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,

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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.

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

Box 3. Relationship between aggression and social dominance

Dominance can be considered as an individual capacity, the capacity to prevail in conflicts [4,97]; or as a relationship quality, the polarity in agonistic interactions [98]. In the 1970s and 1980s fervent debates were held over the question of whether social dominance is a useful concept to describe animal and human behavior, or, in the extreme case, whether it even exists (e.g., [98,99]). Much of the confusion arose because the results of different behavioral paradigms that aimed to measure social dominance or aggressive behavior were not always in agreement. Intuitively, social dominance and aggression may seem intimately linked, and many studies have demonstrated an association between aggressive behaviors and dominance rank (e.g., [100–103]). However, many discrepant observations have also been reported: for example, paradise fish of different social status did not significantly differ in aggression level [104]; the aggressiveness of chickens against a panel of standard opponents did not correlate with their hierarchical rank [105]; and, in Rhesus monkeys, the aggressive dominance score did not relate to competition for females [106]. The ability to form coalitions and alliances is sometimes more important than aggression in determining social (alpha) status in monkeys [107].

Popular laboratory tests of rodent aggression include the resident–intruder model, in which an unfamiliar intruder confronts a larger and more aggressive mouse in its homecage, and the winner–loser paradigm, in which two previously isolated mice share sensory contacts in a partitioned cage and the partition is lifted periodically to allow physical contact [108–110]. In such tests for social dominance or social defeat, the correlation between aggressiveness and social rank in the tube test was not always apparent. Group-housed familiar mice do not exhibit extensive aggressive behaviors towards cage-mates, presumably owing to the suppression of aggression by a stable social hierarchy [104]. When mice were tested in the resident–intruder paradigm against unfamiliar standard opponent mice, aggressive behaviors could be observed. However, rank-1 mice from the tube test did not appear to be more aggressive [111]. Another study showed that administration of (−)Δ9-trans-tetrahydrocannabinol (THC) to rats reduced attacks and threats, but increased winning in the tube test [112]. Such a dissociative effect on tube test and aggression may suggest that the drug influences non-dominance-related factors to affect performance in the tube test (e.g., factor X in Figure 1 in main text) or, alternatively, that there is a distinction between aggression and dominance. Although aggression may initially be necessary to establish a hierarchy, once established a stable hierarchy can suppress further aggression and unwanted fights among the group members [104]. The decision to initiate aggressive behavior is likely the result of a cost–benefit analysis that depends on social context, requires cortical regulation, and is not necessarily restricted to socially dominant individuals [113].

for the mice ranked higher in the tube test to urinate more and closer to the partition [6].

Other paradigms that measure social status among lab rodents test the order of access to resources, the division of labor, or the display of agonistic behavior. In the visible burrow system (VBS), food and water are relatively difficult to retrieve. Because the dominants have priority access, weight change in this paradigm indicates dominance rank [17]. Dominance in the VBS was significantly correlated with rank in the tube test [6]. Social dominance can also be determined in the food competition test – in which cage-mates compete for an appetitive drink or food pellet [18,19]. The labor division test is based on the principle that dominant individuals tend to refrain from labor. In this paradigm, one rat (the 'worker') presses a bar for another rat (the 'parasite') to get water. Interestingly, rats that were selectively bred based on their dominant tube test performance [20] became the 'parasite' in most cases [21]. Agonistic behavior can be frequently observed in a group of mice after transfer to a new and dirty cage, presumably as a way to claim territory in a new environment [6]. More agonistic behavior (mostly chasing, very rarely attacking) has been observed from mice ranked high in the tube test [6]. However, whether the display of aggression and social rank are always correlated is controversial (Box 3).

