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Corresponding Author	Family Name	Mehta
	Particle	
	Given Name	**Pranjal H.**
	Suffix	
	Division	Department of Psychology
	Organization	University of Oregon
	Address	97403, Eugene, OR, USA
	Email	
Author	Family Name	Goetz
	Particle	
	Given Name	**Stefan M.**
	Suffix	
	Division	
	Organization	Wayne State University
	Address	Detroit, MI, USA
	Email	
Author	Family Name	Carré
	Particle	
	Given Name	**Justin M.**
	Suffix	
	Division	Department of Sociology
	Organization	Wayne State University
	Address	Detroit, MI, USA
	Email	

Abstract	This chapter reviews the social neuroscience literature on human aggression, including research in molecular genetics, neuroendocrinology, neuroimaging, and social psychology. The findings indicate that (1) the amygdala and orbitofrontal cortex (OFC) are critical components of the neural circuitry of aggression; (2) the serotonergic system plays a crucial role in modulating aggression; (3) testosterone and cortisol influence aggression, likely through modulation of the amygdala and orbitofrontal cortex; and (4) environmental risk factors (media violence) and protective factors (emotion regulation) may modulate aggression via alterations in these biological systems and neural circuits. We end the chapter by discussing new directions for future research.

Chapter 5
Genetic, Hormonal, and Neural Underpinnings of Human Aggressive Behavior

Pranjal H. Mehta, Stefan M. Goetz, and Justin M. Carré

In 2010, there were 1,246,248 documented cases of violent crimes committed in the United States, and violence is estimated to kill approximately 1.6 million people per year worldwide (www.fbi.gov, Mercy et al. 2002). Although evolutionary theory suggests that aggression and violence were adaptive behaviors that promoted survival and reproduction among our ancestors (e.g., the acquisition of valued resources such as food, shelter, and mates), aggressive behaviors in modern societies have significant social and economic costs (Buss and Shackelford 1997). These include social stigma, job loss, and negative legal consequences for perpetrators as well as substantial monetary and social costs for society (Archer and Southhall 2009).

Research has shown that multiple social and biological factors are implicated in the expression of aggression, but only recently have researchers begun to understand how these factors work together to regulate human aggressive behavior. In this chapter, we review recent studies on the social neuroscience of aggression, including research in the areas of molecular genetics, neuroendocrinology, neuroimaging, and social psychology. Our goal is not to provide an exhaustive review but rather to summarize the main findings from these fields and to highlight recent studies that integrate theories and approaches from disparate areas of research (for a recent comprehensive review, see Siever 2008). We begin by defining aggression and its subtypes. We then selectively review research on the social neuroscience of human aggression with a focus on recent studies. We cover research in neuroimaging, behavioral pharmacology, molecular genetics, neuroendocrinology, and social psychology. We end the chapter by suggesting new directions for future research on aggressive behavior.

What Is Aggression?

Aggression has been defined as "any form of behavior directed toward the goal of harming or injuring another living being who is motivated to avoid such treatment" (Baron and Richardson 1994, p. 7). Although aggression can be intended to cause physical harm (e.g., physical injury or death), not all

P.H. Mehta (✉)
Department of Psychology, University of Oregon, Eugene, OR 97403, USA
mehta@uoregon.edu

S.M. Goetz
[AU1] Wayne State University, Detroit, MI, USA

J.M. Carré
Department of Sociology, Wayne State University, Detroit, MI, USA

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aggressive behaviors are physical. Nonphysical aggression includes behaviors designed to cause psychological harm (direct insults, psychological abuse), social harm (e.g., spreading rumors to damage someone's reputation, social exclusion), or economic harm (e.g., firing a subordinate or decreasing his or her pay). Researchers typically classify aggression as either reactive or proactive. Reactive aggression, also referred to as impulsive aggression, is a behavioral response to perceived or actual provocation and involves retaliation (Dodge and Coie 1987). Commonly referred to as "hot-blooded," reactive aggression is characterized by anger and impulsivity and is often accompanied by disinhibition and affective instability. In contrast, proactive aggression occurs in the absence of direct provocation and is a goal-oriented behavior aimed at the acquisition of a valued resource (Dodge and Coie 1987). Although the proactive form receives widespread media attention (e.g., serial killings, assassinations, genocide), the reactive form likely accounts for most societal problems associated with aggression (Nelson and Trainor 2007). We focus our literature review below on reactive aggression because it has received greater attention in neuroscience research, and its social and biological causes are better understood.

The Social Neuroscience of Human Aggressive Behavior

Empirical studies indicate that human aggressive behavior is influenced by specific genes, hormones, neural systems, and environmental factors. In this section, we review the main findings from these disparate areas of research with a focus on recent integrative studies. First we discuss the neural systems implicated in aggression with a focus on two specific regions: the amygdala and the orbitofrontal cortex. Next, we discuss neurotransmitters and hormones associated with aggression, including serotonin, testosterone, and cortisol. Third, we discuss two environmental factors linked to aggression: violent media exposure and social rejection. Fourth, we discuss two psychological interventions that can reduce aggression: cognitive reappraisal and self-control. Finally, we end the chapter by discussing directions for future research.

Amygdala–Orbitofrontal Cortex Interactions as a Mechanism for Aggressive Behavior

Animal research indicates that an extensive network of cortical and subcortical regions is involved in the expression of aggressive behavior (Newman 1999; Nelson and Trainor 2007; Siegel et al. 2007). Two regions that have received extensive empirical attention in human research are the amygdala and the orbitofrontal cortex (OFC). According to recent models of human reactive aggression, the amygdala plays a critical role in the affective and motivational drive to respond aggressively to social provocation, while the OFC is thought to be a self-regulatory region that inhibits aggressive impulses (see Fig. 5.1). The findings reviewed below are consistent with these models.

