The mouse that roared: neural mechanisms of social hierarchy

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Hierarchical social status greatly influences behavior and health. Human and animal studies have begun to identify the brain regions that are activated during the formation of social hierarchies. They point towards the prefrontal cortex (PFC) as a central regulator, with brain areas upstream of the PFC conveying information about social status, and downstream brain regions executing dominance behavior. This review summarizes our current knowledge on the neural circuits that control social status. We discuss how the neural mechanisms for various types of dominance behavior can be studied in laboratory rodents by selective manipulation of neuronal activity or synaptic plasticity. These studies may help in finding the cause of social stress-related mental and physical health problems.

The concept of social hierarchy

The brain is capable of executing complex social interactions, the most prominent among which is the formation of dominance hierarchies. The concept of a hierarchical structure in social organization was first scientifically described by Norwegian scientist Thorleif Schjelderup-Ebbe in 1921, when he derived a 'pecking order' within a group of domestic fowl and proposed that such a hierarchical structure reduced intense conflicts and injuries, saved energy, and promoted social stability [1]. Since Schjelderup-Ebbe's work it is now generally accepted that the dominance hierarchy is a universal phenomenon among social animals, ranging from insects and fish, to rodents and primates [2]. Pecking order determines which individual has priority access to desirable resources, including food, mates, and resting spots. In humans, the similar concept of socioeconomic status (SES; see Glossary), defined by relative income, education, and occupational position, has been identified as the single strongest predictor of health [3] (Box 1).

To increase our understanding of the neural mechanisms that underlie dominance behavior and, conversely, how social status may influence brain function and health, scientific studies on model organisms are crucial. In this review we first discuss methods typically used to measure dominance in laboratory rodents, with a focus on the dominance tube test. We next summarize our current knowledge on the cortical mechanisms that recognize and regulate social status, highlighting the prefrontal cortex as a central regulator. Finally we propose subcortical brain regions that can potentially execute different types of hierarchical behavior.

Measures of dominance hierarchy in laboratory rodents

Extensive knowledge is accumulating on the brain circuits that execute the behavior of laboratory rodents. These animals provide a pertinent model in which to study the neuronal mechanisms that underlie social behavior. Socially dominant behavior is observed in rodents in the wild (Box 2) and is characterized by: winning in conflict situations, display of agonistic behavior, first access to food, marking of territory, a prominent order in grooming, proactive courtship, and a low participation in labor. For each of these types of natural behavior, a test paradigm was developed to determine social rank among groups of laboratory rodents living in a closed environment.

A useful operational definition of social dominance is consistently winning at points of social conflict, in other words when the motivational priorities of two or more individuals are incompatible [4]. To mimic such a situation,

Glossary

Agonistic behavior: social behavior related to fighting, but broader than aggressive behavior because it includes threats, displays, retreats, placating aggressors, and conciliation.
Crooktail: posture in which a monkey struts with tail held in stiff '?' shape.
Crustacean: arthropod species of animal (such as a crab, shrimp, or lobster) that has several pairs of legs and a body made up of sections that are covered in a hard outer shell.
Fluoxetine: antidepressant drug that blocks the reuptake of serotonin in the brain (also known as Prozac).
Optogenetics: technique used in neuroscience that uses light to control neurons that have been genetically sensitized to light.
Schema: a mental structure of preconceived ideas based on common experiences that helps to understand the familiar world.
Serotonergic: related to the monoamine neurotransmitter serotonin.
Sham rage: display of aggressive behavior without an obvious target.
Socioeconomic status (SES): economic and sociological combined total measure of the work experience of an individual and of the economic and social position of an individual or a family in relation to others, based on income, education, and occupation.
Subordination: the act of forcing someone into a submissive role.
(-)Δ9-*trans*-tetrahydrocannabinol (THC): the principal psychoactive constituent of the cannabis plant.
Transitivity: the mathematical concept of relations stating that if $A > B$, and $B > C$, then $A > C$.

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Box 1. Relationship between social status and health

In developed nations, socioeconomic status shows a steep inverse association with mortality and morbidity rates [82]. It was proposed that chronic psychosocial stress experienced by those in subordinate roles underlies this strong correlation between social status and health [3]. Stress functions to prepare the body for a flight or fight response through activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, leading to the release of the stress hormone cortisol. In response to this rise in cortisol, lymphocytes traffic out of the circulation into effector sites, in anticipation of a potential injury. When periods of heightened psychological stress are long-lasting, and cortisol levels remain chronically high, the immune system becomes suppressed [83]. A strong relationship between social status and stress levels was demonstrated in a study of a baboon society [84]. Social rank and cortisol level were linearly correlated, with levels being high in subordinate baboons and low in dominant ones (with one exception: cortisol levels in the alpha male were also high). In line with this, wound-healing was quicker in socially dominant baboons [85].