In summary, a number of paradigms are available to identify social hierarchies among laboratory rodents. In particular the dominance rank derived from the tube test was found to correlate well with the rank derived from several other laboratory hierarchy tests. The tube test results can therefore serve as an intervening variable to explain multiple other types of social dominance behavior in laboratory mice (Figure 1). Importantly, the order in which the tube test and another measure of social dominance behavior (e.g., weight change in the VBS) were performed did not affect the observed correlations [6], suggesting that the tube test itself did not induce an artificial hierarchy. Compared with social defeat-based models, the tube test may be more natural and less interfering as well as introduce less stress. However, to ensure validity, test procedures need to be standardized to minimize variations; for example, whether animals have undergone tube test training and whether the rank has stabilized or not, which could have an impact on the tube test results. One should especially caution that factors other than dominance could also contribute to the result of each individual dominance assay (Figure 1). Thus when comparing genetically or pharmacologically modified mice with control cage-mates for the role of a gene or neural circuit in establishing dominance rank, it is essential to use at least two dominance assays based on different sensory/motor properties to prevent circular reasoning (Figure 1).

Cortical mechanisms underlying the recognition and regulation of social hierarchy

Social hierarchy behavior depends on a collection of cognitive traits that include recognition of social status, learning of social norms, detection of violation of social norms, reading the intentions of others, monitoring reciprocal obligations [22], and perhaps also effort-based decision-making on whether or not to compete against a conspecific. For social recognition, a variety of sensory cues have been reported to convey social status information in various species. In angelfish, it was proposed that rates of fast approach from dominants serve as a signal for subordinates to restrain their growth [23,24]. In rats, reduced sniffing by subordinates serves as an appeasement signal to reduce aggression from dominants [25]. Many social mammals use scent marking, tail raise, mounting or vocalization to express dominance [2]. In primates, facial expressions are common: direct stare or eyebrow raise are often used to signal dominance, whereas 'fear grimace' is used by subordinates to appease or redirect aggression [26,27]. Recent neuroimaging studies in humans have revealed a distinct network of cortical brain regions involved in social status recognition. Social status inference often recruits part of the occipitotemporal and parietal
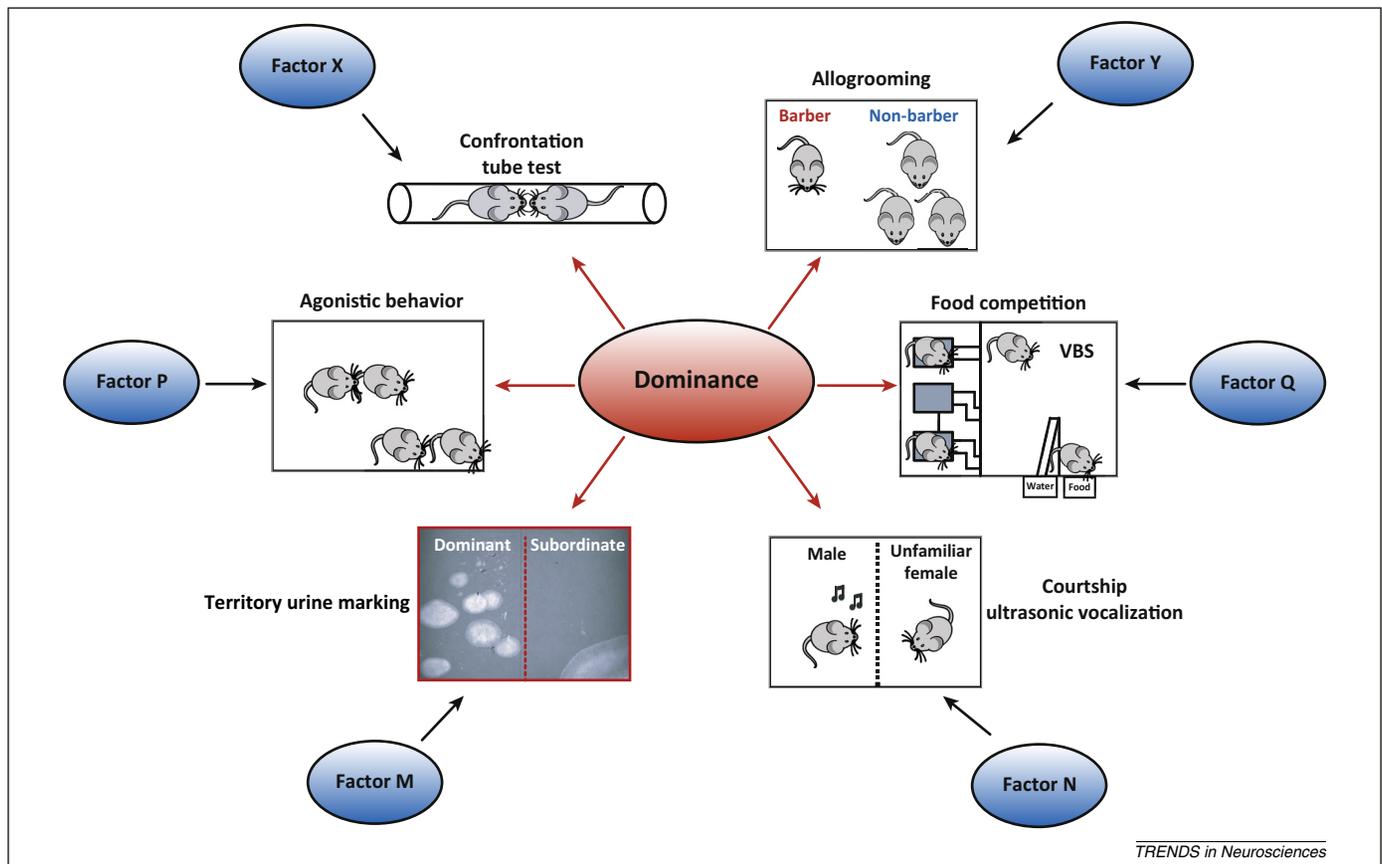
Figure 1. Relationships among different measures of dominance. Dominance is the common factor underlying the six types of rodent behavior depicted (modified from [6]). For each of these behaviors a behavioral paradigm was designed. The performance in each of these paradigms also depends on sensory and motor factors unrelated to dominance (factors M, N, P, Q, X, or Y) – for instance agility in the tube test or vocal abilities in courtship vocalization. We advise using more than one behavioral paradigm to assess social rank, especially between rodents of different genetic backgrounds.

