin study of personality in adulthood as measured by the MPQ found no evidence for sex differences in the magnitude of the genetic and environmental effects on the aggression trait scale (Finkel & McGue, 1997). As highlighted in previous sections, these inconsistencies may be due to differences in age or the mode of measurement and make any direct comparisons across studies tenuous. After accounting for such factors, Miles and Carey (1997), in their meta-analysis, report gender as a significant moderator in the etiology of aggression. These findings, however, were not very robust and yielded only slightly larger genetic contributions for males and greater shared environmental effects for females. Thus, the extent to which gender may moderate the genetic and environmental effects on aggression warrants further inquiry.

Gene-Environment Interactions

Behavioral genetic studies from the aggression literature have typically assumed that genetic and environmental factors operate independently in the etiology of these behaviors. Twin and adoption studies, however, are not bound to this assumption and have the capability of investigating whether the phenotypic expression of a trait is dependent upon the interaction of a particular genotype with certain environmental factors. Though the studies are limited in the aggression and violence literature, two noteworthy findings have demonstrated significant gene by environment interactions in the etiology of these behaviors.

First, in an adoption study, the effect of an adverse home environment in predicting aggressive and delinquent behavior was examined in adoptees with and without a family history of externalizing disorders (Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995). In this retrospective design, 95 male and 102 female adoptees whose biological parents had a documented history of antisocial personality disorder (ASPD) or alcohol abuse and dependence were interviewed in adulthood and compared to a control sample of adoptees whose biological parents had no known history of psychopathology. In addition, adoptive parents were interviewed to assess for an "adverse environment" in the rearing adoptive families as defined by the presence of marital discord (e.g., divorce or separation), substance abuse or dependence in an adoptive parents, another psychiatric condition in an adoptive parent, or legal problems in an adoptive parent. The findings revealed that the interaction of a biological parent with a diagnosis of ASPD and an adverse home environment was a significant predictor of both child and adolescent aggression. Moreover, the interaction of these factors was a more robust predictor of aggression than the presence of either a negative biological background or an adverse rearing environment alone.

Second, Caspi and colleagues (2002) utilized a molecular genetic design to investigate whether a gene encoding for enzyme activity of monoamine oxidase-A (MAO-A) would moderate the predictability of violence in children with a history of maltreatment. This hypothesis was based on prior evidence suggesting that childhood maltreatment (Luntz & Widom, 1994) and genetic deficiencies in MAO-A (Brunner et al., 1993) are associated with increased aggression in humans. A polymorphism (variants of DNA sequence) affecting the expression of the MAO-A gene was genotyped in male participants from the Dunedin Multidisciplinary Health and Development Study. A significant interaction was observed between MAO-A activity and childhood maltreatment. Specifically, 85% of males with a low-activity MAO-A genotype who had experienced severe maltreatment as children developed some form of antisocial behavior (e.g., convictions for violent offenses, a personality disposition toward violence). In conjunction with the findings from Cadoret et al. (1995), these results illustrate the importance of a genetic disposition interacting with adverse environmental events as key to the phenotypic expression of aggression and violence. Nonetheless, further investigation may be necessary, particularly in light of a

recent study which found an increase in shared environmental but not genetic influences to aggression among twins from disadvantaged neighborhoods (Cleveland, 2003).

Molecular Genetic Studies of Aggression in Humans

Methodology

One limitation of behavioral genetic designs is that they are only capable of inferring the role of genes in the etiology of a phenotype and cannot directly identify which genes are relevant to this process. Molecular genetic designs, however, are rapidly advancing and provide methods aimed at elucidating the causal genes in the etiology of a phenotype. In some respects, searching for causal genes for a quantitative (polygenic) trait, such as aggression, may appear misguided given that such traits are thought to be due to the additive influence of several genes which each confer a very small effect size. The search for quantitative trait loci (QTL) offers an alternative method and helps to bridge quantitative and molecular genetic perspectives (see Maxson & Canastar, ch. 1 in this volume). In common with polygenic models, QTL models presume that multiple genes are important to the etiology of a trait or disorder. However, this method further assumes that these genes may have varying effect sizes and that the genes with larger effects can be identified. Molecular genetic investigations for QTL involve the study of variants of DNA sequences known as markers or *polymorphisms* that are found in either the coding (functional) or noncoding regions of genes. Polymorphisms from coding regions (exons) are important in that they may represent mutations in regions of DNA that code for amino acids. Hence, such polymorphisms may have functional significance for certain biological subsystems. In contrast, polymorphisms from noncoding regions (introns), though of no functional significance, may be worth investigating if they are linked with an unknown functional polymorphism on the same gene.

