The Aggressive Brain

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Aggression is a complex, multifaceted behavior often caused by numerous factors and expressed in innumerable ways. Like all complex behaviors, aggression ultimately has its roots in the brain. Although this might sound obvious, discovering the specific neural circuits and neurophysiological processes responsible for engendering aggressive responses has proven anything but simple. The purpose of this chapter is to provide a brief overview of discoveries in both human cognitive neuroscience and animal behavioral neuroscience that have begun to shed light—literally in some cases—on the heretofore mysterious neural processes and connections responsible for producing aggressive behavioral responses.

Basic Principles

Aggressive behavior is nearly ubiquitous across species (see Briffa, 2010). From fruit flies to fish and lower vertebrates to nonhuman primates to humans, virtually all animals display aggression both within their own species and, at times, directed at members of other species. Although the term "aggression" is often (mis)applied in referring to behaviors that are better captured by terms like "assertive" (as in commanding someone's attention), "persistent" (as in a diligent salesperson) or "energetic" (as in a competitive athlete), in psychological terms aggression is defined as any behavior that is intended to harm (or threaten harm to) another individual (e.g., Baron & Richardson, 1994). Aggression by this definition involves a real social exchange, involving at least two individuals (not an imagined interaction); aggression is an observable behavior, not merely a thought or angry feeling; and aggression is intentional, not an accidental injury or social faux pas (see Bushman & Bartholow, 2010). A behavior does not have to result in actual harm to qualify as aggressive; throwing a punch that misses its target is still an aggressive act.

Within modern human societies, aggression is nearly always seen as a maladaptive response, something that should be controlled and that can bring nearly as much harm to the perpetrator (e.g., through societal scorn or retaliatory responses) as to the intended victim. In nonhuman animals, however, the vast majority of aggressive behavior is functional and adaptive. Animals routinely must stake out and defend territories, fend off mating competitors, and protect themselves and their offspring from various threats. With the exception of the actions carnivores must take to secure prey, these types of *functional aggression* in nonhuman animal species rarely result in lasting harm, particularly within species. In contrast, *escalated aggression* often does produce harm, involving more extreme forms of behavior that elevate normal or functional aggression to abnormal and destructive violence.

Human analogues of functional aggression are not difficult to find (e.g., a shoving match between two people over the affections of a third), and though arguably human aggression often involves (or can involve) more high-level thinking compared to that of our nonhuman cousins, the neural bases of aggression appear to be strikingly similar across species. Thus, considerable research has been devoted to understanding the neurophysiological and neurochemical mechanisms responsible for aggression in animals, one aim of which is to apply this knowledge to better understanding human aggression (also see Chapter 2 this volume). It is important to point out that although specific expressions of aggression (i.e., phenotypes) often differ across species (e.g., between humans and other animals), the organization and function of relevant brain structures is often highly similar. In particular, despite some important differences in gene expression, the neuronal organization of limbic structures in rat and mouse brains is known to be very comparable to that of human brains (see Huber & Kravitz, 2010; Nelson & Trainor, 2007). Also, considerable evidence (for a review, see Nelson & Trainor, 2007) points to the conclusion

that multiple neurochemical systems that regulate species-specific aggressive behaviors have co-evolved in humans and mice (for example), making animal models very useful analogues of human neural function in this context (see Cheng et al., 2014). The next section provides a brief review of what scientists have discovered concerning those neural processes.

Neuroanatomy of Aggression

It goes without saying that the brains of virtually all species are extremely complex systems, which scientists have only just begun to understand in any detail. In attempting to understand the brain basis for the kinds of behaviors that support aggression, researchers face a very daunting challenge. A basic premise of understanding brain-behavior dynamics is that as behaviors become more complex their neural substrates likewise become more complicated and multifaceted. This makes the problem of identifying specific neural structures or circuits responsible for complex behaviors like aggression very difficult.

