PERSPECTIVE

Recent advances in the study of aggression

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INTRODUCTION

Aggression is an evolutionarily conserved behavior that controls social hierarchies and protects valuable resources like mates, food, and territory. In most cases, aggression is a normal and necessary component of social behavior. In humans, however, some forms of aggression are considered pathological behaviors that threaten lives, increase the likelihood of future psychiatric disease in victims and witnesses, and incur tremendous economic burdens on society [1]. Furthermore, while abnormal aggressive behavior is a symptom shared across a wide range of psychiatric and neurological diseases, there are few, if any, approved treatments aimed specifically at curbing it [2]. Despite the massive costs of violence on society, the pervasiveness of aggression among psychiatric patients, and our current lack of treatments, aggression historically has been understudied compared with other emotional behaviors in psychiatric patients [3]. While a recent surge in preclinical studies interrogating the neural circuitry underpinning aggression has provided important new findings regarding the brain regions, cell types, and neural ensembles governing specific components of this complex behavior, significant gaps in our understanding remain. In order to successfully develop novel treatments aimed at reducing aggression in a variety of patient populations, it is crucial that we address these gaps systematically, and with the consideration that aggressive behavior is influenced by an interconnected circuitry that integrates processes related to motivation, arousal, impulse control, memory, metabolism, sensory perception, and hormonal signaling, among others.

RECENT ADVANCES IN BEHAVIORAL MODELS OF AGGRESSION

In order to investigate the neural circuit mechanisms underlying pathological aggressive behavior in humans, it is critical that researchers utilize animal models that fully capture the essential features of excessive human violence (see Table 1). Clinically, aggressive behavior is commonly classified as either proactive or reactive, and each of these classifications is generally associated with specific behavioral characteristics relevant to psychiatric disorders [4]. However, until recently, animal models of aggression have largely not distinguished between domains of behavior relevant to specific clinical subtypes of aggression. This may be an important reason for why our understanding of the neural circuitry of aggressive behavior remains tenuous.

Proactive aggression is commonly defined as aggression that is purposeful, goal-driven, and characterized by low emotional reactivity (hypoarousal). Under certain conditions, proactive aggression bears resemblance to drug addiction: aggression is

sought compulsively despite adverse consequences (jail) and relapse to aggression following abstinence is common (recidivism) [5]. Consistent with this notion, researchers have recently developed animal models of aggression that are inspired by classical models of drug reward like self-administration and conditioned place preference (CPP) [6–9]. These models have been used to identify a handful of classical reward circuits that may be important for pathological aggression, and we argue for their widespread use in future investigations.

Reactive aggression is commonly defined as aggression that is impulsive, hostile, and characterized by high emotional reactivity (hyperarousal). Current animal models that are potentially relevant to reactive aggression include instigation/frustration models, alcohol exposure models, and anabolic steroid exposure models, as these models result in hyperarousal-associated aggression. However, it is important to note that in many humans and animal models, aggression cannot simply be defined as either proactive or reactive. Thus, it is important that animal models of aggression strive to recapitulate specific behavioral domains of proactive versus reactive aggression most relevant to those found in psychiatric patient populations.

STEPPING OUTSIDE OF THE VMH

A large portion of what we currently know about the circuitry governing aggression relates to the ventromedial hypothalamus (VMH), which was first identified as a site for driving the initiation of intermale attacks in the 1960s [10] (for review, see [11]). This focus has been driven by the idea that gaining a more detailed understanding of the control points for the expression of rodent species-typical aggressive behavior will promote the development of effective treatment strategies for humans displaying abnormal aggression [12]. Despite the appeal of this approach, there is scarce evidence that the VMH is involved in abnormal human aggression [4]. Rather, clinical neuroimaging studies have identified nuclei that are likely upstream of attack initiation nodes like the VMH as dysregulated in patients displaying aggression [13]. We argue that the wide range of aggressive behavior observed in human psychiatric patients is likely the result of aberrant activity within multiple neural circuits across the brain, each of which carry different streams of information that converge on attack initiation nuclei to control aggression. The development of effective treatments for aggression will require a deeper understanding of the functional connectivity and behavioral roles of each of these circuits in animal models that reflect the heterogeneity of aggressive behavior observed in human patients (see Table 1).