There are two primary approaches to identifying genes relevant to the etiology of a particular trait or behavior: *Linkage analysis* and *allelic association*. In linkage analysis, DNA from large multigenerational pedigrees with a history of family transmission for a particular trait or disorder are assayed to detect genetic markers whose location on a chromosome is known and sufficiently near a causal gene. The markers themselves which are implicated need not have any known association with a biological function and may simply be in noncoding regions of a gene. However, these markers tend to remain near the causal genes within genetically homogenous families as result of nonrandom segregation of genes. A variant of this method, sibling-pair linkage analysis, obviates the inherent problems of identifying large multigenerational pedigrees and entails an examination of the number of alleles shared by siblings who are either concordant or discordant for a certain trait or disorder. If the number of shared alleles is significantly greater than expected by chance (approximately 50%, on average, for biological siblings), then the causal gene is thought to be close to the marker being examined. Although these methods may be successful at identifying the causal agents for single-gene (monogenic) disorders such as Huntington's disease, they have comparatively less power to detect genetic effects for polygenic traits such as aggression.

Allelic association assesses whether a known polymorphism or allelic variant of a candidate gene is related to a particular phenotype in a sample of unrelated individuals from the population. Unlike linkage analysis, this method requires that the target marker itself cause the association and code for a particular structure or function (e.g., an enzyme or amino acid) or be in close proximity to the candidate gene or QTL. The frequency of the marker or candidate gene is then compared in individuals with and without a disorder or who are high or low on a specific trait. Notably this approach, which is distinctly suited to the investigation of polygenic phenotypes, requires a previously known association between the function of the specific candidate gene and the phenotype under study. With respect to aggression, most candidate genes selected for investigation have been genes directly implicated in the synthesis or metabolism of the neurotransmitters dopamine and serotonin.

Candidate Genes

Dopamine, an important neurotransmitter associated with individual differences in personality traits and various forms of psychopathology, has been previously linked to novelty seeking in humans (Benjamin, Patterson, Greenberg, Murphy, & Hamer, 1996; Ebstein et al., 1996) and approach behavior in animals (Cloninger, 1987). Several molecular genetic studies have yielded significant associations between dopamine receptor

genes and aggression across a variety of disorders. For example, 4-year-olds with long allele repeats of the dopamine D4 receptor gene (DRD4) were rated as more aggressive by their mothers on the CBCL than children with short allele repeats of this gene (Schmidt, Fox, Rubin, Hu, & Hammer, 2002). Dopamine receptor genes have also been implicated in studies of aggressive Alzheimer's dementia (AD) patients. Sweet and colleagues (1998) examined whether polymorphisms for several dopamine receptor genes were associated with psychotic and aggressive behaviors in these patients and found aggressive behavior to be significantly prevalent among AD patients who were homozygous for the DRD1 B2 allele. Likewise, Holmes et al. (2001) found variation in the DRD1 receptor gene to be associated with aggression in AD patients. This relationship, however, was observed in heterozygotes as well as homozygotes for the B2 allele.

Related to the investigation of dopamine receptor genes, other studies have observed associations between aggression and a functional polymorphism in the gene for catechol-O-methyltransferase (COMT), a key enzyme in the metabolism of dopamine. Variations of the COMT polymorphism result in either high or low enzyme activity. Associations between the low activity allele of the COMT gene and aggression in schizophrenic patients have been reported (Kotler et al., 1999; Lachman et al., 1996, 1998; Strous, Bark, Parsia, Volavka, & Lachman, 1997). In an effort to replicate these findings, this association was investigated in a larger sample of schizophrenics (Jones et al., 2001). However, the subsequent finding of an association between aggression and schizophrenics who were homozygous for the *high*-activity COMT allele suggests that the specific relationship between the COMT alleles and aggression is equivocal.