Orbitofrontal Cortex

The OFC is located in the prefrontal cortex, a portion of the brain that appeared later in evolutionary history than subcortical regions such as the amygdala (Kringelbach and Rolls 2004). A number of studies suggest that the OFC functions as a self-regulation and impulse control region and is involved in the top-down inhibition of aggressive behavior. Patients with lesions in the OFC exhibit

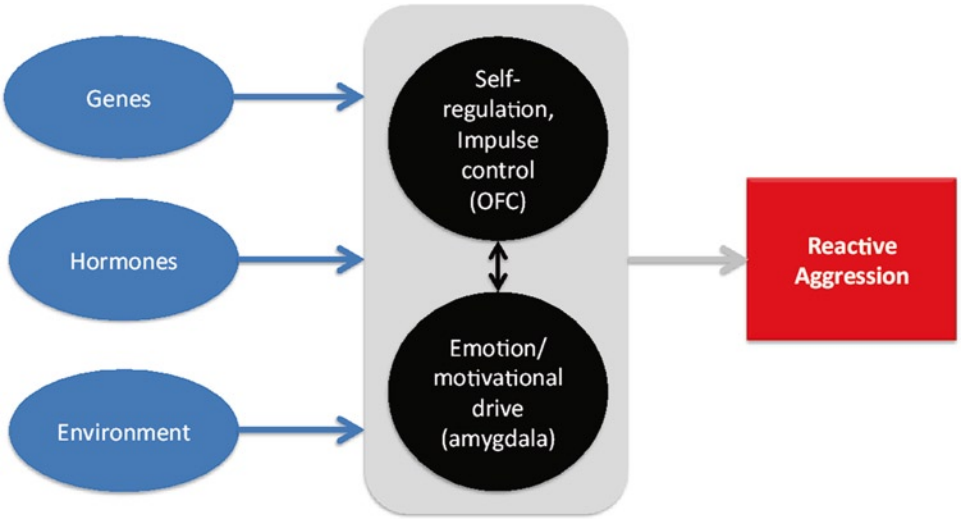

Fig. 5.1 A social neuroscience model of reactive aggression

hyperaggressive behavioral reactions to social provocation (Bufkin and Luttrell 2005; Damasio et al. 1994; Davidson et al. 2000; Koenigs and Tranel 2007; Moretti et al. 2009; Strüber et al. 2008), and human neuroimaging studies indicate that increased OFC activity is associated with low levels of reactive aggression (Bufkin and Luttrell 2005; Damasio et al. 1994; Davidson et al. 2000; Strüber et al. 2008). For example, a recent study examined the relationship between OFC activity and aggressive behavior in the Ultimatum Game, a laboratory model of social decision-making in which people choose between aggression and monetary reward (Mehta and Beer 2010). This game involves two players: a proposer and a responder. The proposer makes an offer as to how to split a sum of money (the stake) with the responder. The responder then decides whether to accept or reject the offer. If the offer is accepted, the stake is split as proposed. However, if the offer is rejected, then both players receive $0. After the responder makes a decision, the game is over. Although responders almost always accept fair offers (e.g., proposer gets 50% and responder gets 50% of stake), responders often reject unfair offers (e.g., proposer gets 80% and responder gets 20% of the stake). Accepting unfair offers guarantees monetary reward, so why do people ever reject them? Psychological evidence indicates that these unfair offer rejections are a form of reactive aggression aimed at retaliating against the other player in the face of perceived social provocation (unfair treatment) (Mehta and Beer 2010).

In this fMRI study, participants were scanned while playing the Ultimatum Game in the role of responder ostensibly with 40 other proposers in one-shot interactions (participants were told they would never play with the same proposers twice). In reality, the offers were experimentally manipulated such that half were relatively fair ($5:$5 split) and the other half were relatively unfair (e.g., an offer of $8 for the proposer and $2 for the responder). The researchers assessed how often participants rejected unfair offers (a behavioral measure of reactive aggression) as well as OFC activity in response to unfair offers compared to fair offers. In support of the hypothesis that OFC is involved in the inhibition of aggressive behavior, the results indicated that bilateral activity in the medial OFC was negatively related to aggressive behavioral reactions to unfair offers. Specifically, individuals who showed decreased activity in the medial OFC after receiving unfair offers tended to reject these offers (high levels of reactive aggression), whereas individuals who showed increased activity in the medial OFC after receiving unfair offers tended to accept these offers (low levels of reactive aggression) (Mehta and Beer 2010).

Other human studies provide convergent support for a relationship between OFC function and the inhibition of impulsive aggression. In a (positron emission tomography) PET study with criminal offenders, Raine and colleagues (1997) reported that affective murderers (i.e., reactively aggressive inmates) demonstrated increased glucose metabolism in subcortical structures (including the amygdala) and decreased glucose metabolism in the prefrontal cortex. Also, psychiatric disorders characterized by high levels of reactive aggression are associated with reduced OFC activity (Coccaro et al. 2007), and lower gray matter volume in the OFC is linked to low impulse control (Matsuo et al. 2009). Although the precise psychological function of OFC in inhibiting aggression is still unclear, it has been theorized that the OFC is part of a self-regulation and impulse control system that integrates emotion, motivation, and cognition to guide context-appropriate behavior (cf. Mehta and Beer 2010). Indeed, not only do patients with OFC lesions show increases in reactive aggression (Blair 2004; Rolls et al. 1994), but they also show increases in impulsive behavior, socially inappropriate behavior, and impaired decision-making (Beer et al. 2003, 2006; Rahman et al. 2001; Bechara et al. 2000; Tucker et al. 1995). These behavioral deficits have been theorized to occur because of a failure to monitor behavior such as failing to consider longer term rewards (Moretti et al. 2008; Beer et al. 2006; De Martino et al. 2006; Bechara et al. 2000). A complementary account of OFC function is that this region is involved in how individuals weigh the costs and benefits of behaving aggressively versus nonaggressively following social provocation, with increased medial OFC activity tipping the cost-benefit analysis toward nonaggression (cf. Mehta and Beer 2010). [AU2]