cortex, which are involved in perceptual and attentional process [28–30]. These findings dovetail nicely with research showing that primates, including humans, generally pay greater attention to high-status than to low-status individuals in a social group [31].

Perhaps most information related to social hierarchies is processed in the prefrontal cortex (PFC), the center for executive behavioral control [32]. In participants of a study that are engaged in an interactive simulated social context, viewing the face of a superior versus an inferior player selectively activated the dorsolateral PFC (DLPFC) [28], a region implicated in top-down attentional control [33,34], interpersonal judgments [35], social norm compliance [36], and social moral judgment [37]. In an unstable hierarchy setting, the medial PFC (mPFC) is activated [28]. The mPFC is involved in signaling prediction errors of action values [38], as well as recognizing the intentions and motives, and forming judgments, of other people [39]. Nonverbal cues for high social status in humans, such as body posture, lead to the activation of the ventrolateral PFC (VLPFC). The VLPFC receives information from the temporal lobes, particularly the superior temporal cortex (STC) [40], which responds to faces and body movements, and has been implicated in processing status cues [41]. In addition, monkey studies suggested that the PFC registers elements of social state. PFC neuron activity increased in dominant monkeys and decreased in subordinate ones

during social engagement [42]. Furthermore, lateral PFC neurons of monkeys represent winning and losing in competitive video games [43]. For monkeys that live in large social groups, the volume of grey matter in the rostral PFC (rPFC) correlates with their dominance status, suggesting that having larger rPFC may confer a social advantage [44]. Human studies also supported an association between PFC grey matter volume and social success [45].