Serotonin, a monoamine neurotransmitter, is perhaps the most thoroughly investigated neurobiological substrate in the etiology of aggression. Dysfunctional serotonergic activity is related to impulsive aggression across a variety of populations and phenotypes (Coccaro, 1989) and has generated extensive research seeking possible candidate genes in the pathogenesis of aggression (see New, Goodman, Mitropoulou, & Siever, 2002). A detailed review of the neurobiology and genetics of serotonin and its associations with aggression is given by Manuck, Kaplan, and Lotrich (ch. 4 in this volume) and is not reproduced here. However, a brief précis of this literature is relevant to the present discussion.

A functional polymorphism in the promoter region of the serotonin transporter gene (5-HTLLPR), which regulates the transcription of this gene and results in either high or low transporter production, has been targeted as a candidate gene for aggression but has yielded variable findings. For example, the presence of a short (S) allele was significantly greater among violent suicide attempters than controls (Courtet et al., 2001). Conversely, the long (L) variant of this allele was associated with aggression in a sample of AD patients (Sukonick et al., 2001). A polymorphism in the noncoding region of the gene for tryptophan hydroxylase (TPH), an important rate-limiting enzyme in the synthesis of serotonin, has also been linked to aggression. Again, however, the findings have been inconsistent regarding the U and L alleles of this gene. Although some studies have demonstrated increased aggression in individuals homozygous for the U allele of this polymorphism (cf. Manuck et al., 1999), others have noted a similar association in individuals homozygous for the L allele (New et al., 2002; Nielsen et al., 1994). This discrepancy notwithstanding, the relevant function of this polymorphism is not entirely clear, given that it is found in a noncoding region of the TPH gene. Thus, its significance may lie more as a marker in close proximity to a functional polymorphism directly related to TPH production.

Finally, a polymorphism in the gene for MAO-A, a key enzyme in the metabolism of serotonin, dopamine, and noradrenaline, has generated considerable speculation as a candidate gene of aggression. As noted earlier, Brunner and colleagues (1993) found that a point mutation in the structural gene for MAO-A resulted in complete and selective deficiency of this enzyme's activity in males from a Dutch kindred who exhibited abnormal impulsive behavior including aggression. Although it is debatable whether such a rare mutation leading to complete MAO inactivity would generalize to studies of normal MAO allelic variation in the population, subsequent studies have been promising. This finding was extended to the larger population and a significant association between allelic variation in the promoter region of the MAO-A gene and several indices of aggression was discovered (Caspi et al., 2002; Manuck, Flory, Ferrell, Mann, & Muldoon, 2000). Thus, functional polymorphisms involved in MAO-A activity remain a viable target for future molecular genetic investigations of aggression and violence.

Conclusions, Implications, and Future Directions

In this chapter we have reviewed the human quantitative genetic literature on aggression across the life span. Overall, the findings suggest that genes begin to emerge as a significant factor in the etiology of aggression in early childhood and continue to influence the stability of these traits well into adulthood. Additionally, the influence of genetic factors appears to increase over the course of development and is followed by a concomitant decrease in contributions from the shared environment. Furthermore, genetic effects on aggression do not appear to operate in isolation and may be moderated by gender differences, as well as interactions with adverse environmental factors.

In this chapter we also attempted to highlight important areas in this literature that require further investigation and clarification. These issues most notably include (a) variable findings based on the method of assessing aggression, (b) inconsistent operational definitions of the construct, and (c) the lack of clearly defined boundaries for the aggression phenotype.

First, in the childhood behavioral genetic literature, estimates of the heritability of aggression have varied as a function of the method of assessment (e.g., parent report vs. observational ratings). Additionally, adult behavioral genetic studies of aggression have been dominated by the use of self-report questionnaires, with little attention to comparable observational or laboratory paradigms. As previously advocated by Miles and Carey (1997), these issues suggest that future research on the etiology of aggression would benefit greatly from multitrait-multimethod approaches (cf. Campbell & Fiske, 1959). Specifically, future studies should strive to obtain reports from multiple informants to account for rater bias or rater-specific contributions to variance in these traits (cf. Hudziak et al., 2003). As well, adult behavioral genetic designs should utilize both self-report questionnaires and laboratory paradigms within the same design in order to assess the degree to which genetic and environmental estimates vary by mode of assessment. Though extant laboratory paradigms of aggression have been criticized for lacking construct validity (see Tedeschi & Quigley, 2000), their inclusion in adult behavioral genetic studies could yield worthwhile insights into the etiology of aggression, as well as fill a notable gap in this literature.

