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Advances in understanding neural mechanisms of social dominance

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Dominance hierarchy profoundly impacts social animals' survival, physical and mental health and reproductive success. As the measurements of dominance hierarchy in rodents become established, it is now possible to understand the neural mechanism mediating the intrinsic and extrinsic factors determining social hierarchy. This review summarizes the latest advances in assay development for measuring dominance hierarchy in laboratory mice. It also reviews our current understandings on how activity and plasticity of specific neural circuits shape the dominance trait and mediate the 'winner effect'.

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Introduction

Social dominance is a universal phenomenon among social animals, ranging from insects [1], fish [2], to rodents [3] and primates [4]. Dominant individuals win more frequently in social competitions. Dominance status strongly impacts an animal's survival, physical and mental health and reproductive success [4–6]. A lack of motivation to compete in social contests may prevent individuals from realizing their potential. Therefore, understanding the central neural mechanism determining social hierarchy status is of critical importance.

Both intrinsic (physical and mental factors that are inherent and located within, for example, body size/strength, courage/fear, grit/persistency, stress level) and extrinsic factors (factors that are not inherent, acting from the outside, for example, environment, state of ally and opponents, experience such as history of winning/losing) contribute to social status determination. To understand the neural mechanisms underlying these intrinsic and extrinsic factors, simple and robust measurements for social dominance hierarchy are essential. In this review, we summarize the latest advances in the development of social dominance assays. We will also discuss the neuroendocrine regulation and circuit-specific neural activity as two examples of intrinsic factors, and the history of winning/losing as an example of extrinsic factor, and review the major findings in understanding how those factors determine social dominance status.

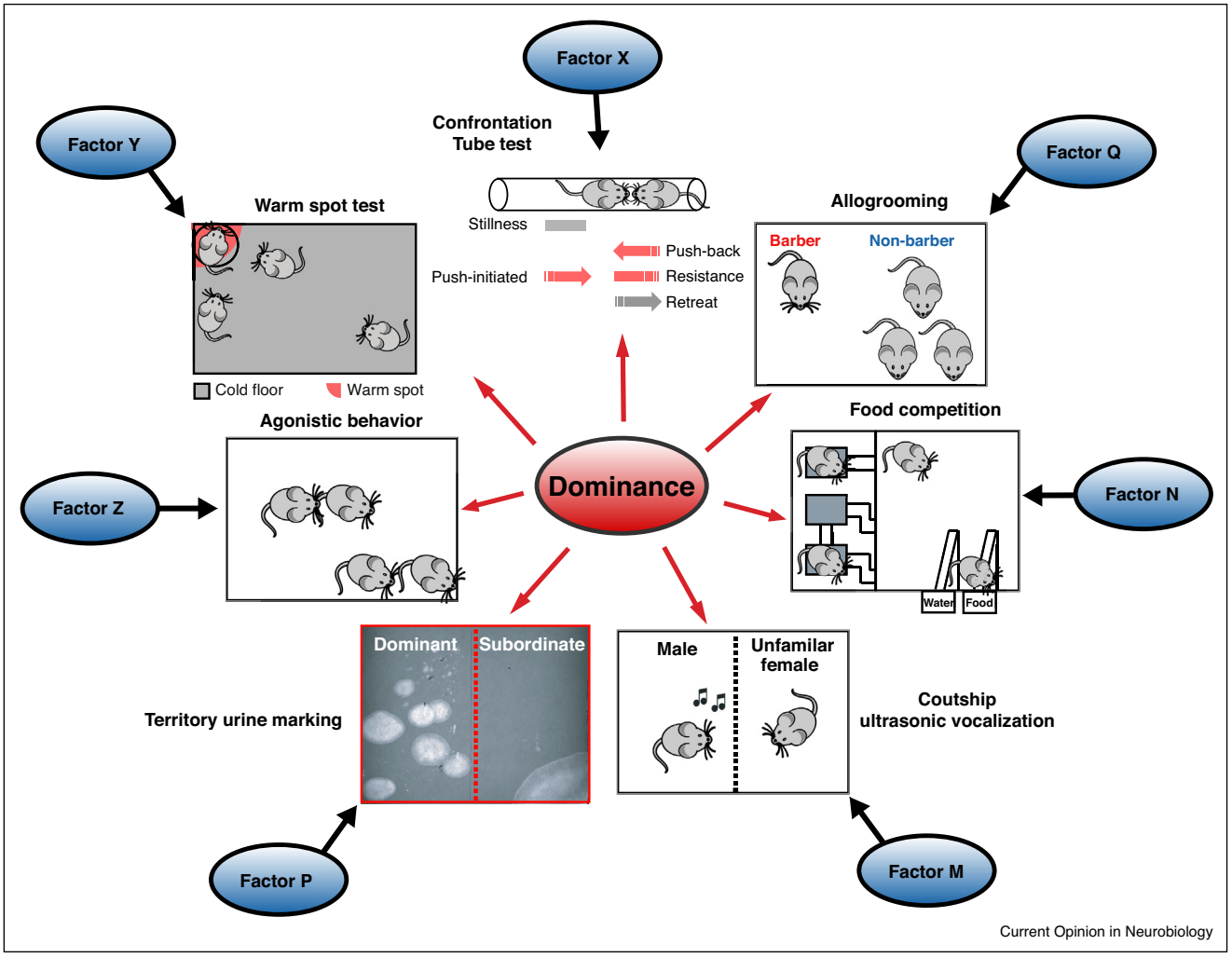
Measurements of dominance hierarchy in laboratory mice