Investigating the neural substrates of aggression in humans is especially challenging. Historically, knowledge on this topic came largely from case studies of individuals who suffered lesions to various neural structures as the result of disease or injury. For example, the famous case of Phineas Gage, the 19th Century railroad worker who survived a horrific accident in which an iron tamping rod, measuring nearly four feet in length (1.2 meters) and weighing over 13 pounds (5.9 kg), was blasted through his left cheek and out the top of his skull, provided some of the first clues about the role of specific cortical areas in shaping interpersonal responses, including aggressiveness. It was initially considered something of a miracle that Gage had not died from his massive head wound, particularly because the iron rod had "[broken] up considerable portions of brain" (Harlow, 1848, p. 389). Subsequent to his initial recovery, his

apparent retention of his mental faculties—"he has memory as perfect as ever" (Harlow, 1848, p. 392)—seemed to indicate an extreme plasticity in the functions of brain areas.

Later, however, those close to him began to notice dramatic changes in Gage's temperament. In reporting on his case, J. M. Harlow, the physician who treated and subsequently observed him for many years, remarked, "Previous to his injury, though untrained in the schools, he possessed a well-balanced mind, and was looked upon by those who knew him as a shrewd, smart business man, very energetic and persistent in executing all his plans of operation. In this regard his mind was radically changed [following the injury], so decidedly that his friends and acquaintances said he was 'no longer Gage'" (Harlow, 1868, p. 338). Gage was described as fitful and irreverent, "indulging at times in the grossest profanity (which was not previously his custom)," and "at times pertinaciously obstinate" (p. 338).

Prefrontal cortex. Because some of Gage's mental abilities were spared (e.g., his memory; basic functions like walking and talking), whereas his personality and social behaviors were drastically altered, his case represents an early example of discoveries related to neural specialization. More specifically, the location of Gage's injury provided some of the first clues concerning the importance of frontal lobe structures, particularly the portion generally termed *prefrontal cortex* (PFC), in regulating emotions including anger and social behaviors including aggression (see Blair, 2004; Damasio et al., 1994). While somewhat difficult to rigidly define, the PFC is generally said to consist of the most anterior parts of the frontal lobe, especially regions directly behind the forehead and the eyes, encompassing Broadmann areas 8-11 and 44-47 (see Garey, 2006). The PFC is primarily associated with high-level cognition and executive functioning (see Fuster et al., 2000; Goldman-Rakic, 1996; Roberts, Robbins, & Weiskrantz,

1998), suggesting that aggressive actions often result from a failure of self-regulatory control (see Giancola, 2000; Giancola, Mezzich, & Tarter, 1998; Seguin & Zelazo, 2005).

A large body of research has confirmed that PFC structures play an important role in regulating aggression. For example, one study found that men who performed poorly on at least some cognitive tests thought to rely on PFC functioning behaved more aggressively after being provoked in a laboratory setting, relative to their peers who performed better on the cognitive tests (Giancola & Zeichner, 1994). Another study linked increased aggression in humans to poor functioning in the orbital prefrontal cortex (Giancola, 1995), an area severely damaged in Gage's accident, confirming earlier reports of increased aggression in rats following orbital prefrontal lesions (de Bruin et al., 1983). Other studies have used lesion (e.g., Anderson et al., 1999; Grafman, 1996) and brain imaging methodologies (e.g., Yang et al., 2010) to document the negative association between prefrontal functioning and aggression.

Social behavior network. Of course, the PFC is not the only patch of neural real-estate involved in the generation and regulation of aggression. Moreover, the areas of the brain that appear to control aggression are not specialized for this purpose, leading some to suggest that aggression is an emergent property of a larger neural network involved in the regulation of numerous social behaviors (Newman, 1999). This proposed network includes several structures often considered part of the limbic system, including the anterior hypothalamic nucleus (AHN), ventromedial hypothalamus (VMH), medial amygdala (MA), bilateral septum (BLS), periaqueductal gray (PAG), and the bed nucleus of the stria terminalis (BNST). PFC structures are thought to interact with the structures of the social-behavior network, largely functioning to inhibit or modulate their activation (see Nelson & Trainor, 2007). Evidence supporting this interpretation has come from studies with rats showing that lesions of the BLS, BNST, AHN and

MA tend to reduce aggression between males (Kruk, 1991), whereas lesions of the orbitofrontal cortex tend to enhance aggression (de Bruin et al., 1983).

