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Studying dominance and aggression requires ethologically relevant paradigms

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Abstract

Although aggression is associated with several psychiatric disorders, there is no effective treatment nor a rigorous definition for "pathological aggression". Mice make a valuable model for studying aggression. They have a dynamic social structure that depends on the habitat and includes reciprocal interactions between the mice's aggression levels, social dominance hierarchy (SDH), and resource allocation. Nevertheless, the classical behavioral tests for territorial aggression and SDH in mice are reductive and have limited ethological and translational relevance. Recent work has explored the use of semi-natural environments to simultaneously study dominance-related behaviors, resource allocation, and aggressive behavior. Semi-natural setups allow experimental control of the environment combined with manipulations of neural activity. We argue that these setups can help bridge the translational gap in aggression research toward discovering neuronal mechanisms underlying maladaptive aggression.

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Introduction

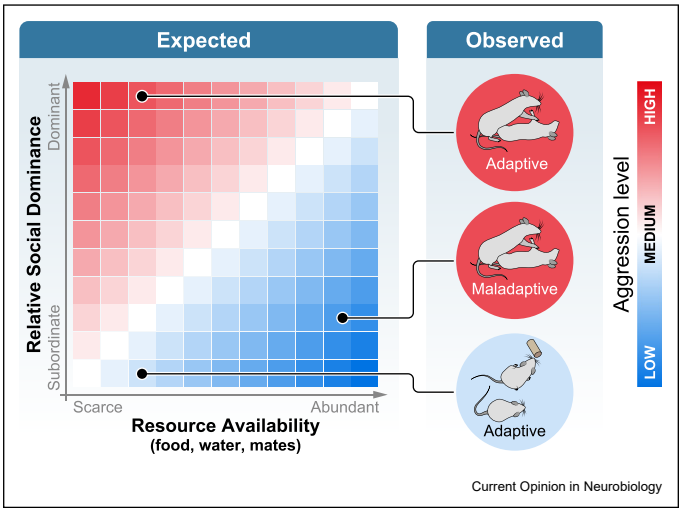
Aggression is a significant cause of human suffering worldwide. It is abundant in various contexts and diverse forms, from bullying in schools and toxic behavior on social media to school shootings, hate crimes, organized crime, and international warfare [1]. Although elevated or pathological aggression is not considered a defining symptom of any psychiatric disorder, it is associated, to some extent, with several (e.g., Antisocial Personality Disorder and Post Traumatic Stress Disorder) [2].

Aggression is an efficient strategy to defend and gain resources, but it is also risky and energetically costly and, therefore, must be tightly regulated. Groups of individuals in many species form social hierarchical structures that, once established, dictate agreed differential access to resources and typically reduce excessive aggression [3]. Once established, social dominance hierarchy (SDH) can be maintained by indirect aggression, such as threats and submissive gestures, or by direct aggression. Hence, social dominance hierarchy (SDH) can reduce aggression but does not necessarily exclude it. The house mouse (*Mus musculus*), a primary animal model in behavioral neuroscience, is characterized by a flexible hierarchal structure that depends on resource availability and can exhibit both SDH and high levels of aggression [4]. In mice, dominant individuals typically direct their aggression towards subordinates, but subordinates can also display aggression in times of hierarchical instability or as defensive aggression [5]. Thus, research on aggression in animal models should consider SDH, availability of resources, and the potential risks involved in a conflict [3,6] (Figure 1).

One of the primary goals of studying the underlying neural mechanisms of excessive aggression and SDH in animal models is to translate findings to humans and ultimately develop new therapeutic agents to treat it. However, two major translational obstacles hinder attaining this central goal. The first involves conceptual and terminological differences between aggression in animals and humans, and the second involves the oversimplified behavioral paradigms used to measure aggression in animal models.