Consistent with these correlative studies, selective lesions of some of the above-mentioned PFC areas have impacted dominance-related social–emotional behaviors. Clinical reports have suggested that lesions of the VLPFC, VMPFC, or DLPFC impair processing of social hierarchy information in humans [35,46,47]. Patients with lesions in the DLPFC showed deficits in using social cues to make interpersonal judgments [35]. Monkeys with lesion in anterior cingulate cortex (ACC) showed reduced social interest in other macaques [48]. MPFC lesioned rats were more subordinate in agonistic encounters, attended less daily feeding sessions, and acted more timidly – consistent with a lowered social rank [49]. The rodent mPFC can be divided into the dorsal part, including the ACC and prelimbic cortex, and the ventral part, the infralimbic cortex [50]. Lesions of the ACC in rats affected interest in other rats, caused a reduction in social memory, as well as a defect in effort-based decision-making [51]. Recently, the ACC has also been implicated in the coding of competitive effort

against peer animals: ACC neurons fired significantly more when rats were on the trajectory that led to food competition with a subordinate rat than to a dominant rat [52]. In mice, the prelimbic cortex is activated upon social interaction with an unfamiliar conspecific, and lesions of the prelimbic area changed their behavior during social interactions [53].

These studies indicate that the PFC may be involved in the recognition, representation or regulation of social status. However, with correlation or loss-of-function lesion data alone, results can be difficult to interpret. For example, lesions could damage fibers of passage and cause side effects. To overcome this problem, Avale *et al.* used a mouse model that has altered motivation for social interaction due to a deficiency in the nicotinic acetylcholine receptor (nAChR), and restored their social behavior by selectively rescuing nAChR function in the prelimbic area of the mPFC [53]. This study suggests that cholinergic input to the mPFC is important for attentional control of social interactions. Wang *et al.* investigated the functional consequence on the dominance status of mice by promoting or blocking synaptic plasticity selectively in dorsal mPFC (including prelimbic cortex and ACC) neurons. The viral expression of AMPA-receptor subunit GluA4 or signaling protein Ras in excitatory neurons of the mPFC led to an increase in their average synaptic strength, whereas the expression of the GluA4 C-tail or Rap decreased average mPFC synapse strength [6]. These manipulations potentially change the output activity of the mPFC to downstream brain structures. Strikingly, these manipulations resulted in bidirectional changes in dominance rank in both the tube test and courtship ultrasound: subordinate mice moved up in the tube test rank and produced more ultrasound vocalizations towards females when their synapses in the dorsal mPFC were strengthened; conversely, dominant mice became subordinate when their mPFC synapses were weakened (Figure 2). This study demonstrates a bidirectional causal relationship between

dorsal mPFC activity and dominance status. Because two very different types of hierarchy-related behaviors (tube test rank and courtship ultrasound production) are controlled by mPFC synapses, it is likely that the mPFC plays a central role in the regulation of social status. In addition, this experimental strategy depends upon synapse manipulation, and thus tends to mimic the natural physiological changes occurring during behavioral plasticity [54]. This strategy, in combination with optogenetic approaches to alter neuronal firing, may be used in future studies to probe the functions of different brain regions in mediating dominance behavior.