Unequally distributed resources are a cause of psychological stress in individuals of low social status. In groups of laboratory rats that have unlimited access to food and water, subordinates and dominants have similar glucocorticoid levels [86]. However, when food resources become limited, subordinate rats exhibit significantly higher glucocorticoid levels than their dominant cage-mates [87]. Low social status can also be stressful as a result of subordination by more dominant individuals. Subordination of a mouse by a dominant intruder for consecutive days leads to anxiety-like behavior, chronic elevation of glucocorticoid levels, and suppression of immune responses [88]. Notably, psychological stress due to social subordination has more severe effects on the immune system than physical restraint stress, causing reduced survival rates upon the immunological challenge of influenza infection [89].

Box 2. Social plasticity in rodents

Rats and mice are highly adaptive in their social behavior [90]. The most prominent example of this social plasticity in the wild is the adaptation to population density. At low densities, groups of rats or mice live within their selected territory, and display territorial behavior towards intruders. The mature male patrols the boundaries of the territory and deposits urine to mark their own territory and likely to countermark deposits of competitors. In case of an encounter with an intruder, the male displays agonistic or aggressive behavior causing the intruder to flee. Such territorial behavior can only persist when invasions of a territory are infrequent. Therefore, at high population densities rats and mice become socially tolerant and adapt to a despotic social system, with one male being socially dominant and the other males subordinate [91,92]. Rodents also demonstrate their social plasticity when placed in a laboratory setting. Groups of rats or mice in captivity develop a strict social hierarchy as a necessity of the restraint of their cage. Agonistic behavior by the dominant male serves to solidify social hierarchies and avoid fighting. Only if the subordinate does not respond with appropriate submissive behavior, violence is used by the dominant [93]. The stability of a hierarchy decreases with an increased number of mice per cage [94]. In addition the introduction of objects into a cage can destabilize the social hierarchy, likely because the objects are seen as a resource that needs to be defended [95,96].

the tube test was developed as a paradigm to score social dominance in laboratory rodents [5]. After mice or rats are trained to walk through a narrow tube, a nonviolent conflict situation is created when two rodents are allowed to enter the tube from opposite ends and meet in the middle. The one that consistently forces the opponent to retreat is scored as the more dominant of the pair. By applying a round-robin match arrangement, the rank order can be determined for any size of social group. This assay shows good stability and transitivity when applied to either unfamiliar mice from different inbred strains [5] or familiar cage-mates from the same strain [6].

The observation that tube test winners are also dominant in other types of social behavior supports the validity of the tube test as a measure of social dominance. One of the strongest correlates of the tube test rank is the ‘Dalila effect’. The Dalila effect is an excessive type of grooming regularly observed among laboratory mice in which the most dominant mouse barbers the hair and plucks the whiskers of its cage-mates. Several studies have shown that the barber is generally the winner over its cage-mates in the tube test [6–8]. When regrouping barber mice from different cages, these mice first fought severely whereupon the losers would then be trimmed by the winners, indicating that whisker trimming is a behavioral trait of dominance [9]. One study, however, found that barbers were not significantly more dominant in the tube test [10]. A potential reason for this contradictory result could be the difference in the tube test procedure: whereas the latter study did not include a training session, and limited test sessions to one day, the studies that did show a strong correlation between tube test rank and barbering [6,9] ensured that the mice were first well trained to pass the tube before conflict situations were presented, and in these studies test sessions were performed on consecutive days to derive a stable rank.

Male mice that are dominant in the tube test are also more inclined to actively woo a female. 70 kHz ultrasonic vocalization is a prominent male characteristic during courtship behavior [11], and has been linked to sexual motivation [12]. Several studies have shown that male mice that were top-ranked in the tube test emitted significantly more vocalizations and had a quicker response when receiving a female stimulus, whereas subordinates exhibited almost no ultrasonic vocalization [6,11,13]. Importantly, in these studies ultrasonic production was tested in male mice with no sexual experience, and in a novel environment. Conversely, when pairs of sexually experienced male mice were exposed to a female stimulus in their home cage, the subordinate mice emitted more 70 kHz vocalizations than their dominant cage-mate when the latter was removed from the home cage [14]. Such differences suggest that social context or sexual experience may modulate courtship behavior.

Urine marking is a common means of social communication in many mammalian species. The chemical cues in urine convey social messages including territorial boundary and social status [15]. When two previously single-housed male mice were paired together, they first went through aggressive encounters. When they were subsequently separated by a wire partition, the dominant mice deposited small drops of urine to mark the entire floor, whereas the subordinates only voided urine in a few pools in the cage corner [16]. The dominant–subordinate relationship expressed by urine marking appears less apparent in group-housed compared with single-housed mice, presumably because aggressiveness was reduced to a low level in group-housed mice with stable ranks [6]. Nevertheless, there was also a trend