Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Psychology

Animal models of excessive aggression: implications for human aggression and violence

Sietse F de Boer

Escalated interpersonal aggression and violence are common symptoms of multiple psychiatric disorders and represent a significant global health issue. Current therapeutic strategies are limited due to a lack of understanding about the neural and molecular mechanisms underlying the 'vicious' shift of normal adaptive aggression into violence, and the environmental triggers that cause it. Development of novel animal models that validly capture the salient features of human violent actions combined with newly emerging technologies for mapping, measuring, and manipulating neuronal activity in the brain significantly advance our understanding of the etiology, neuromolecular mechanisms, and potential therapeutic interventions of excessive aggressive behaviors in humans.

Address
Department of Behavioral Neuroscience, Groningen Institute for Evolutionary Life Sciences (GELIFES), University of Groningen, P.O. Box 11103, 9700 CC Groningen, The Netherlands

Corresponding author: de Boer, Sietse F (s.f.de.boer@rug.nl)

Current Opinion in Psychology 2017, **19**:81–87

This review comes from a themed issue on **Aggression and violence**

Edited by **Brad J Bushman**

http://dx.doi.org/10.1016/j.copsyc.2017.04.006

Introduction

Across the animal kingdom, aggression is the behavioral weapon of choice for individuals to gain and maintain access to desired resources (food, territory, mating partners), defend themselves and their progeny from rivals and predators, and establish and secure social status/hierarchical relationships. Clearly from a biological point of view, aggressive behavior is considered a highly functional form of social communication leading to active control of resources and the social environment, and thus is essential for individual and population survival and evolutionary preserved. It is characterized by a ritualized set of species-typical behaviors performed in close interaction with another individual (see Refs [1•] and [2] for more detailed descriptions of the various forms of aggression and the different aggressive acts and postures displayed in the commonly used resident–intruder aggression paradigm). Although most individuals engage in social conflicts with appropriate and well-controlled (functional) forms of aggressive behavior, a relatively small fraction of individuals can become excessively aggressive and extremely violent. In humans, this small percentage (ranging from 3 to 7%) of violent aggressive individuals is a major source of death, injury, social stress and ensuing disability, thus constituting one of the most devastating societal problems worldwide. These violent and pathological forms of aggression observed in our human society and clinically, co-morbid across a wide spectrum of DSM-V-defined psychiatric and neurological disorders, have motivated much of the scientific interest in aggressive behavior in animals. In particular, there is a need to understand these problematic behaviors in terms of their underlying causal mechanisms and modulating factors. Although once regarded as a typical human proclivity, lethal violence is also expressed in 40% of mammalian species and has significant phylogenetic roots [3•]. Therefore, animal models can be developed that captures the essential features of human violence and obtain experimental support of the causal nature of underlying molecular genetic mechanisms and environmental triggers.

Violence is the pathology of functional aggressive behavior

Although aggression is basically highly functional, it can be potentially harmful for both the victim and aggressor. Therefore, throughout the animal kingdom, strong inhibitory feedback mechanisms are operative such as taboos, ritualization, submission, reconciliation and appeasement to keep physical aggression in control and to prevent its potentially adverse (*i.e.*, injury or death) consequences. Yet, how these are embedded in neural mechanisms to gate the expression of aggression is largely unknown. Until a decade ago, most ethological studies of aggression have focused on the ultimate and proximate mechanisms of this normal adaptive aggressive behavior, while clinically the focus is predominantly on violent individuals and excessive or inappropriate forms of human aggressiveness. Actually, the lack of biologically relevant and valid animal models for these pathological forms of aggressive behavior is the main reason for the gap in our knowledge about the neurobiological roots and molecular genetic mechanisms of violence in humans. Therefore, new experimental animal models have been developed that focus more on provoking escalated and uncontrolled forms of aggressive behavior in order to capture the problematic clinical violent phenotype.