Subcortical mechanisms underlying the processing of social hierarchy behavior

Prefrontal regulation of social hierarchy can be achieved via control of downstream subcortical nuclei, which may be involved in different aspects of dominance-related behaviors (Figure 3). For example, projections from the mPFC can drive the expression of emotional behavior through activation of the basolateral nucleus of the amygdala (BLA) [55,56], which has heavy reciprocal direct connections with the mPFC [57,58]. The amygdala processes social–emotional stimuli such as facial expression [59] and interpersonal space [60]. People with a larger and more complex social network have an increased amygdala volume [61], as well as stronger connectivity within amygdala–cortical networks [62]. In humans, the amygdala plays an important role in the emergence and representation of knowledge about social hierarchies [63], and is activated together with the mPFC when the social hierarchy becomes unstable [28]. Amygdaloid lesions have produced different outcomes with regard to dominance: some resulted in loss of dominance and competitive behaviors [64,65], whereas others caused an increase in aggression [66]. Recently, refined lesions of the amygdala in monkeys yielded an increase of the crooktail dominance display and elevated confidence in social interactions [67,68]. These different consequences are probably due to
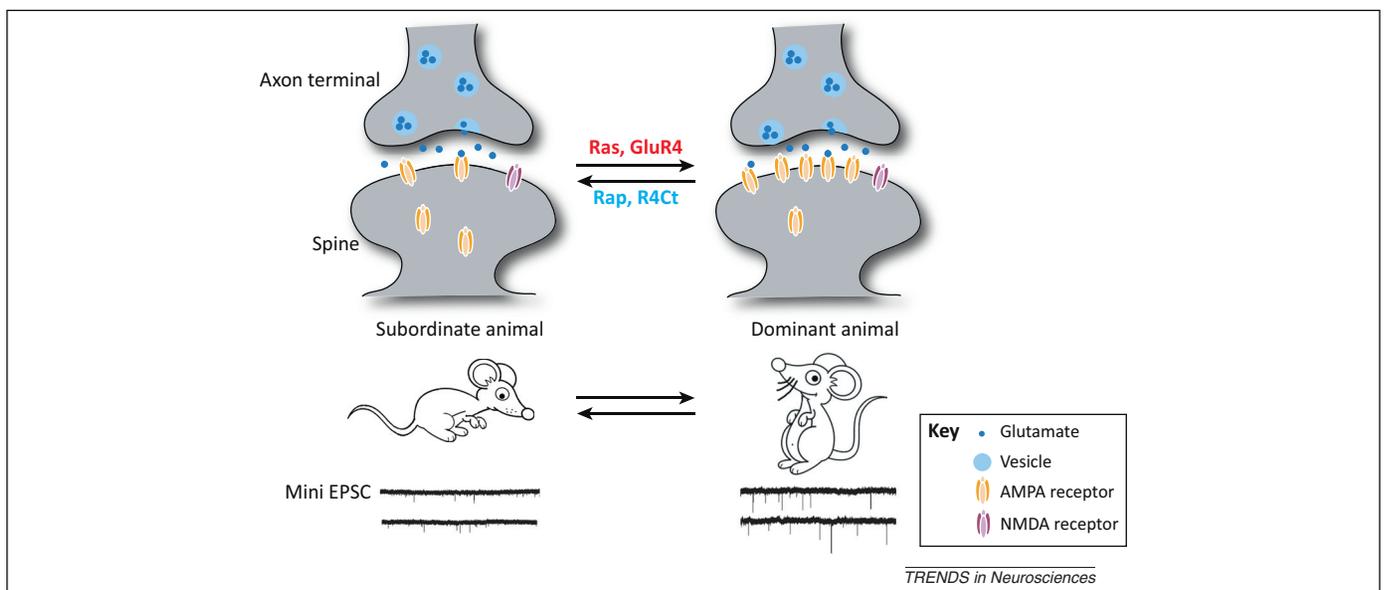