Amygdala

The amygdala is a limbic structure that plays a critical role in processing potentially threatening stimuli and mediating various autonomic, neuroendocrine, and behavioral responses that enable an organism to adapt to social and environmental challenges (see Davis and Whalen 2001; LeDoux 2000 for reviews). Animal research indicates that the amygdala is an important component of a neural circuitry that modulates aggressive behavior. Although there is less direct evidence for the amygdala's role in human aggression, indirect evidence suggests that amygdala reactivity may be an important precursor for aggressive behavior in humans. Across a number of studies that used different methodologies, there is robust evidence that amygdala activity increases in response to emotional signals of social provocation (angry faces) and that this amygdala reactivity is stronger in individuals susceptible to aggressive behavior (e.g., Coccaro et al. 2007; Beaver et al. 2008; Lee et al. 2008; Chan et al. 2010; Carré et al. 2012). These findings suggest that hyper-amygdala reactivity to social provocation may be a neural marker for one's propensity to engage in reactive aggression (see Carré et al. 2011, for review)

A recent neuroimaging study more directly linked amygdala function to aggression (Gospic et al. 2011). In this study, participants were scanned while playing the Ultimatum Game in the role of responder using procedures similar to the study described earlier (Mehta and Beer 2010), but the design of this newer study was optimized to detect rapid and slower neural responses to unfair offers. Results showed a rapid amygdala response to unfair offers that was positively related to aggressive behavior (rejecting unfair offers). Interestingly, administration of a benzodiazepine prior to performing the Ultimatum Game effectively reduced amygdala reactivity to unfair offers, and also decreased rejections of unfair offers (Gospic et al. 2011). In line with the study discussed earlier (Mehta and Beer 2010), Gospic and colleagues (2011) also found that prefrontal regions such as the OFC were activated to support the inhibition of unfair offer rejections, but these prefrontal responses came on line later. Together, the findings support a dual-systems model of reactive

aggression in line with Fig. 5.1; amygdala activation is associated with a rapid emotional and motivational drive to respond aggressively to social provocation (being treated unfairly), while the OFC is engaged later in the decision-making process to inhibit aggressive impulses.

Amygdala–OFC Connectivity

The studies reviewed above support the view that amygdala is involved in the emotional response to social threat and encourages reactive aggression, whereas the OFC is a self-regulation and impulse control region that inhibits aggression. Recent studies suggest that the functional connectivity between the amygdala and OFC may be another mechanism for aggressive behavioral reactions to social provocation. More specifically, healthy individuals show coupling between amygdala and OFC, but this connectivity is disrupted in psychiatric patients vulnerable to aggressive behavior (cf. Coccaro et al. 2011). Thus, not only do the amygdala and OFC influence aggressive behavior independently, but the neural communication between the two regions seems to play an important role in the inhibition of aggression. This mechanism is supported by neuroanatomical findings, which indicate that the OFC and amygdala have reciprocal connections with one another (Kringelbach and Rolls 2004).

Genetic and Neurochemical Modulators of Human Aggression

Research suggests that various neurotransmitters, genes, and hormones are involved in human aggression. In this section, we synthesize the main findings from these different areas of research. We focus our discussion on a few factors that have received empirical attention in human studies: serotonin, testosterone, and cortisol. We discuss how these factors may regulate human aggressive behavior along with their putative neural mechanisms.

Serotonin

A large correlational literature indicates that enhanced activity in the serotonin system is related to decreases in reactive aggression (Siever 2008; Coccaro et al. 2011). Recent research with pharmacological manipulations provides much needed causal evidence for the role of serotonin in mediating aggression. In one demonstration of this causal relationship, individuals with and without a life history of physical aggression were randomly assigned to receive 40 mg of paroxetine (a drug that acutely augments serotonergic activity) or placebo (Berman et al. 2009). Participants were then placed in the Taylor Aggression Paradigm, a laboratory task that measures physical aggression in response to social provocation. In this task, participants are told they are competing with another participant in a reaction time game, and electric shocks are received and administered. The amount of maximum shock delivered in response to social provocation was the primary measure of aggressive behavior in this study. The findings revealed that augmentation of serotonergic activity via paroxetine significantly reduced physical aggression after social provocation, but only in individuals with a life history of aggression. These findings suggest that enhanced serotonin activity causally reduces aggressive behavior in individuals prone to physical aggression.

If heightened serotonin activity can decrease aggression, might reductions in serotonergic activity increase aggression? Another study provided causal support for this relationship (Crockett et al. 2008). Healthy participants were randomly assigned to receive placebo or tryptophan depletion, a pharmacological manipulation that reduces serotonergic activity. Then participants played the Ultimatum Game in the role of responder, and the fairness of the offers was experimentally manipulated similar to the Ultimatum Game studies reviewed earlier. The results showed that reductions in serotonergic activity via tryptophan depletion causally increased aggressive behavior (rejection of unfair offers) (Crockett et al. 2008).