In humans, aggression within societies is considered abnormal, and like other abnormal behaviors, aggression and its subtypes are defined by symptoms and not by biological markers or characteristics of brain circuits. Human aggression is dichotomously divided into proactive and reactive-the first is a calculated effort to obtain desired objectives, and the second is a

Figure 1



Relative social dominance and resource availability affect aggression levels. Left: expected level of aggression based on SDH and resource availability. The highest aggression level is expected from a dominant mouse when resources are scarce, whereas the lowest level is expected from a subordinate mouse living in a habitat with abundant resources. Right: observed level of aggression. If the aggression level is higher than expected (the color in the circle indicates higher aggression than in the relevant location in the graph), aggression can be considered maladaptive.

spontaneous, impulsive act aiming to harm another person [7]. The term' violence' is applied to aggression when it involves a conscious attempt to cause physical harm, while 'pathological aggression' is defined as an extreme and unreasonable act, relying on multiple criteria such as personality and context [8]. Contrary to humans, the terminology for aggression used by ethologists studying non-human animals is far less elaborate yet more objective. The term 'violence' is rarely used to describe even lethal aggressive acts, which are considered adaptive survival-oriented measures. Similarly, subjective definitions based on the aggressor's intent and reason, such as pathologic aggression, are avoided [9].

Despite these terminological discrepancies, aggression is rooted within our mammalian evolutionary heritage. Humans are social and territorial mammals that, until a few thousand years ago, still displayed a high level of conspecific killing similar to other social and territorial species [9]. Hence, certain aspects of aggression and context-dependent inhibition of aggression, its underlying neural mechanisms, and its disruption or absence in certain physiological conditions and pathologies are shared across species. Mice offer an unprecedented opportunity to reveal the neuronal mechanisms that regulate aggression in the laboratory. Accordingly, careful experimental design, considering how the social and environmental context, potential risks, and adaptive value help regulate aggression, can yield insights into the conserved components between the two species and make the scientific findings more translational. Alas, the classical approach for measuring aggression and SDH in mice is reductive with limited translational relevance. The tests are short, performed in a deprived environment, cannot be conducted simultaneously, and do not account for the gain or loss of resources [10,11]. Recent advances in pose estimation, tracking, and behavior recognition technologies enable automatic monitoring of the animal's individual and group complex behaviors over long time periods [12–14]. This enables the simultaneous study of aggression, SDH, and resource allocation in semi-natural environments, and a deeper understanding of context-dependent aggression regulation. Hence, as we argue below, the emerging research field of 'computational neuroethology' holds promising translational value for studying human aggression.

Mice display a versatile social structure that is affected by resource availability

Mice live primarily near human dwellings in houses, barns, and food stores. With their high fertility rate and adaptability to a wide range of habitats and temperatures, they are the second most efficient mammalian colonizers after humans [4]. The plasticity in mice's social structure is remarkable-they reveal different SDH structures and can be highly aggressive toward conspecifics in some cases or tolerant in others [15–17]. When resources are limited, males fight furiously to dominate the territory, and territorial males are more reproductive and survive more than invaders or wanderers [15]. However, when resources are abundant, and population size increases, a clan that consists of several reproductive individuals of both sexes can be established [18].

When 30 male mice were introduced to a large semi-natural setup with *ad-libitum* food, they spontaneously split into two sub-communities. Each sub-group engaged in aggressive encounters at different setup locations and formed stable, long-lasting hierarchies [17]. However, in mixed groups, space quickly becomes a limited resource, even though food can still be abundant. In this case, group members gain weight and become reproductively inactive once the group size reaches a certain density. Under such conditions, neighboring territories do not accept individuals who leave their territory, these individuals become wanderers and probably do not survive [16]. The broad ecological niche of mice makes them an excellent animal model for studying the environment's effects on aggression, establishment and maintenance of SDH, and resource allocation [18].

Aggression, SDH, and resource allocation are coregulated to maintain group homeostasis

'Aggressiveness' is a subjective state that humans can self-report, but it is more challenging to measure in other animals. Nevertheless, the behavioral output of this internal state (e.g., attacks, bites, threat postures) is intuitive to detect and measure in many animals. Resource deprivation, such as hunger, is also an internal state that reciprocally interacts with aggression, and the behavioral output of hunger (e.g., foraging, risk-taking) can also be measured in animals. Resource deprivation and aggression are affected by and affect SDH [3]. Hence, all three states can induce reciprocal interactions and competing motivated drives to maintain homeostasis [19] (Figure 1).