Figure 2. Efficacy of mPFC synapses bidirectionally modulate the dominance status in mice. Socially dominant mice have stronger mPFC excitatory synapses compared with subordinates (e.g., [6]). Synapse strength is determined by recording AMPA receptor-mediated miniature excitatory post-synaptic currents (mini EPSC). Upon selective strengthening of the mPFC synapses by expression of Ras or the AMPA receptor subunit GluR4, subordinate mice moved up the hierarchical ladder. Reversely, socially dominant mice decreased in rank when their mPFC synapses were weakened by expression of Rap or the GluR4 C-tail (R4Ct).
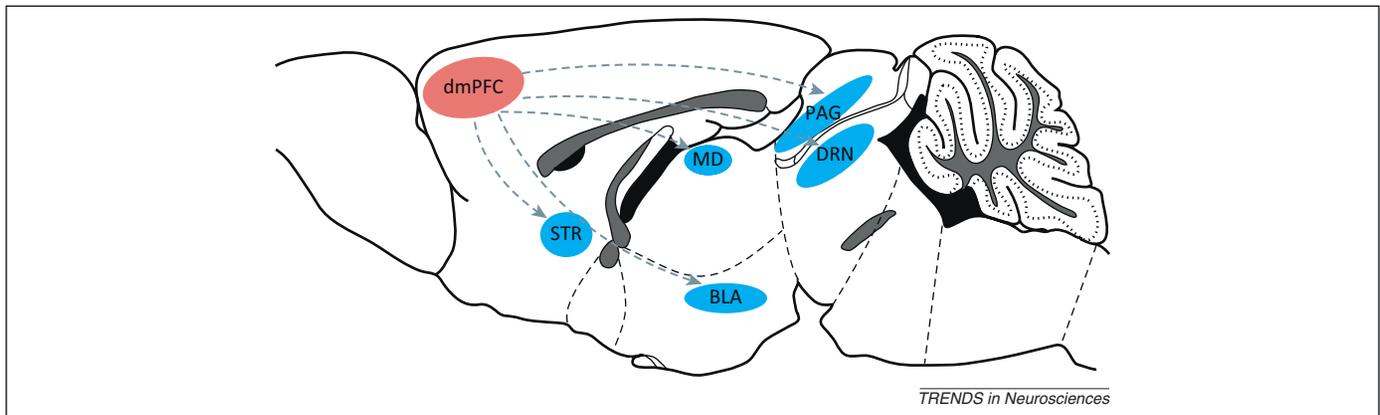
Figure 3. Potential neural pathways of social dominance downstream of the mPFC. Abbreviations: BLA, basolateral amygdala; dmPFC, dorsomedial prefrontal cortex; DRN, dorsal raphe nucleus; MD, mediodorsal nuclei of thalamus; PAG, periaqueductal grey; STR, striatum.

functional heterogeneities within the amygdalar subnuclei in regulating dominance behavior. Although future studies are necessary to dissect more precisely the function of individual subnuclei, these studies suggest that the amygdala conveys important information about social status, either downstream or upstream of mPFC.

Another mPFC downstream target implicated in the expression of dominance behavior is the brainstem dorsal raphe nucleus (DRN), the main serotonergic nucleus in the brain. The relationship between serotonergic signaling and dominance status has been most extensively studied in crustaceans [69]. Injection of serotonin into crayfish or lobsters tends to reduce the likelihood of retreat and increases the duration of fighting [70,71]. Dominance status also changes the modulatory effect of serotonin on the neural circuit involved in the escape response [72,73], correlating with changes in their behavioral patterns [69,74]. In vertebrates with more cortical development, serotonergic modulation of dominance seems to be different than that observed in crustaceans (reviewed in [69]). In vervet monkeys, enhancing serotonergic signaling by fluoxetine caused reduced aggression, more affiliative behavior, and better social skills; all of which contribute to higher social status. By contrast, monkeys with lowered serotonergic function showed higher levels of impulsive aggression and lower social status [75]. Studies in mice also suggest that lowered serotonergic function is associated with increased impulsive and aggressive behavior [76,77]. These studies suggest that the serotonergic system is likely an intrinsic part of the neuronal circuitry that influences

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Box 4. Outstanding questions and future directions

- *What are the molecular determinants of dominance trait?*
  Dominance status can be regulated by both internal traits (size, weight, aggression, courage, persistency, motivational drive, social and fighting skills) and external factors (prior history of winning, seniority, allies, prior residency). Dominance has been linked to heritable personality traits in humans [114], and can be genetically selected [20], suggesting a molecular genetic basis of dominance trait. Several molecules have been implicated in dominance-related behaviors, including the paternally imprinted gene Grb10 [115] and the oxytocin system [25,116]. Notably, the oxytocin system is also involved in mediating pair-bonding [117], suggesting that the neuronal mechanisms that mediate social dominance and those that are used for building partnerships overlap. It is interesting to speculate that the ability to form alliances within a social group positively affects the social status of an individual or, conversely, that social status influences the capacity for pair-bonding. Future work will be necessary to identify systematically the genetic and epigenetic factors that determine or regulate the dominance trait.