Serotonergic Gene Polymorphisms

Common variations (polymorphisms) within genes that regulate the serotonergic system can alter human brain function and aggression (Hariri and Weinberger 2003). Two polymorphic genes that have been widely studied in relation to human aggression are monoamine oxydase A (*MAOA u-VNTR*) and the serotonin transporter (*5-HTTLPR)*.

The first evidence in humans for the importance of MAOA in aggression came from the study of large Dutch kindred, whose males were notorious for impulsive aggression (Brunner et al. 1993). Brunner and colleagues (1993) discovered a missense mutation of the *MAOA* gene that resulted in a premature stop codon causing MAOA to be nonfunctional, thus, effectively producing functional MAOA knockouts. Although this finding is informative, the mutation is rare in the population. Nevertheless, within the *MAOA* gene, a more common polymorphism has been described, which is located 1.2 kb upstream of the MAOA coding sequences and consists of a 30-bp repeated sequence present in 3, 3.5, 4, or 5 copies. This variable number of tandem repeats (VNTR) polymorphism is functional: alleles with 3.5 or 4 copies of the repeat sequence are transcribed 2–10 times more efficiently ("high-expression alleles") than those with three or five copies of the repeat ("low-expression alleles") (Sabol et al. 1998). A well-known longitudinal study revealed that the presence of the low-activity allele interacted with a history of childhood maltreatment to predict increased levels of aggression and violence in adults (Caspi et al. 2002). This *MAOA* gene × childhood adversity interaction has conceptually replicated in other studies (e.g., Frazzetto et al. 2007; Reif et al. 2007). Although most studies assessed aggression through self-reported or objective real-world markers of aggression (e.g., violent crimes), one recent study showed an association between the *MAOA* gene and a well-validated behavioral measure of aggression (McDermott et al. 2009). In the study, participants were paid to punish others whom they believed had taken money from them. In reality, participants were playing with a fictitious player whose behavior was experimentally controlled by the researchers. Participants punished their opponents by administering varying amounts of aversive hot sauce, which served as the measure of aggressive behavior. The findings revealed that individuals with the low expression *MAOA* allele behaved more aggressively after social provocation relative to individuals with the high expression allele. That is, low expression allele carriers delivered higher amounts of hot sauce to their opponent, but only after their "opponent" had taken a large amount of money from them.

The serotonin transporter (5HTT) regulates the availability of synaptic serotonin. A widely studied gene within this system is a common functional polymorphism (*5HTTLPR*) (cf. Heils et al. 1996). Individuals with the short allele of this gene have reduced transcriptional activity and therefore reduced reuptake of synaptic serotonin compared to individuals with the long allele. These low activity allele carriers are at greater risk for affective psychiatric disorders such as anxiety and depression, particularly in combination with a life history of stress (e.g., Caspi et al. 2010). Other research has linked low activity allele status to aggressive behavior. Individuals with low activity allele variants in *5HTTLPR* are more likely to show increased childhood aggression (Beitchman et al. 2006), and low activity allele carriers who have adverse childhood environments are more

vulnerable to aggressive behavior as adults (Reif et al. 2007). This *5-HTTPLPR* gene effect emerges above and beyond effects of the *MAOA* gene discussed above, suggesting that both of these genes uniquely account for variance in human aggressive behavior (Reif et al. 2007).

Mechanisms for Serotonin-Modulated Aggression

The precise mechanisms for the effects of serotonin activity on human aggression remain unclear, but recent evidence suggests that the OFC, amygdala, and their connectivity are all candidate neural [AU3] mechanisms. One PET study using found increased metabolic glucose response in the left OFC to a serotonergic challenge (meta-chlorophenylpiperazine) in healthy participants, but not among borderline personality disorder (BPD) patients with impulsive aggression (New et al. 2002). Interestingly, this same research group found that administration of fluoxetine (a serotonin reuptake inhibitor) to individuals with BPD was associated with increased glucose metabolic rate in the OFC and an overall decrease in impulsive aggression (New et al. 2004). These findings suggest that serotonergic modulation of the OFC may have an inhibitory effect on impulsive aggression.

In support of heightened amygdala reactivity as a putative mechanism underlying reactive aggression, research suggests that genes that regulate serotonin function are associated with increased amygdala reactivity to facial signals of threat (see Buckholz and Meyer-Lindenberg 2008 and Hariri 2009, for reviews). For instance, Hariri and colleagues (2002) were the first to demonstrate that individuals carrying the "short" allele of the *5HTTLPR* gene demonstrate heightened amygdala reactivity to facial signals of threat, a finding that has been replicated several times (see Munafo et al. 2008, for review). Other research suggests that the *MAOA* gene may bias the socio-emotional circuitry of aggression, including the amygdala (Meyer-Lindenberg et al. 2006). Specifically, individuals with the low expression variant of the *MAOA* gene demonstrated heighted amygdala reactivity to facial signals of threat. Other work indicates that individuals with the low expression variant of the *MAOA* gene scored higher on a trait measure of aggression and interpersonal hypersensitivity and also demonstrated heightened dorsal anterior cingulate cortex (ACC) reactivity to social rejection (Eisenberger et al., 2008). Notably, the positive relationship between interpersonal hypersensitivity and aggression was mediated by heightened dorsal ACC reactivity to social rejection (Eisenberger et al. 2008). Another mechanism may involve connectivity between [AU4] the amygdala and the prefrontal cortex. Passamonti et al. (2012) found that acute reductions in serotonergic activity via tryptophan depletion reduced functional connectivity between the amygdala and prefrontal cortex in response to angry faces (e.g., connectivity with ventrolateral prefrontal cortex as well as ventral ACC), which may increase one's risk for reactive aggression. Collectively, these findings converge to suggest that serotonergic function may influence aggressive behavior via its interactions with receptors located within a neural circuitry including the amygdala, OFC, and ACC.