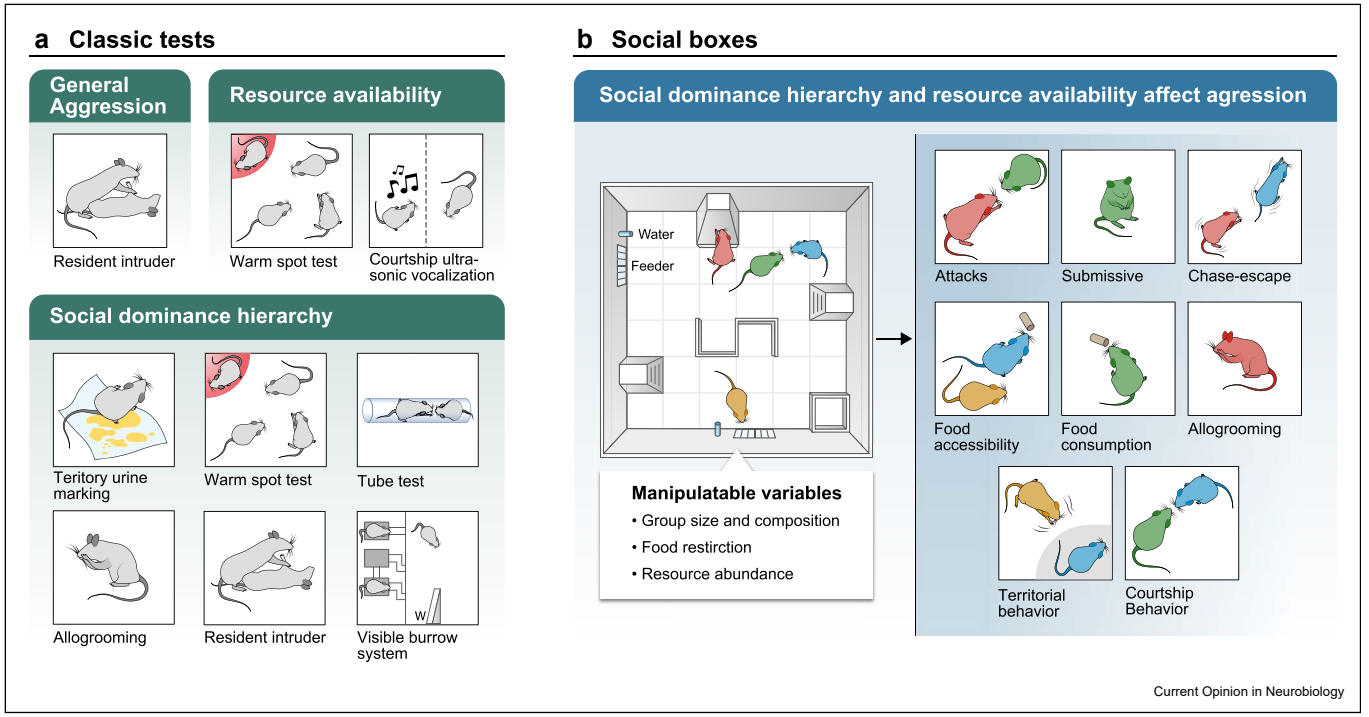
Using advanced mouse genetics tools and classical behavioral tests, scientists discovered various neural circuits and cell-type specific components mediating aggression, SDH, and resource seeking. To mention a few-four subcortical regions were found to compose the Core Aggression Circuit (CAC), which is a part of the social brain network (the Medial Amygdala (MeA), the Bed Nucleus of the Stria Terminalis (BNST), the ventrolateral part of the Ventromedial Hypothalamus (VMHvl), and the pre-mammillary nucleus [20]. Activation or silencing of any CAC region evokes or suppresses aggression, respectively, which points to the central role of these regions. In mice, the CAC receives aggression-provoking inputs mainly from olfactory signals and is top-down regulated by the Lateral Septum (LS) [21,22] and the medial Prefrontal Cortex (mPFC). The mPFC and its input and outputs are also involved in SDH - an increase or decrease in mouse dorsomedial PFC activity causes a gradual upward or downward shift in social status, respectively [23–26]. Another CAC region, the MeA, is also involved in territoriality and resource-seeking. The MeA receives projections from the Arcuate neuropeptide Y neurons (Arc-NPY) that modulate territorial behavior under resource deprivation [27], and the Arc-NPY neurons contribute to higher risk-taking during foraging under hunger [28]. Although aggression and SDH in humans are way more complex than in mice, there is a certain degree of evolutionary conservation at the neuronal molecular and physiological levels [20,29,30]. Further understanding of the extent of conservation depends on adequate behavioral measures of aggression in mice.