Basically, valid models should demonstrate excessive, injurious and impulsive aggressive behavior that exceeds and/or deviates from normal species-typical levels or patterns (see Refs [4–6,7•,8] for elaborate descriptions). In this view, violence can be defined as a pathological form of aggressive behavior that is not subjected to inhibitory control mechanisms and that has lost its function in social communication (*i.e.*, aggression out of proportion, control, and context). Hence, this loss of the social communicative nature of the aggressive interaction in the currently available animal models of escalated aggressive behavior are operationally characterized by five factors: (1) Low provocation threshold, short latency to initiate attack; (2) High rate and intensity, leading to significant tissue damage; (3) Disregard of appeasement signals, (4) Lack of species-normative behavioral structure (*i.e.*, attacks are deficient in conveying signaling intention and targeting opponent's body parts), and (5) lack of context in that critical features of the opponent such as age, sex or situation are misjudged [5,6,7•,8,9]. Several of these signs and symptoms of violent-like aggressive display are reliably engendered in the following animal models that have achieved, at least to a variable extent, similarity with human violent aggression in terms of symptomatology and phenomenology (face validity), phylogenetic and ontogenetic origins (construct validity), and response to clinically established treatments using clearly understood neurobiological mechanisms (predictive validity).

Current animal models of escalated, violent-like aggression

(1) Escalated aggressive behavior in unselected feral animals and selective breeding for escalated aggression

Compared to highly domesticated laboratory-bred conspecifics, feral rats and mice display much higher levels and broader ranges of innate and normal adaptive offensive aggression [10•]. More interestingly, escalated aggressive and violent characteristics can be engendered in approximately 8–12% of these constitutionally medium to high-aggressive individuals upon experiencing repeated victorious episodes of social conflict (Figure 1; [6,11,12]). Enhanced levels of offensive aggression and an increased probability of winning an aggressive encounter following previous victories (the so-called 'trained fighter' or 'winner' effect) have been demonstrated frequently in a wide variety of animal species [13].

Numerous studies in a wide variety of animal species have convincingly demonstrated that in addition to securing access to resources, the most intriguing consequence of winning an aggressive conflict is the self-reinforcing or rewarding effects. Actually, individuals seek out the opportunity to fight and engaging in aggressive behavior, even in the absence of threat-provoking cues. The most persuasive evidence that acts of aggression are rewarding is that animals will show operant learning for future aggression (*i.e.*, animals are willing to work, such as by pressing a bar for aggression [14]), and will exhibit conditioned place preference for a location associated with a previously successful aggressive encounter [15,16].

This feral animal model affords the opportunity to identify the dynamic molecular changes in the neural 'aggression' control circuits that are hypothesized to underlie the shift of normal adaptive aggression into inappropriate violent-like forms [6]. High-aggressive residents in comparison to low- or non-aggressive residents, show an increased number of activated (Fos-expression as a surrogate molecular marker for neural activity) neurons in medial and extended amygdala, ventrolateral portion of the Ventromedial Hypothalamus, Nucleus accumbens shell, orbital Prefrontal cortex, lateral/ventrolateral Peri-Aquaductal Gray and Dorsal Raphe Nucleus, whereas in the ventromedial Prefrontal Cortex, Lateral Septum and dorsolateral PAG a reversed pattern was seen [17,18]. This supports the view that a quantitatively different number of activated neurons within several nodes of the 'aggressive' brain Social Behavior Network (SBN, see below) underlie the different levels of expressed offensive aggressiveness. However, the extent to which similar or different sets of neurons within these brain regions are involved in the divergent levels and/or abnormal forms of aggression remains a challenging issue for future studies.

The functional activity of this neural network, and thereby the tendency to aggress more or less, is also determined by a wide variety of neurotransmitters such as the monoamines serotonin (5-hydroxytryptamine; 5-HT) and dopamine (DA), the 'social' neuropeptides oxytocin (OXT) and vasopressin (AVP), the 'stress' neuropeptide CRF, the 'stress' HPA- and 'sex' HPG-axis's steroid hormones (corticosterone, testosterone, estrogen) and their cognate receptors and intraneuronal signaling molecules. Indeed, high- and low-aggressive WTG rats or SAL/LAL mice show profound differences in the oxytocinergic innervation and modulation of the central nucleus of the amygdala [19], the vasopressinergic neurons in the bed nucleus of the stria terminalis and its innervation of the lateral septum [20] the striatal dopaminergic mechanisms, and particularly the auto-inhibitory control mechanisms of serotonin neurotransmission [6,12]. Notably, animals that escalate their aggressiveness demonstrate 5-HT_{1A} autoreceptor supersensitivity and diminished 5-HT reuptake functionality that may be the causative link in the cascade of neurochemical events leading to 5-HT deficiency characterizing these violent-like animals. Similar to excessively aggressive humans and other primate species, only violent-like feral rat and mouse subjects exhibit dysfunctional brain serotonergic neurotransmission (Figure 2; [6]). Capturing this