Testosterone

Testosterone (T) is a steroid hormone derived from cholesterol. It is produced and released primarily by the testes in men and by the ovaries and adrenal cortex in women. T belongs to a class of hormones called androgens, which are those hormones that are responsible for the development and maintenance of masculine characteristics. In addition to supporting basic physical development, T is also critically involved in regulating social behavior. Naturally occurring and experimentally elevated testosterone levels are positively associated with aggressive behavior in a variety of animal

species, especially when the status hierarchy is unstable (Giammanco et al. 2005; Collias et al. 2002; Ruiz-de-la-Torre and Manteca 1999; Oliveira et al. 1996; Sapolsky 1991; Wingfield et al. 1990). In stark contrast to the animal literature, the relationship between individual differences in T and human aggression is relatively weak (see Archer et al. 2005, for review). Even though some studies in humans show that higher circulating T is related to aggression, social dominance, and hyperreactivity to status threats (e.g., Archer et al. 2005; Mehta and Beer 2010; Mehta et al. 2008; Mazur and Booth 1998), other studies have produced inconsistent or null results (Archer et al. 2005). One explanation for these weak effects is that relatively stable levels of T (baseline T) may play less of a crucial role in human aggression than situationally induced fluctuations in T levels (see Carré et al. 2011, for review). It is well-known that T levels rise and fall in competitive social interactions, but only recently have researchers investigated whether dynamic rises in T encourage aggressive and dominant behaviors in humans. In the next section, we review this literature on context-driven T dynamics and human social behavior.

Challenge Hypothesis

John Wingfield and colleagues proposed the *Challenge Hypothesis* to explain how T changes influence social behavior in birds (Wingfield et al. 1990). According to this theory, T levels rise during the breeding season to encourage social competition for mates, and T drops during the non-breeding season to suppress competitive aggression and facilitate care for offspring. Mazur (1985) proposed a similar *Biosocial Model of Status* for T-behavior associations in humans. According to this model, status-relevant social interactions such as competition should cause T levels to fluctuate, and these fluctuations in T should encourage or discourage subsequent status-seeking behaviors such as dominance and aggression.

Although researchers had long known that T levels change during and after competition (Mazur and Booth 1998), researchers had simply assumed that these competition-induced changes in T would influence subsequent status-seeking behaviors. We conducted the first study in humans that explicitly examined the relationship between post-competition fluctuations in T and subsequent social behavior (Mehta and Josephs 2006). We experimentally rigged a competition and collected saliva samples before and after the competition to measure changes in T (Mehta and Josephs 2006). After participants provided the second saliva sample, we measured dominance behavior by asking participants whether they wanted to (a) rechallenge their opponent to a second competition, or (b) complete an alternative noncompetitive task. The results showed that changes in T after losing predicted who wanted to compete again in a second competition. Losers who rose in T were more likely to choose to rechallenge their opponent (73%) than losers who dropped in T (22%). These findings are consistent with the reciprocal model and suggest that a rise in T after a loss of status motivates individuals to reclaim their lost status (choosing to compete again).

We conducted a second study to test whether T responses to competition would also predict subsequent aggressive behavior (Carré et al. 2009). Similar to the previous study, participants provided a saliva sample before and after a rigged competition. After the second saliva sample, participants completed the Point Subtraction Aggression Paradigm (PSAP), a well-validated laboratory task that measures reactive aggression. In this task, participants are paired with a fictitious opponent (actually a computer program) and earn points by pressing Button 1 as quickly as possible or Button 2 to steal points from their opponent. Participants are told their total points will be exchanged for money at the end of the study. During the task, participants have points taken from them by their fictitious opponent, which serves as the experimental manipulation of social provocation. Stealing money from the fictitious competitor by pressing Button 2 is considered aggressive behavior because, like the Taylor Aggression Paradigm and the Ultimatum Game, this behavior represents an intent to cause harm. Consistent with the results of the earlier study (Mehta and Josephs 2006), this study found that

changes in T after losing in a competition predicted aggressive behavior in the PSAP. Individuals who lost the competition and rose in T showed more aggressive behavior (stealing more points from their opponents after social provocation) than individuals who lost the competition and dropped in T (Carré et al. 2009). More recent follow-up studies from our labs also show relationships between dynamic T changes and aggressive behavior (Carré et al. 2010; Geniole et al. 2010; Mehta et al. 2010). Together, this recent wave of studies provides strong support for the *Challenge Hypothesis* and *Biosocial Model of Status*, showing that dynamic T responses in status-relevant social interactions have implications for aggression and dominance behaviors. Although all these human studies on dynamic T were correlational, they fit with experimental research in animals, which demonstrates a causal influence of experimentally administered T after competition on aggressive behavior in a second competition (see Gleason et al. 2009 and Oliveira 2009, for reviews).

Neural Mechanisms for Testosterone's Influence on Aggression

Recent studies suggest that T influences human aggression through the OFC and amygdala. In one fMRI study, T levels were measured in saliva and then participants played the Ultimatum Game while being scanned (Mehta and Beer 2010). The findings showed that higher T levels predicted increased aggressive behavior (rejection of unfair offers), and decreases in bilateral medial OFC activity following unfair offers significantly mediated the association between testosterone and aggression. This finding suggests that T increases reactive aggression in part through impairments in the neural circuitry of impulse control and self-regulation (medial OFC). Other recent studies show that T (a) increases amygdala reactivity to angry faces (Hermans et al. 2008; van Wingen et al. 2008), and (b) reduces functional connectivity between OFC and amygdala (van Wingen et al. 2010), providing two additional neural mechanisms for how testosterone may modulate human aggression.