Several tests were designed to measure aggression and SDH in rodents (Figure 2(**a**)). Aggression is commonly measured using the 'resident-intruder' (RI) test, quantifying the readiness of a male mouse to defend its home-cage (the 'territory') from an unfamiliar juvenile intruder during a 10-min encounter [31]. SDH in mice is commonly measured using the Tube Test (TT), a dyadic confrontation where each individual is positioned on an opposite side of a narrow tube, and the mouse that pushes the other out is declared the 'winner' [32]. Competition over food or water in rodents is typically measured by inserting a dyadic unfamiliar conspecific into an arena for a few minutes with access to a single feeder or bottle of water [33].

Classical behavioral tests led to important insights into neuronal networks that regulate aggression and SDH. Nevertheless, the strengths of these tests are also their main weaknesses-they are reductive, dyadic, strictly controlled, short, and only measure specific behavioral readouts out of more general and complex phenomena. Hence, such tests that are designed to maximize standardization might have limited ethological relevance [6,34]. For instance, in the RI test, the intruder is a juvenile to prevent injuries. However, it results in a baseline level of attacks or aggressive chases toward the juvenile that is often too low, even after the resident is isolated for a week (a manipulation with profound and intricate social consequences) [31]. In the TT, only ~30% of groups of C57 male mice tend to form stable SDH [35]. Hence, classical behavioral tests raise concerns about potential selection bias and misinterpretation of limited behavioral readouts. One way to overcome these limitations is to combine multiple tests to address a specific behavior. For instance, complement the TT with other measures of SDH that rely on different sensorimotor modalities. Nevertheless, this practice is time-consuming and complex and is thus scarce.

A semi-natural setup offers the ability to tease apart different behavioral domains such as aggression, SDH, metabolism, or fear and examine the interactions between them in different environments and under different levels of resource availability [36,37] (Figure 2(**b**)). The next section will review studies that constitute the first steps toward achieving this goal.

Figure 2



Semi-natural setups facilitate studying how SDH and resource availability affect aggression levels. (**a**) Classical behavioral paradigms separately assess aggression, resource availability, or SDH during dyadic interactions. (**b**) Semi-natural setups enable simultaneous measuring of aggressive behaviors, group hierarchy, resource allocation, and their intricate relationship. Resources, such as food, water, and shelter, can be manipulated automatically to assess the effect of resource availability on aggression.

Measures of aggression, hierarchy, and resource allocation in a semi-natural setup

In the past decade, several research groups have developed semi-natural setups for long-term automatic monitoring and detection of multiple complex behaviors in groups of freely interacting mice (Figure 3). These setups include enriched environments with feeders, water ports, shelters, and other resources. Different setups utilize different technologies, such as Radio Frequency Identification (RFID), video recording, or depth-sensing cameras [34,38,39]. Our group established a paradigm named the 'Social Box' (SB), in which color-marked mice are video recorded under a naturalistic light−dark cycle for days [40], and DeepLabCut [12] is used for pose estimation of each mouse in every video frame. Utilizing the pose estimation data combined with a supervised machine learning approach [41], we train classifiers to automatically identify behavioral events based on extensive and validated manually labeled ones. The relative simplicity of the social box setup enables behavioral characterization of 12 groups or more simultaneously [42].