Tube test

The tube test was developed in 1961 to measure dominance tendency between different mouse strains [7]. For a long time, it was used as a standard assay to screen the behavioral phenotypes of genetically modified mouse lines [8]. Wang *et al.* established in C57Bl/6 inbred cagemate mice that dominance ranks derived from the tube test are highly linear, stable, and correlate well with ranks derived from several other measures that reflect dominance hierarchy, including barbering, courtship ultrasonic vocalization, food competition in the visible burrow system, territory urine marking, and agonistic behaviors [9] (Figure 1). Tube test is simple and robust, introducing little stress and without causing injuries to the animals. It has since been used to investigate social dominance in mouse models of schizophrenia [10•], and the impact of dominance status on urination [11•], social interaction [12•], and vulnerability to social defeat [13••].

To analyze the detailed behavioral interactions during a tube test, Zhou *et al.* conducted a fine-grained video analysis [14••]. They quantified both behaviors generated voluntarily when mice faced an opponent in the tube (push-initiation) and the coping response when the opponent generated a push (push-back, resistance or retreat, Figures 1 and 2). These detailed analyses revealed insights on the potential internal states during social

Figure 1



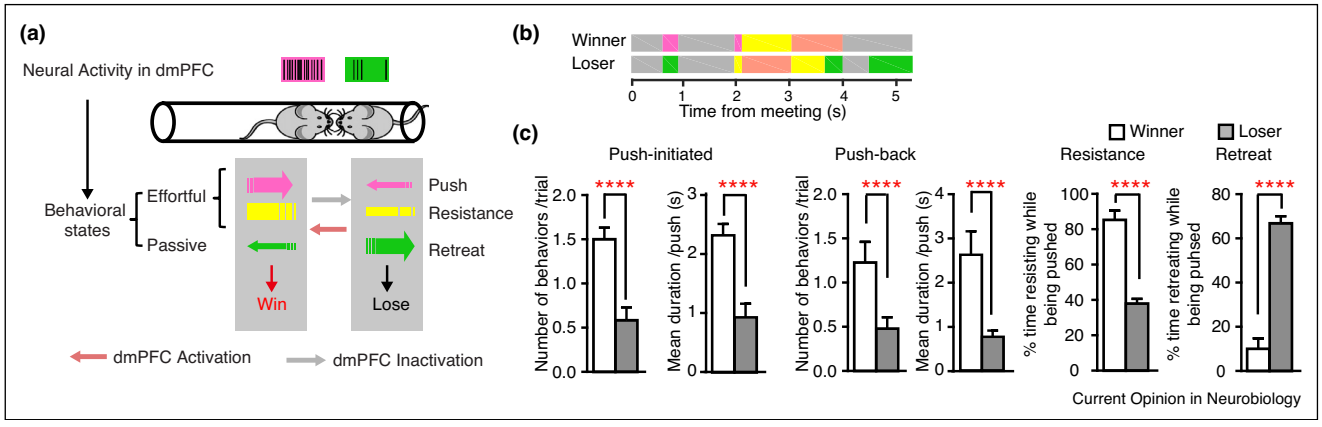
Different measures of dominance in mice (modified from Wang *et al.* [9]). Performance in each of these paradigms is commonly regulated by dominance but also depends on sensory and motor factors unrelated to dominance (factors M, N, P, Q, X, Y or Z) — for instance, cold tolerance for the warm spot test or agility for the tube test. To rule out the interference of these other factors, we advise using more than one behavioral paradigm to measure social rank, especially between mice of different genetic backgrounds or with drug treatments.