Androgen Receptor Gene

Recently, researchers interested in the genetics of human aggression have turned their attention to a common polymorphism found in the androgen receptor gene. The trinucleotide repeat (*CAG*) has been found to be highly polymorphic (Choong and Wilson 1998) and ranges from 9 to 31 repeats in the human population (e.g., Edwards et al. 1992). *CAG* repeat length is negatively associated with the expression of the androgen gene and androgen receptor (AR) sensitivity (Chamberlain et al. 1994). T exerts its effects primarily through these receptors which are expressed throughout the brain, including regions important in regulating aggression (e.g., amygdala and OFC) (Rubinow and Schmidt 1996; Mehta and Beer 2010, respectively). Thus, AR sensitivity to T may serve as a mechanism to modulate its effects on brain development and subsequent aggressive behavior.

Researchers have found that men who have fewer *CAG* repeats score higher on sexually dimorphic behavioral traits. For example, Simmons and Roney (2011) found that *CAG* length was negatively correlated with prestige and dominance (traits associated with intra-sexual competition) in a sample of men. Other work indicates that rapists and murderers have significantly fewer *CAG* repeats compared to controls in a sample of Indian men (Rajender et al. 2008). Furthermore, a study with adolescent males found that *CAG* repeat length interacted with T to predict a self-report measure of aggressive risk-taking (Vermeersch et al. 2010). Specifically, the authors found that T was positively correlated with aggressive risk-taking, but only among men with relatively fewer *CAG* repeats.

Other work has specifically linked variation in the *CAG* repeat to amygdala reactivity to facial signals of threat. Manuck and colleagues (2010) found an inverse relationship between *CAG* repeats

and bilateral ventral amygdala (the principal input region of the amygdala) reactivity when viewing threat cues (angry/fearful faces). On the other hand, reactivity in the dorsal amygdala (principal output region of the amygdala regulating physiological reactivity) was positively correlated with T independent of genotype. These results suggest that the *CAG* polymorphism modulates androgen-sensitive neural circuits associated with aggression.

The Dual-Hormone Hypothesis: Interactions Between Testosterone and Cortisol

Glucocorticoids are a class of hormones that are released by the adrenal glands during physical and psychological stress. The primary glucocorticoid in humans is cortisol (C). Most research on C has focused on the dispositional and situational variables that cause acute changes in C (e.g., Dickerson and Kemeny 2004), but some research indicates that C is negatively associated with aggressive behavior. In one longitudinal study of 314 boys, low basal C levels during preadolescence (age 10–12 years) predicted more aggressive behaviors 5 years later (Shoal et al. 2003). Other studies, however, have shown null effects of C on aggression. These mixed findings suggest that C may interact with other biological systems to modulate human aggression.

We recently proposed the *dual-hormone hypothesis* to reconcile mixed findings on the roles of T and C in human social behavior (Carré and Mehta 2011; Mehta and Josephs 2010). According to the dual-hormone hypothesis, T should have a strong influence on aggression and dominance only when C is low, but T's effect on social behavior should be blocked when C levels are high because C inhibits the neurobiological pathway between T and behavior at multiple levels (see Mehta and Josephs 2010 for a biological rationale). Consistent with the dual-hormone hypothesis, Popma et al. (2007) studied a group of male adolescents and found that T was positively related to physical aggression only in individuals with low C. In individuals with high C, there was no association between T and aggression. Mehta and Josephs (2010) showed a similar pattern of findings in studies of social dominance. A hormone profile of high T and low C was associated with increased dominance across multiple studies. Intriguingly, a profile of high T and high C was associated with submissive behavior after social threat. These dual-hormone effects on social behavior vary across social contexts (threat versus no threat, Mehta and Josephs 2010; social inclusion versus exclusion, Geniole et al. 2010). Together, these findings suggest that T and C jointly modulate human aggression and dominance behavior in a context-dependent fashion. Although the neurobiological mechanisms for dual-hormone modulation of behavior have yet to be studied, the amygdala and OFC are clear candidate regions. Indeed, androgen and glucocorticoid receptors are located in both of these regions, and T and C modulate neural activity in the amygdala and OFC.

Environmental Risk Factors

The research reviewed above provides insights into the biological factors implicated in aggressive behavior. In this section, we review research on environmental risk factors. We focus on two risk environmental factors that have received attention in scientific research – exposure to media violence and interpersonal rejection – and we discuss possible biological mechanisms.