Semi-natural setups provide an unprecedented tool for studying how aggression shapes (and is then shaped by) differential access to resources and SDH under various social and environmental conditions. Groups of male mice that are supplied with *ad-libitum* food maintain stable SDH as measured by aggressive chases [42,43]. In the SB, dominant individuals spent more time outside the nest and near the feeders and water ports than subordinates, reflecting an expected association between two key aspects of SDH - aggression and resource allocation [44]. Dominants also frequently chase subordinates into the nest, presumably referring to the open area as a resource [42].

We further utilized the SB to decipher complex tradeoffs between aggression, social avoidance, SDH, and resource allocation in two mouse models of increased aggression: (i) a model of early-life exposure to an enriched environment (EE) and (ii) a model of oxytocin receptor deficiency (OxtR−/−). While EE is thought to increase aggression as an adaptive response to external stimuli, hyper-aggression in OxtR−/− is accompanied by marked abnormalities in social behavior. We found that the probability of each social encounter becoming aggressive in the EE groups was much higher than in the control groups that were raised in standard cages. Crucially, EE groups were more socially avoidant than control, had more stable SDH, and dominance was correlated with access to resources, as expected from typical SDH. In the OxtR−/− experiment, mice engaged in excessive aggressive chasing compared to OxtR+/+ groups and exhibited SDH that was not correlated with access to resources [44]. These results suggest that aggression in mice exposed to EE in adolescence is adaptive in terms of gaining resources and avoiding unnecessary aggression, while aggression in OxtR−/− groups is maladaptive.

Advanced genetic techniques, such as chemogenetics, optogenetics, and brain recording, greatly enhance the understanding of neural circuits underlying behavior, and integrating them into the social box is of the highest priority. We found that chemogenetic inhibition of MeA Urocortin3 neurons in the SB increased sociability but not aggression-all group members (male-only) spent more time outside the nest without an increase in aggression than control groups. Interestingly, direct contact was also increased, but in dependence on SDH - increased approaches of 'middle-rank' towards other 'middle-rank' group members, but not towards dominants or subordinates [45].

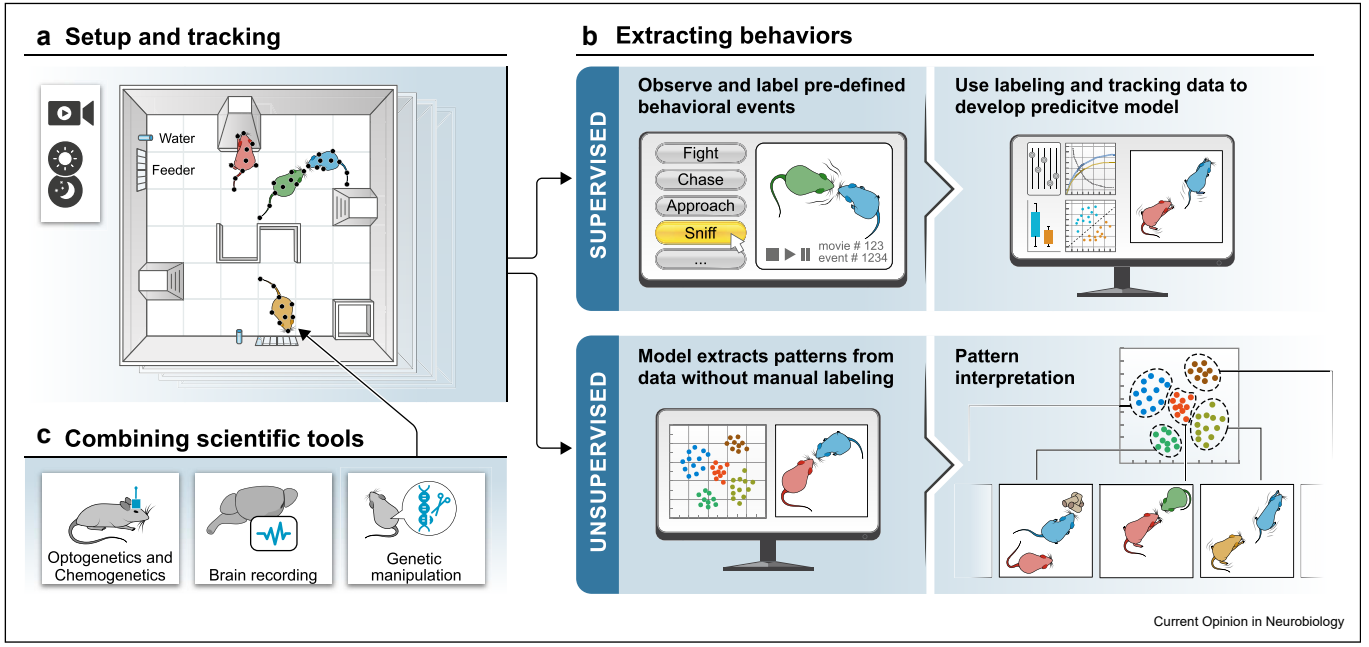
We also developed a wireless optogenetic device and induced prolonged activation of oxytocin (OT) neurons in the paraventricular nucleus of the hypothalamus in the SB to study the effect on sociability and aggression. Interestingly, this manipulation caused an increase in sociability (e.g., more contacts and approaches) between the mice on the first day of activation. However, on the second day, the optogenetic activations of the PVN-OT neurons induced agonistic behaviors (e.g., anogenital sniffing) and direct aggression (e.g., aggressive chases) [46]. These findings support the notion that the OT regulates the salience of social cues and is not solely a pro-social agent.