competition: Do mice win by initiating more pushes or by being more persistent and resisting more pushes, or both? Do they lose because of lower endurance or by avoiding social engagement and initiating retreat voluntarily? Indeed, Zhou *et al.* found that winner mice initiated more pushes with longer duration, generated more push-backs and resistance when being pushed. In contrast, loser mice showed a higher probability of retreat (Figure 2). Understanding the whole process rather than only the outcome may help rule out undesirable secondary effects. For example, a less interesting scenario of winning might be caused by the mouse remaining still all the time until the opponent retreats. It is important to distinguish these possibilities especially when analyzing animals with genetic modifications or with drug treatments (Figure 1). Defects in locomotion, social memory and muscle strength also need to be ruled out before conclusions about social dominance can be made [14••].

Warm spot test

In addition to the assays mentioned above, a novel social hierarchy paradigm — the warm spot test — has been recently developed, making use of animals' desire to stay warm [14••]. In this test, four cagemate mice are placed on an ice-cold floor with a warm spot in the corner, which can only accommodate one mouse at a time. Mice show competition to occupy the warm corner (Figure 1). The amount of time each mouse occupies the warm spot within the 20-min test is used to score social dominance. The warm spot test mimics the natural competition where the resources are limited and dominant individuals pay more efforts to occupy the desirable territory. Social

Figure 2



Neural mechanism of win/lose determination during tube test. **(a)** Behavior patterns of two mice in tube test are illustrated by different color-blocks in the grey shade. Mice with higher neural activity in the dmPFC generate more effortful behaviors (including push and resistance) and less passive behavior (retreat) during tube test confrontations, leading to winning. Activation/inactivation of dmPFC increase/decrease effortful behaviors and lead to winning/losing respectively. **(b)** Sample behavior annotations of a pair of mice in a tube test trial. **(c)** Winner mice generate more and longer push initiations and push-backs, and show more resistance when being pushed, while loser mice show a higher probability of retreat. Modified from Zhou *et al.* [14••].

dominance hierarchy ranked by the warm spot test correlates well with the tube test rank, cross-validating that these two assays share dominance as a common core variable.

A single behavioral assay can be affected by multiple sensory and motor factors, and each assay can also have its own caveats. For example, warm spot test can be affected by variation in temperature sensitivity or cold tolerance across individual mice. Tube test can be affected by agility or stress. Thus to increase confidence on the conclusion about social dominance, it is ideal to use at least two different dominance assays (Figure 1). When mice behave more dominant in multiple assays, the caveats of each assay can then be minimized.

The establishment of these simple and robust measures of social hierarchy has enabled investigation into the neural mechanism of social dominance determination. Both internal traits (size, weight, courage/fear, grit/persistency, aggressiveness, social and fighting skills) and external factors (prior history of winning, allies, prior residency) can have a significant impact on dominance status. Below we review the neural mechanism underlying some of these intrinsic (neuroendocrine, neural circuit activity) and extrinsic (winning experience) factors in social dominance determination. We also summarize the major findings on factors regulating social dominance in rodents in Table 1.