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Table 1. Animal models of abnormal aggression

Animal model	Abnormal characteristic(s) of attack	Corresponding human etiological feature	Relevant human disorder(s)	References
Glucocorticoid deficiency	Increased attack of vulnerable body parts, decreased arousal, and social signaling of aggression	Hypoarousal-associated antisocial aggression	Personality disorders	Haller et al. [34]
Acute alcohol exposure	Increased attack duration	Alcohol-induced aggression	Substance abuse/addiction	Miczek et al. [35]
Acute psychostimulant exposure	Increased attack duration, attacks directed at females	Psychostimulant-induced aggression	Substance abuse/addiction	Gobrogge et al. [36]; Ricci et al. [37]
Post-weaning social isolation	Increased attack duration, attack of vulnerable body parts, attacks directed at submissive opponents; decreased social signaling of aggression	Aggression induced by early childhood neglect	Mood and anxiety disorders	Toth et al. [38]
Anabolic steroid exposure	Increased attack duration	Anabolic steroid-induced aggression and irritability	Substance abuse	Ambar and Chiavegatto [39]
Frustration/instigation	Increased attack duration and arousal	Hyperarousal-associated aggression	PTSD, intermittent explosive disorder (IED)	de Almeida and Miczek [40]
Aggression self-administration	Increased motivation to attack submissive intruders	Goal-directed, instrumental aggression	Personality disorders, substance abuse/addiction	Falkner et al. [6]; Golden et al. [7]
Aggression conditioned place preference (CPP)	Increased preference for contexts associated with submissive intruders	Heightened aggression seeking	Personality disorders, substance abuse/addiction	Golden et al. [8, 9]

INFLUENCES OF MOTIVATION ON AGGRESSION

A growing number of studies in humans and animals illustrate that the propensity to carry out violent acts is influenced by the degree to which an individual finds aggression rewarding [14]. This suggests that neural circuits controlling the positive valence of aggressive social interactions are dysregulated in some patients displaying abnormal aggression, though it is unclear precisely how primary reward centers interact with aggression initiation circuitry. In support of this, neuroimaging studies in human psychiatric patients, particularly those with personality disorders, describe structural and functional abnormalities in key reward-related regions like the striatum that are correlated with aggression [15, 16]. Consistent with human studies, recent investigations utilizing animal models of aggression CPP have identified functional roles for both the nucleus accumbens (NAc) [17] and the lateral habenula (LHb) [9] in the reinforcing effects of aggression. Interestingly, the VMH itself has also been reported to control aggression-seeking behavior in an operant model, indicating that this nucleus is not simply functioning as an on/off switch for attack, but may integrate information from primary reward centers to reinforce aggressive behavior [6]. A very recent study also found that the ventral premammillary nucleus (PMv) plays an important role in aggression and the establishment of social hierarchy via divergent projections to the supramammillary nucleus (SuM) and the VMH [18]. Although PMv inputs to the SuM promote aggression CPP without impacting aggression, PMv inputs to the VMH promote aggression without impacting aggression CPP. These results suggest that circuits controlling these two aspects of aggressive behavior (valence versus initiation) may be dissociable. Much work is required to determine how non-hypothalamic regions like the LHb and the NAc interface with the VMH or other aggression initiation circuits to promote aggression and its rewarding effects. Multisynaptic tracing and functional mapping studies will be important for determining this. In addition, we know that levels of aggression increase with repeated experience, a phenomenon akin to drug-induced sensitization, which is prominently regulated by reward circuits including the NAc and LHb. Thus, a key future question is how aggression experience shapes reward-related neural and behavioral responses to guide future aggressive interactions. Does aggression intensity mirror changes in the reward valence and is this associated with reward circuit plasticity? Understanding these important questions may be highly relevant for the treatment of extremely aggressive individuals exhibiting high rates of recidivism.

INFLUENCES OF EMOTIONAL REACTIVITY AND IMPULSE CONTROL ON AGGRESSION

Although some psychiatric patients exhibiting abnormal aggression do so because they find violence rewarding (termed proactive aggression, see previous section), others may do so because of inappropriate emotional reactivity to perceived social threats and poor impulse control (termed reactive aggression) [13]. Perhaps unsurprisingly, a large body of evidence suggests that the circuits controlling these two types of aggressive behavior differ significantly [4]. Clinical neuroimaging studies broadly suggest that reactive aggression involves simultaneous hypofunction of the medial prefrontal cortex (mPFC) and hyperfunction of the amygdala [13]. Activation of the amygdala and extended amygdala promotes aggression in a variety of animal models [19]. However, preclinical studies investigating the role of the mPFC in aggression appear conflicting. For example, there is evidence that optogenetic stimulation of the mPFC both reduces [20] and increases [21–23] aggression and dominance. These discrepant findings may be explained by differences in the animal models of aggression used. It is possible that mPFC hypofunction underlies reactive forms of aggression, whereas PFC hyperfunction underlies

proactive forms of it. In addition, it may be that specific outputs from the mPFC play opposing roles in aggression such that broad manipulation of this nucleus provides inconsistent results. This idea is somewhat supported by a recent study that found differential roles for mPFC outputs to the mediobasal hypothalamus and lateral hypothalamus, which drive species-typical versus species atypical (escalated) aggression, respectively [24]. Future work should aim to functionally dissect the specific roles of mPFC cell types and their outputs in models of proactive versus reactive aggression. Furthermore, the downstream circuit mechanisms by which the mPFC and amygdala influence the initiation of aggression should be fully explored.