Utilizing a miniature wireless electroencephalographic (EEG) brain recording device in the SB, we found increased dark-phase slow-wave activity combined with a pronounced increase in light-phase REM sleep in subordinate mice, which may reflect a response to aggressive social interactions during the preceding dark phase [47]. These suggest that SDH might have sustained physiological and mental effects.

Future directions

Computational ethology and ethologically relevant setups promise to improve our understanding of mechanisms underlying complex behavior in rodents, including aggression. Nevertheless, experimental design and interpretation should consider the extent of evolutionary conservation between humans and rodents for such an approach to be translationally-relevant. For instance, reactive aggression in humans is exceptionally low compared to other mammals, while proactive aggression, which also includes wars, is exceptionally high. It is hypothesized that language, subordinate coalitions, and punishment reduce reactive aggression in humans, and elaborate symbolic communication enhances proactive aggression. Such typical human features of aggression cannot be modeled in mice [48].

Figure 3



The SB paradigm. (**a**) Setup and tracking-color-marked mice are placed in a 60 × 60 cm arena containing feeders, water, nests, and other enrichments and, using a sensitive light camera, are recorded under a dark–light cycle for several days. Up to 16 arenas can be used simultaneously in our laboratory settings. Pose estimation of each mouse is obtained for each frame. (**b**) Extracting behaviors-using unsupervised machine learning and manually labeled behavioral events, such as chases or sniffing, we extract classification models that can automatically identify behavioral events in new videos. (**c**) Combining scientific tools-various scientific tools can be combined with the SB, including optogenetics, chemogenetics, genetic manipulation, and recording of neural activity.

However, reactive and proactive aggression in humans presumably developed from more primitive and conserved features. For instance, mice display plasticity in hierarchal structure and in the level of intragroup aggression that depends on resource availability. Hence, brain circuits that mediate inhibition and disinhibition of aggression under different ecological conditions in mice might be conserved to some extent in human reactive aggression. Similarly, some evidence points to the similarity in mammalian mechanisms that regulate proactive aggression and hunting: both require planning and attacking [48]. Hence, brain mechanisms that regulate hunting in mice might shed light on proactive human aggression. A single or multi-arena array of semi-natural setups offers the possibility to model inhibition and disinhibition of aggression under various group structures, resource availability, immigration/emigration challenges, and even predation. To that aim, challenges and stressors must be incorporated into the semi-natural setup. For instance, increased competition over food and mates or a threat (e.g., foot shock) that should be avoided during foraging for food. Such challenges can be induced through automated real-time activation of actuators in the setup. As open-source platforms for advanced behavioral monitoring and assessment become increasingly available [14], we hope that diverse approaches will become more common in the field, ranging from classic behaviorism to ethologically relevant laboratory research.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data were used for the research described in the article.

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