Of the structures in this social-behavior network, the hypothalamus appears to have particular significance for aggression. Early lesion studies with cats established the hypothalamus as important for the control of rage-related behavior (Bard, 1928). More recently, focused electrical stimulation of the AHN has been shown to increase aggression in both rats (Bermond et al., 1982; Kruk et al., 1984) and cats (see Siegel et al., 1999), whereas micro-injection of a vasopressin-receptor antagonist into the AHN reduces aggression in hamsters (Ferris & Potegal, 1988). Studies with nonhuman primates appear to confirm the key role of the hypothalamus in aggressive responding. For example, electrical stimulation of the AHN in rhesus monkeys and the VHA in marmosets increases aggressive displays and attacks on subordinate males (see Nelson & Trainor, 2007). Research with humans likewise points to an important role for the hypothalamus in triggering escalated, abnormal levels of aggression (see Haller, 2013).

Shedding light on neural function. Such electrical and chemical stimulation studies represent a major advance over earlier "knife cut" lesion studies (e.g., Bard, 1928) or other neural ablation techniques, which often afford little precision in targeting specific structures or groups of neurons for study. Still, even these more advanced stimulation techniques can be problematic because the current (in the case of electrical stimulation) activates both the neurons of interest and the fibers connecting them with other cells and structures, making it difficult to know whether observed behavioral effects result only from stimulation of the area of interest. This problem is particularly acute when using mouse or insect models, whose neural structures are tiny in comparison with other model organisms like cats or primates. A very recent

development from genetic research, known as *optogenetics*, provides a solution to this problem. With optogenetics, scientists engineer neurons in a given location to be activated by specific frequencies of light. This is accomplished by delivering a gene that encodes light-sensitive protein onto the cells of interest. Those cells can then be activated with high temporal and spatial precision using light delivered via an implanted optic fiber aimed at the region of interest (see Boyden et al., 2005). Unlike with electrical current delivered through an implanted electrode, the photons that inadvertently shine on nearby cells that have not been genetically altered will have no effect on their activation.

Using this optogenetic technique, recent studies have shown that very specific neurons in the ventrolateral portion of the VMH (VMHvl) in mice, a microscopic area comprised of only around 10,000 cells, control male attack behaviors. One study found that attack responses—but not males' social investigation behavior—are strongly suppressed by VMHvl inhibition, and that aggression returns to normal levels when VMHvl activity is restored (Lin et al., 2011). A more recent study provided perhaps the strongest evidence yet that aggression is an emergent property of a neural network subserving a range of social behaviors (Lee et al., 2014). By adjusting the intensity of the light delivered to VMHvl neurons, researchers could reliably control whether mice engaged in sexual mounting behaviors (low-intensity light) or attack behaviors (high-intensity light); intermediate intensity of the light prompted a mixture of attacking and mounting behaviors. These data show not only the exquisite sensitivity of VMHvl neurons to varying levels of stimulation (mimicking changing levels of neurochemical signaling that might occur in response to changing environmental circumstances), but also that the functional significance of their activation ranges dramatically, from the highly prosocial to the extremely antisocial. Such findings represent an important step away from a so-called "brain mapping" approach, in which

particular behaviors are mapped onto specific neural structures, and toward a more nuanced understanding of multidimensional neural systems governing whole classes of behavioral responding.

Neurochemistry of Aggression

Even within a circumscribed cluster of cells like VMHvl, there is variation with respect to the presence of receptors for differing neurotransmitters. This means that not all cells within a given structure are responsive to the same kind of neurochemical signaling and, ultimately, are probably not all responsible for regulating the same kinds of behaviors. This property of neurochemical heterogeneity among physically proximal neurons proved to be very important in the optogenetic study just described (Lee et al., 2014). Specifically, it was a relatively small subset of VMHvl neurons, distinguished by the presence of a receptor for the hormone estrogen, that were responsible for the scalable mounting-to-attacking behaviors elicited by the optical stimulation.