- *How do social interactions shape a dominance hierarchy?*
  Social status is relative by nature. The same animal can act dominantly over a more subordinate opponent, but become submissive against a more dominant one. Therefore, during the establishment of a dominance hierarchy there must exist a dynamic process through which animals adjust their own behavior and neural activity based on the outcome of the interaction with other social objects. How do winning and losing experiences modulate the activity of the neural circuitry underlying dominance behavior? And how do such changes lead to behavioral plasticity affecting future social interactions? For instance, it is possible that elevated stress levels during a first social encounter lead to a submissive role [118] due to a stress-hormone-induced change in the capacity for synaptic plasticity [119]. It will also be interesting to assess to what extent social network size and social enrichment affect the neuronal circuits that control dominance behavior.

- *How is behavioral specificity generated by the mPFC circuitry in social hierarchy behavior?*
  In addition to dominance behavior, the mPFC has been implicated in the control of a diverse array of behaviors including working memory, decision-making, attention, fear response, and social interaction. How does the mPFC manage to process all these different types of functions? Are there separate mPFC microcircuits that communicate through distinct upstream and downstream connections? It is also possible that the mPFC plays a more generic role, by planning actions based on schemas [120,121]. According to this scenario, in the context of a social confrontation for instance, the mPFC receives input on the current situation (e.g., is the social opponent strong or weak, what's at stake, etc.), compares this information with previous encounters that were of similar nature, and, based on what was learned from those experiences, activates the downstream circuit for actions that proved most beneficial in the past. New molecular and optogenetic tools will help delineate the mPFC circuits involved in these processes.

- *How does social status regulate health and other emotional behaviors?*
  As detailed in Box 1, social status has a strong impact on health. Rodent models of social hierarchy provide an excellent opportunity to ask whether animals of higher or lower rank have more compromised immune potency, or a higher propensity for anxiety, depression, addiction, or other diseases. Understanding whether and how mPFC and its downstream circuits mediate the health effects of social status should shed light on the treatment of related mental and physical health problems.

the expression of dominance behavior. Notably, optogenetic activation of mPFC-to-DRN projection in mice increased the motivation to act in challenging conditions [78]. It is interesting to speculate that, in a socially dominant individual, a stronger mPFC output to the DRN may improve the motivation to compete in a social conflict.

In addition to the DRN, the hypothalamus and periaqueductal grey (PAG) are the other potential downstream areas with reciprocal connections to mPFC that are implicated in the 'sham rage' response and in the regulation of agonistic behavior [79]. It will be relevant to assess how the mPFC modulates the activity of these subcortical aggression circuits and whether manipulating the pathway from mPFC to these nodes is sufficient to modify aspects of dominance behavior. The mPFC also strongly innervates the striatum [57], which is particularly active during socially rewarding events [80]. Social status information evokes a ventral striatal response that is influenced by one's own subjective social economic status [81]. Given the rewarding property of winning, it will be interesting to investigate whether the mPFC–striatum circuit is involved in the reinforcement of the social status through repeated winning or losing experiences.

Concluding remarks and future directions
Both human and animal studies have achieved great progress in identifying brain regions involved in social dominance behavior. The PFC is identified as a prominent mediator in the regulation and processing of social hierarchy. Excitatory synapses in the mPFC were shown to be stronger in dominant mice compared with subordinates, and manipulation of synaptic strength in the mPFC changed social status [6]. Possibly, winning in hierarchical competitions leads to strengthening of mPFC synapses, whereas losing weakens them. During social confrontations, the mPFC may communicate with the amygdala for emotional processing, with the serotonergic system for motivation to act, and with the striatum for assigning salience. Although the neuronal circuits that regulate social dominance are beginning to emerge, many open questions remain (Box 4). It is our hope that understanding the neuronal circuits of dominance hierarchy may give new insights into the future development of therapies for social stress-related clinical phenomena.

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