Second, inconsistencies in operationalizing or defining aggression, particularly in the adult literature, have made it difficult to integrate findings across behavioral genetic studies of these traits. Moreover, there exists a lack of behavioral genetic studies investigating alternative typologies of aggression (e.g., reactive vs. proactive aggression, Crick & Dodge, 1996; relational vs. physical aggression, Crick & Grotpeter, 1995). Research of this kind could potentially address important questions regarding the etiology of known expressions of this construct. For example, research on the genetic and environmental contributions to both reactive and proactive aggression could address whether there are common or distinct etiologies to these diverse motivations. Moreover, such research may ultimately enhance our understanding about the etiology of broader motivational subsystems that underlie such behavior (Konorski, 1967). In any case, recognition of the multifaceted nature of aggression represents a promising endeavor for future behavioral genetic investigations of the construct.

Third, the inherent difficulty in defining the boundaries of the construct represents another challenge to future research on the etiology of aggression. In some respects, narrow phenotypic definitions of aggressive behavior that ignore the co-occurrence of these behaviors with other externalizing behaviors (e.g., delinquency) may hinder the search for "general" genes that confer a susceptibility to a range of behavioral problems. On the other hand, an overinclusive approach examining the etiology of such multidimensional traits as Type-A personality may create considerable phenotypic and genotypic heterogeneity in these studies and obscure the relevance of the findings. Accordingly, these issues necessitate a model that can address both *bandwidth* and *fidelity* in defining the boundaries of the aggression construct. As described earlier in this chapter, a hierarchical model which delineates both broad (e.g., externalizing) and specific manifestations of the construct (e.g., hostility) may help guide future research by allowing for the estimation of both common and unique etiologic contributions to aggression and related phenotypes (cf. Krueger et al., 2002).

On a final note, our review of molecular genetic studies of aggression illustrates the feasibility of identifying candidate genes in the etiology of these behaviors. It cannot be overstated, however, that aggression is multifactorial and likely due to the influence of several genes. Thus, caution is warranted in interpreting significant associations with candidate genes without further knowledge of the amount of variance in the phenotype accounted for by these genes. Moreover,

given the evidence for genetic nonadditivity in some studies of aggression in adulthood (e.g., Tellegen et al., 1988), future molecular genetic investigations are also encouraged to explore whether interactions of genes within and across alleles (i.e., dominance and epistasis) significantly contribute to the etiology of aggression. Last, the preponderance of evidence demonstrating significant genetic contributions is not meant to undermine the importance of nonshared environmental factors to aggressive behavior. Given previous findings (e.g., Caspi et al., 2002), behavioral and molecular genetic studies may also be well served to investigate the interaction of genetic and environmental factors in order to more precisely delineate the etiologic and developmental course of aggression and violence.

Notes

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1. Readers interested in the related behavior genetic literature on antisocial behavior and criminality are referred to reviews by Carey and Goldman (1997), Ishikawa and Raine (2002), and McGuffin and Thapar (1998).

2. The equations given for h^2, c^2, and e^2 derive from Falconer (1960) estimates and represent one of the simplest means of computing values for additive genetic, shared, and nonshared environmental parameters. However, modern analysis of twin data utilizes structural modeling approaches involving maximum likelihood estimation to more precisely estimate these parameters (see Neale & Cardon, 1992, for a review of these methods).

3. Of course, MZ twins may experience more similar environments because their genes have led to such an outcome. Consider, for example, a pair of MZ twins with a genetic predisposition toward athletic talent, both of whom succeed in the childhood pursuit of athletic excellence and, as a result, become world-class athletes in adulthood. This type of phenomenon would not logically violate the assumption, but would instead be a form of gene-environment correlation (cf. Scarr & McCartney, 1983).

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