Research involving other populations of neurons in other structures also underscores the critical role of specific neurotransmitters in regulating aggressive and other social behaviors. One study found that optogenetically modified neurons in the medial amygdala with receptors for gamma-Aminobutyric acid (GABA) promote aggression when stimulated with high-intensity light, social grooming when stimulated with moderate-intensity light, and sex-related mounting when stimulated with low-intensity light (Hong, Kim, & Anderson, 2014). A different group of medial amygdalar neurons with receptors for glutamate (but not GABA) promote asocial repetitive self-grooming when activated using the optogenetic technique. Moreover, the two groups of neurons appear to prompt mutually inhibitory responses, in that activation of the GABAergic neurons suppresses self-grooming, whereas activation of the glutamatergic neurons

reduces social responses (aggression and mounting). These findings underscore that even within individual brain structures or groups of neurons, neural function is not homogeneous.

Other neurotransmitters linked to aggression include monoamines such as dopamine (DA) and serotonin (see de Almeida et al., 2005). In addition to mice, *drosophila melanogaster*—the common fruit fly—provides an excellent laboratory model for the study of aggression (see Chen et al., 2002). Male fruit flies routinely fight when confronted with other males, particularly when food or a mating opportunity is at stake. Their relatively simple brains, consisting of only around 100,000 neurons, offer an opportunity to understand the role of specific monoaminergic neurons in modulating aggression. DA is particularly tricky in this regard because it is implicated in so many different kinds of behaviors (Huber & Kravitz, 2010). However, researchers were able to identify two pairs of DA neurons in the fruit fly that modulate aggression but have no significant impact on other behaviors, providing some of the first direct evidence of a specialized role for DA in aggression (Alekseyenko, Chan, Li, & Kravitz, 2013).

Considerable research implicates serotonin in regulating aggressive responses. In humans, serotonin appears to be particularly implicated in the kinds of responses often associated with reactive, angry aggression. Serotonin appears to play an important role in regulating affective responses. In very simple terms, too little serotonin can make people irritable and less able to control anger, and therefore can indirectly lead to aggression. In correlational studies, brain serotonin levels have been negatively related to violence in both human epidemiological (Moffitt et al., 1998) and clinical samples (Goveas et al., 2004), as well as in nonhuman primates (see Higley et al., 1992; Westergaard et al., 1999).

More direct support for the role of serotonin in aggression comes from experimental laboratory studies showing that short-term reduction in serotonin levels, achieved by decreasing

dietary tryptophan, increases aggressive responding, whereas increasing serotonin levels via dietary supplements of tryptophan decreases aggressive responding (e.g., Cleare & Bond, 1995; Marsh et al., 2002; Pihl et al., 1995). Brain imaging studies show a potential mechanism for this effect. For example, one study found that tryptophan-depleted participants showed weaker co-activation of limbic (amygdala) and prefrontal cortical structures during viewing of angry faces, compared to non-depleted participants, suggesting that prefrontal regulation of anger-related responses is more difficult when serotonin levels are low (Passamonti et al., 2012). This hypothesis is consistent with the idea that factors that increase aggression by reducing inhibitory control (e.g., alcohol consumption) have their effects through decreases in serotonin levels (see McCloskey, Berman, Echevarria, & Coccaro, 2009). Drug studies similarly have shown that acutely increasing serotonin levels—for example, using drugs like fenfluramine (see Cherek & Lane, 2001) and paroxetine (Berman, McCloskey, Fanning, Schumacher, & Coccaro, 2009)—reduces aggression in the short term, and prolonged exposure to medications that increase serotonin levels chronically reduce impulsive aggression in patients with personality disorders (e.g., Coccaro & Kavoussi, 1997; Salzman et al., 1995).

But the link between serotonin and aggression is more complicated than it might seem. A recent review summarized and integrated laboratory findings in cats, rodents and humans and concluded that serotonergic neurotransmission in the hypothalamus, among other mechanisms, distinguishes reactive/emotional aggression from proactive/low-arousal aggression (Haller, 2013). Specifically, reactive, high-arousal aggression is associated with increased activation in the mediobasal portion of the hypothalamus, which is accompanied by increased vasopressinergic and decreased serotonergic neurotransmission. In aggression models associated with low arousal (unemotional/proactive aggression), the lateral but not the mediobasal

hypothalamus is over-activated and the link between aggression and serotonergic neurotransmission is lost. This conclusion accords with previous findings showing that serotonin influences impulsive (but not planned) aggression (see Berman et al., 1997).