Violent Media Exposure

A number of studies have examined the effects of exposure to violent media on aggressive behavior. In a recent meta-analysis of over 300 studies, the authors found reliable evidence that exposure to violent video games increases aggressive thoughts, feelings, and behavior and decreases empathy and prosocial behaviors (Anderson et al. 2010). Most of the evidence comes from studies of short-term effects (laboratory experiments), but some longitudinal studies also support media violence exposure as a causal risk factor in human aggression. In one recent study of 1,237 German adolescents, media violence exposure at time one predicted a greater propensity toward aggression 12 months later (Krahe and Moeller 2010). Neuroscience studies support the hypothesis that media violence exposure may increase aggression by altering the neural circuitry of aggression. One fMRI study showed that exposure to media violence decreased lateral OFC activity and reduced amygdala–OFC coupling (Kelly et al. 2007), and another study demonstrated that adolescents who reported frequent exposure to violence media had decreased lateral OFC density (Strenziok et al. 2010). These findings suggest that violent media exposure may cause both short-term and long-term changes in aggression by influencing OFC and amygdala function (see Carnagey et al. 2007 for these and related neural mechanisms). Another study suggests that that violent media cues may increase aggression through elevated T levels (Klinesmith et al. 2006). Participants in this study were randomly assigned to interact with a toy gun or a children's toy for 15 min and then could administer various amounts of hot sauce to another person (a measure of aggressive behavior). Saliva samples were collected before and after the experimental manipulation and were analyzed for T levels. The findings showed that people who interacted with the gun administered more hot sauce to the other participant than people who interacted with the child's toy, and this effect of gun exposure on aggression was significantly mediated by increases in T levels after gun exposure. Given previous research linking T to amygdala and OFC, it seems plausible that the effect of increased T levels on aggression following gun exposure may be driven by changes in the amygdala–OFC neural circuit.

Interpersonal Rejection

The act of being rejected or devalued by other people has been shown to be a clear risk factor in aggressive behavior. In fact, a Surgeon General's report concluded that social rejection was the most significant risk factor for violence among adolescents, even more potent than factors such as low socioeconomic status, gang membership, or drug use (cf. Leary et al. 2006; Office of the Surgeon General 2001). A spate of school shootings in the United States illustrates the social isolation–violence relationship. In an analysis of 15 school shootings between 1995 and 2001, 13 out of the 15 perpetrators had a history of being socially rejected – including teasing, bullying, and chronic ostracism (Leary et al. 2003). Experimental evidence also supports a causal effect of interpersonal rejection on aggressive behavior. In many of the experiments, individuals were randomly assigned to receive rejecting or accepting relational feedback from another person (in fact, the feedback is bogus), and factors such as anger, relational aggression (e.g., social derogation), and reactive aggression (e.g., administering varying amounts of aversive hot sauce) were measured after the rejection or acceptance experience. Rejection increased anger and aggression compared to acceptance in many of the studies (see review by Leary et al. 2006). This effect of social rejection on aggression depends on individual differences in social sensitivity and biological differences

in serotonergic activity. People high in rejection sensitivity or insecure attachment are more likely to respond to interpersonal rejection with aggression (Leary et al. 2006). Moreover, as described earlier in the chapter, low expression *MAOA* allele carriers show increased activity in the dorsal ACC after social rejection, a region implicated in emotional distress and anger (Eisenberger et al. 2007). These results suggest that the influence of social rejection on aggression may be driven by hyperreactivity in socioemotional neural circuits to rejection experiences (e.g., dorsal ACC, Buckholtz and Meyer-Lindenberg 2008).

Other research indicates that social rejection can increase levels of C, a hormone implicated in psychological stress. In an experiment in which participants were socially rejected or received no rejection, self-esteem moderated cortisol and aggressive behavioral responses to social rejection (Ford and Collins 2010). Compared to individuals high in self-esteem, individuals low in self-esteem showed heightened relational aggression (partner derogation) and increased C in response to social rejection. The association between low self-esteem and relational aggression was mediated by changes in C. Taken together, the findings suggest that social rejection augments aggressive behavior through biological systems associated with stress and socioemotional sensitivity (cortisol, dorsal ACC).

Psychological Interventions

Above, we reviewed some of the biological and social risk factors implicated in human aggressive behavior. In this section, we discuss psychological interventions that can reduce reactive aggression. Although there are many possible interventions, we focus our discussion on two in particular: (1) cognitive reappraisal and (2) self-control training.

Cognitive Reappraisal

Emotion regulation involves cognitive strategies to alter one's emotional response to environmental stimuli. In the context of reactive aggression, cognitive strategies that prolong anger are likely to upregulate aggression, while strategies that reduce anger responses should decrease the propensity toward aggression. In line with this reasoning, rumination – which involves continuing to think about the anger-induced provoking event in a way that prolongs anger – increases anger and reactive aggression (Denson et al. 2011b; Fabiansson et al. 2012). An emotion regulation strategy that may be beneficial for reducing reactive aggression is cognitive reappraisal, which involves reinterpreting an emotional event to reduce its negative emotional impact. For example, an individual who is insulted by another person may try to think about what lessons he or she could learn from the event or think about the event from the perspective of an objective third party (Fabiansson et al. 2012). Recent research supports the hypothesis that cognitive reappraisal can reduce anger and reactive aggression. One study showed that individuals who thought about an anger-inducing event and then engaged in cognitive reappraisal showed less anger compared to participants who thought about an anger-inducing event and then engaged in anger rumination (Fabiansson et al. 2012). A second study used a longitudinal design and found that people who received reappraisal training over the course of a semester showed reduced trait vengeance – an important predictor of aggressive behavior – compared to participants in the control condition (Bartlett and Anderson 2011). Hence, not only can cognitive reappraisal reduce the propensity toward aggression in the short term but also in the longer term. These findings are preliminary, but they suggest that cognitive reappraisal training courses may reduce aggressive behavioral reactions to social provocation in individuals prone to violence.

Neuroscience studies suggest that the aggression-reducing benefits of reappraisal may be due to more effective engagement of prefrontal neural regions including medial and lateral OFC, reduced amygdala activity, and changes in functional connectivity between the frontal cortex and subcortical regions (Fabiansson et al. 2012; Goldin et al. 2008; McRae et al. 2008; Ochsner et al. 2002, 2009). Overall, reappraisal training may reduce the likelihood of reactive aggression through increased top-down neural control and blunted emotional reactivity to social provocation.