INFLUENCES OF SOCIAL CONTEXT ON AGGRESSION

Recent work suggests that circuits conveying information about social context influence the activity of attack nuclei. For example, the capacity for optogenetic stimulation of VMH neurons to initiate aggression is affected by whether residents and intruders are single or group housed prior to testing [25]. Although stimulation of VMH neurons is sufficient to drive aggression independently of pheromone sensing capabilities, gonadal hormone status, and physical cues indicating the presence of a conspecific in single-housed males, this manipulation is insufficient to initiate attack in group-housed males [25, 26]. This suggests that VMH neurons may in fact be regulated by circuits conveying social context, such as those relevant to olfaction and ultrasonic vocalization. As VMH neurons have the capacity to distinguish male versus female conspecifics [27], it is possible that the VMH also encodes other social information about male conspecifics within a group, including their status in the social hierarchy, to control whether aggression is initiated. Mechanistic insights into this phenomenon may enable us to reduce violence in patients through the therapeutic normalization of circuits signaling whether aggression is appropriate in given social contexts.

OTHER FACTORS INFLUENCING AGGRESSION

In many psychiatric patients, violent behaviors intensify during certain times of day, indicating that circadian circuits controlling arousal may be important modulators of VMH neurons driving aggression [28]. Though this effect has been well documented in clinical populations, only one recent study has investigated the relevant circuit mechanisms in an animal model of aggression [29]. Researchers found that there is indeed a daily rhythm of aggressive behavior in mice that resembles clinical patterns of aggression in psychiatric patients [29]. This rhythm appears to be controlled by a multisynaptic circuit from the suprachiasmatic nucleus to the VMH via the subventricular zone (SVZ). Inhibitory inputs to VMH neurons from the SVZ were found to be more active during the day than at night, thereby resulting in increased aggressive behavior in the early night. The findings of this study have potentially important implications for future studies on aggression, which will require the consideration of behavioral testing time in the design of experiments and interpretation of results. These results also suggest that psychiatric patients who display daily oscillations in aggressive behavior, such as those with Alzheimer's disease or psychosis, may respond well to treatments targeting this circuit. It is very likely that other circuits conveying information about an individual's internal state (hunger, thirst, etc.) are also playing roles in aggressive behavior, though these have yet to be explored.

AGGRESSION IN FEMALES

A central question that remains is whether the same circuits controlling aggression in males are involved in female aggression. Comparisons of the mechanisms of male and female aggression in

animal models have classically proven difficult because of fundamental differences in the contexts in which males and females attack. However, a handful of recent studies have begun to investigate this. One recent study found that optogenetic activation of aromatase-positive neurons in the amygdala promotes both intermale aggression and maternal aggression [30]. Interestingly, optogenetic stimulation of VMH neurons promotes aggression in intact, but not ovariectomized females [25, 31, 32], suggesting that unlike in males, female gonadal hormone signaling is downstream of VMH. Moreover, although VMH neural ensembles encoding sexual versus aggressive behavior appear to largely overlap in males, these populations display little overlap in females [31]. These differences in VMH circuitry, as well as potential differences in the contributions of various inputs to VMH neurons of males and females, should be explored. It also remains unknown whether recent findings describing the capacity for male rodents to be highly reinforced by aggression extends to females. Considering the propensity for women, particularly those with neuropsychiatric disorders, to carry out premeditated violent acts [33], it is crucial that the field extends its efforts to interrogate underlying circuit mechanisms of reward, if any, in female animal models of aggression.

CONCLUSIONS

In order to develop more effective treatments for neuropsychiatric illnesses marked by heightened aggression, we must consider the fact that aggression symptoms in clinical populations take various forms, which likely involve different mechanisms and underlying circuitry. For example, while treatments for patients with personality disorders may require reducing the valence of aggression to prevent future violent acts, treatments for aggressive patients with Alzheimer's disease may require a normalization of circadian dysfunction. Patients who display reactive aggression, such as those with Intermittent Explosive disorder, may require treatments that improve function in circuits controlling behavioral inhibition and top-down impulse control. Moreover, there are clear sex differences in aggression that we need to better understand before we can adequately address aggression circuitry in men versus women. Ultimately, our ability to develop personalized treatments for the broad array of aggressive disorders will require the systematic utilization of a variety of animal models, informed by studies of human illness, which recapitulate specific etiological factors driving aggressive behavior.

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ADDITIONAL INFORMATION

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