Neural Responses Associated with Aggression

Thus far, the current chapter has focused primarily on evidence of the neural foundations of aggression from studies in which neural structure and function have been manipulated, either naturally (i.e., via injury) or in laboratory lesion and neural activation studies. Another class of studies from cognitive and behavioral neuroscience involves measuring naturally occurring neural responses either as aggressive behaviors are enacted or as environmental cues associated with aggression are processed. Work of this type is important for establishing links between aggression-related triggers in the environment and the neural processes that give rise to overt behavioral expression of aggression. This section provides a brief review of some of that research.

A considerable amount of human aggression research is concerned with factors in the external environment (e.g., perceiving hostility in others; witnessing others' aggressive acts; seeing others in pain) that are believed to elicit aggressive or anti-aggressive (i.e., empathic or prosocial) behavioral responses. Studies of this type often involve participants being asked to view violence-related stimuli while their brain activity is measured. For example, one correlational study found that repeated viewing of violence in the media is associated with reduced neural responding to depictions of real-life violence, seen as attenuated amplitude of the P3 (or P300) component of the event-related brain potential (ERP) when violent images are shown (Bartholow, Bushman, & Sestir, 2006). An experimental study showed that, among participants who typically do not expose themselves to large amounts of media violence, playing

a violent video game (versus a nonviolent game) in the lab for 25 minutes also reduced the P3 response to images of violence (Engelhardt, Bartholow, Kerr, & Bushman, 2011). ERPs represent electrical responses generated by the post-synaptic firing of (primarily cortical) neurons during information processing (see Fabiani, Gratton, & Federmeier, 2007). The P3 is a voltage deflection occurring roughly 300-700ms following the onset of a stimulus (e.g., an image of violence), which has been associated with the activation of approach and avoidance motivational systems in response to positive and negative images (e.g., Schupp et al., 2000; Hilgard, Weinberg, Hajcak, & Bartholow, 2014; Weingberg & Hajcak, 2010). Thus, the findings reported by Bartholow and colleagues (2006, 2011) suggest that exposure to virtual violence can lead to desensitization of avoidance motivational responses to real-life violence (also see Bailey, West, & Anderson, 2011).

As mentioned in the previous section, functional magnetic resonance imaging (fMRI) also has been used to study the specific neural structures involved in processing violence and in regulating aggressive responding (e.g., Passamonti et al., 2012). In a nutshell, fMRI involves the measurement of blood flow to specific brain areas in response to specific stimuli or events, which can be used to infer that those areas were activated by those stimuli or events (see Huettel, Song, & McCarthy, 2014). In one study, researchers used fMRI to investigate neural structures that increase and decrease in activation during violent video game play (Weber, Ritterfeld, & Mathiak, 2006). These researchers found a negative linear relation between the potential for violence in a game scene and the fMRI signal change in the rostral anterior cingulate cortex (rACC), amygdala, and orbitofrontal cortex, structures implicated in affect/emotion-related processing and self-regulation. More recently, researchers compared neural activity during video game play between individuals with mostly violent or mostly nonviolent game experience

(Gentile, Swing, Anderson, Rinker, & Thomas, 2014). ACC and amygdala activity during violent games (compared to nonviolent games) was higher in individuals with predominantly nonviolent game experience, suggesting that these individuals were more emotionally reactive to the violence in the game than were individuals with considerable violent gaming experience. These results complement those using ERPs (Engelhardt et al., 2011), providing validation of the desensitization hypothesis using a different technique.