Self-control

Theory and research suggest that reduced self-control is a critical psychological mechanism for aggressive behavioral reactions to social provocation. Individuals prone to aggressive behavior are often impulsive (low in self-control), and experimental studies show that reduced self-control mediates the association between social provocation and increased aggressive behavior (Denson et al. 2011b). These studies suggest that self-control training interventions could decrease reactive aggression. A recent study tested this hypothesis by having participants practice motor self-control (using their nondominant hand to do everyday tasks such as brushing teeth) between 8 a.m. and 6 p.m. over a period of 2 weeks (Denson et al. 2011a). The findings revealed that this self-control intervention decreased anger and aggressive behavior following social provocation for individuals high in trait aggression. Although the precise biological mechanisms for the effect of self-control training on aggression remain unknown, it is plausible that the self-control intervention promoted engagement of prefrontal regions implicated in self-regulation and impulse control such as medial OFC, which resulted in the inhibition of aggressive behavior (Mehta and Beer 2010).

Directions for Future Research

There are a number of important directions for future research on the social neuroscience of human aggressive behavior. Here, we discuss some of these directions.

Gene × Hormone Interactions

One area of research that needs more attention is studies that search for theoretically informed gene × hormone interactions. It has been speculated, for example, that T may interact with the serotonergic system to modulate human aggression. Promising new evidence provides initial support for this hypothesis, demonstrating a *MAOA* × T interaction on aggression (Sjoberg et al. 2008). Individuals with the low expression allele who were also high in T levels showed the greatest risk for aggressive behavior. Another study found a *5HTTLPR* × T interaction on stress reactivity. S carriers with high T showed heightened cortisol reactivity to social threat (Josephs et al. 2011), suggesting that these same individuals may be prone to greater emotional reactions to social provocation and reactive aggression. Finally, some studies have shown that hormone receptor genes are related to the neural circuitry of aggression (e.g., androgen receptor genes and amygdala reactivity to angry faces, Manuck et al. 2010), but there has been considerably less work that has tested for biologically relevant hormone receptor gene × hormone interaction on aggression (e.g., androgen receptor gene × T interactions; but see Vermeesch et al. 2010 for a recent example of this fruitful approach). Human research on gene × hormone interactions has

only just begun, and we believe that research that takes this approach will greatly improve our understanding of the neurobiology of aggression.

Neuropeptides

Animal research indicates that the neuropeptide vasopressin plays an important role in aggressive behavior in part through interaction with other biological factors such as T, but very little work has examined the influence of vasopressin on human aggression. An earlier study found that individual differences in cerebrospinal fluid arginine vasopressin (AVP) were positively correlated with self-reported aggression (Coccaro et al. 1998). A more recent paper administered AVP and found some initial evidence that it alters psychophysiological correlates of aggressive behavior (Thompson et al. 2004, 2006), but clearly much more research on vasopressin and aggression in humans is needed. Oxytocin is another neuropeptide that also influences social behavior, and its effects on human behavior have been much more well-studied (Bartz et al. 2011). Although most biological theories suggest that oxytocin should encourage prosocial behavior (trust, cooperation), recent human studies suggest that this view is overly simplistic. This research shows that oxytocin administration has divergent effects on human social behavior directed toward ingroup versus outgroup members. More specifically, oxytocin increased aggressive motivation toward outgroup members (outgroup hate) even though oxytocin increased prosocial motivation toward ingroup members (ingroup love) (De Dreu et al. 2010). These results indicate that the effects of oxytocin are context-dependent, which fits with animal models suggesting that oxytocin can promote defensive maternal aggression.

Longitudinal Studies

There is a need for more longitudinal studies that measure a host of biological factors and psychological factors along with aggressive behavior at multiple time points. Such longitudinal studies can illuminate how changes in biological systems (e.g., T levels, OFC function) may track changes in aggressive behavior over time. Such longitudinal studies can inform theories of the psychobiological mechanisms through which environmental risk factors (e.g., media violence) and protective factors (e.g., parental training in cognitive reappraisal) early in life can influence the expression of aggressive behavior in adulthood.

Gender Similarities and Differences

More theoretical and empirical attention is needed to understand how males and females are similar and how they are different in the psychobiological mechanisms of aggressive behavior (Josephs et al. 2011). For example, most research on T and social behavior has focused on males, but a series of recent studies suggest that basal T may also predict social behaviors in females (e.g., social dominance, Mehta et al. 2008, 2009). Other research, however, suggests that acute fluctuations in T predict aggression and dominance only in men (Carré et al. 2009; Mehta and Josephs 2006). Moreover, a greater understanding is needed for how men's and women's aggressive behavior may be expressed differently. Recent research suggests that boys are more likely to show direct forms of confrontation (physical aggression, direct name calling) compared to girls, whereas boys and girls

are equally likely to show indirect aggression (sabotaging friendships or romantic relationships, spreading gossip, social exclusion) (Card et al. 2008). Greater attention to biological and cultural issues surrounding gender is required to build more accurate theoretical models of human aggression.

Conclusion

Aggressive and violent behaviors affect millions of people worldwide every year (Mercy et al. 2002). This chapter reviewed the research on the social neuroscience of human reactive aggression, including research on the genes, hormones, neural systems, and environmental factors implicated in aggressive behavior. Researchers have only begun to integrate these perspectives to build comprehensive models of human aggression. Promising new directions for research include longitudinal studies that better delineate the social and biological mechanisms that increase risk for adulthood violence as well as studies that attempt to reduce aggression in at-risk populations through novel pharmacological and psychosocial interventions.

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