Other brain imaging studies also point to areas in the prefrontal cortex as important for regulating anger and aggression. These data are consistent with the neuropsychological data reviewed previously. For example, participants in one study were insulted and induced to ruminate while in the fMRI scanner (Denson, Pedersen, Ronquillo, & Nandy, 2009). The results showed that activity in areas of the PFC was positively related to self-reported feelings of anger and to individual differences in self-reported aggression, suggesting less efficient PFC engagement is associated with more difficulty regulating angry feelings. In another study, women received injections of testosterone while viewing slides depicting angry and happy faces (Hermans, Ramsey, & Van Honk, 2008). The results showed consistent activation to angry versus happy faces in brain areas known to be involved in reactive aggression, such as the amygdala and hypothalamus.

Integration

This chapter has presented a lot of information concerning the neural foundations of aggression, while at the same time not providing much in the way of an explanation for how various neurochemical and neurophysiological processes give rise to aggression. One scholar reviewed the genetic and brain imaging literatures related to violent and antisocial behavior and proposed a model in which specific genes produce structural and functional brain alterations that

predispose certain individuals to behave in an aggressive manner (Raine, 2008). Based in large part on research in psychopathy, this model proposes a key role for the prefrontal cortex (as well as limbic structures, such as the amygdala) in regulating aggression and violence. Critically, however, the model goes beyond mere biology by incorporating the influence of environmental factors that may alter gene expression in these areas, "to trigger the cascade of events that translate genes into antisocial behavior" (Raine, 2008, p. 323). For example, a common polymorphism (i.e., an individual difference in the form or expression of a biological process) in the monoamine oxidase A (MAOA) gene, which produces an enzyme important for breaking down neurotransmitters such as serotonin and dopamine, has been associated with both antisocial behavior (Moffitt et al., 2002) and reduced volume of brain structures, such as the amygdala and orbitofrontal cortex, important for emotion and self-regulation. Future treatments for violent, antisocial behavior could therefore include drug therapy to regulate levels of MAOA activity.

In summary, the available biochemical, neuropsychological, and brain imaging data all indicate areas of the prefrontal cortex and a social-behavior network (mainly comprised of limbic structures) as important for regulating aggressive behavior across species. In particular, both human and animal models point to a critical role for hypothalamic neurons in a range of social behaviors, including aggression. Moreover, serotonergic neurotransmission in the hypothalamus appears critical for angry, reactive (or escalated) forms of aggression, but not for low-arousal, proactive or functional forms.

Although both humans and other species engage in both of these forms of aggression, this distinction appears to be much larger in modern human aggression than in either animal or even historical human forms of the behavior. In recent history, humans have become much more adept at escalated forms of aggression and violence than have other animals, and have developed

much more sophisticated and deadly ways of behaving aggressively. From arrows and rifles to drones and warships to cyberattacks, modern weapons allow humans to inflict massive amounts of harm from long distances, often without directly confronting or even seeing their victims. This more detached form of escalated aggression differs dramatically from the aggression perpetrated by nonhuman animals and even our relatively recent human ancestors, in several ways. For one, this kind of aggression often occurs in the absence of an instigating emotional response, such as anger, and diverts subsequent emotional responses that often arise following an aggressive act, such as empathy for others' pain and suffering, which can help to inhibit future aggression (see Funk et al., 2004). Additionally, being physically removed from the location of an aggressive action, as in the case of launching a missile attack from hundreds of miles away, allows us to avoid the potential for being harmed ourselves (at least in the short term). In the not-too-distant past, causing physical harm to another person meant engaging in hand-to-hand combat, in which the perpetrator risked being injured as much as the victim. It seems likely that the quantum leap in humans' ability to aggress in more detached and emotionless ways represents a decoupling of aggressive actions from the neurochemical and neurophysiological processes that evolved to support functional aggression.

The aim of this chapter was to provide a brief overview of recent advances in behavioral and cognitive neuroscience research investigating the neural foundations of aggressive behavior. Although in many cases these approaches are complementary, representing the essence of translational research across levels of analysis, the preceding discussion highlights some important ways in which human and animal aggression have diverged. Given such distinctions, it would seem that understanding uniquely human forms of aggression and violence, such as

mass shootings and acts of war, likely will be achieved primarily through human behavioral, neuropsychological and psychophysiological research.

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