Neural mechanism underlying the intrinsic trait of social dominance

Neuroendocrine mechanism

To understand the factors contributing to internal traits, early studies were centered around hormonal effects and identified that the level of androgens, especially testosterone, plays a correlative or even causal role in shaping the dominance trait [16–20]. Testosterone levels rise rapidly (within 45 min) [21] in species ranging from rodents to humans after social competition, generally more in winners than in losers [22]. After testosterone injection, low-ranked hens increased their pecking order and rose to the top of the hierarchy [23]. Conversely, dominance behaviors disappeared in castrated rats [24]. However, such hormonal manipulations were mostly administrated chronically, and changes in dominance hierarchy were only observed weeks or even months afterwards [23]. This time delay makes it difficult to interpret whether testosterone acts gradually to reshape the animals' dominance character, or whether reorganization of social hierarchy structure requires accumulated changes in social interactions.

Less obvious is the relationship between levels of glucocorticoid stress hormones (corticosterone or cortisol) and social dominance, which appears to be complex and depends on several aspects of the social context. Subordinates generally show higher glucocorticoid levels than dominant individuals [6,25], which seems to be particularly the case in colonies with despotic dominants [26]. However, under social instability or high reproductive pressures, high-ranking male monkeys display higher cortisol levels than low-ranking males, suggesting that dominance may also carry costs [6,27]. While this evidence suggests that corticosterone might merely reflect individual's stress state regardless of social rank, studies in rats have highlighted a role for corticosterone in the consolidation of a subordinate status. Acute stress experienced by one of two male rats during their first encounter leads to social subordination and facilitates the

Table 1

Summary of major findings on factors regulating social dominance in rodents

Underlying factors	Animals (all in males)	Dominance assay used	Major findings related to social dominance
Neural circuit activity	C57BL/6 mice	Tube test Ultrasound vocalization Agonistic interaction Allogrooming Territory urine marking	Tube test rank is linear, transitive and correlates well with ranks measured by other methods. Synaptic strength in dmPFC determines social dominance status [9].
	C57BL/6 mice	Tube test Warm spot test	Activity of dmPFC neurons instantaneously controls social dominance behavior. MDT-dmPFC pathway mediates the winner effect that can be generalized [14••].
	C57BL/6 mice	Tube test	Metabolic profile in NAc is related to both social status and vulnerability to stress [13••].
	Wistar rats	Offensive and defensive behaviors during social encounter	Mitochondrial function in NAc is important for social hierarchy establishment and relates to the low social status associated with high anxiety [61].
	Wistar rats	Offensive and defensive behaviors during social encounter	Systemic injection of anxiolytic drug diazepam improves social competitiveness and NAc mitochondrial function [63].
Neuroendocrine	*Mus musculus*	Offensive and defensive behaviors during social encounter	Testosterone level in male mice correlates with dominance status [16].
	CD1 mice	Offensive and defensive behaviors in pair-house and large vivarium	Social environment is a key modulator of the relationship between social status and corticosterone and testosterone levels [26].
	CD1 mice	Offensive and defensive behaviors in large vivarium	Elevated GnRH level in the mPOA detected in subdominant mice in a social ascending paradigm [33••].
	Long-Evans rats	Agonistic behaviors in resident-intruder test	Adding testosterone in the preoptic area of castrated rats restores dominance [24].
	Long-Evans rats	Body weight combined with offensive and defensive behaviors in VBS	Subordinate has higher glucocorticoid levels than dominate individuals [25].
	Wistar rats	Water competition test	Stress shapes social hierarchy establishment by promoting memory of hierarchy [28].
	Wistar rats	Food and water competition test	Corticosterone level following a first social encounter modulates social status [29].
	Wistar rats	Food and water competition test	Oxytocin in the medial amygdala regulates stress potentiated social hierarchy [30].
Genetics	A/alb mice C3H mice DBA/8 mice	Tube test	This study compared the tube test dominance between different mouse strains, and the results are: A/alb>C3H>DBA/8 [7].
	C57BL/6 X S129Sv mice	Tube test Allogrooming	Mice with schizophrenia-linked mutation show dominance-like behaviors including tube test dominance and barbering [10•].
	C57BL/6 mice	Offensive and defensive behaviors during social encounter	Dominant mice express more male pheromones and this trait is heritable [81].
	CD1 mice	Offensive and defensive behaviors in large vivarium	Social status is associated with variation in mRNA of plasticity genes in hippocampus [80].
	CD1 mice	Offensive and defensive behaviors in large vivarium	Individual variation in dominance status is associated with brain gene expression [15].

long-term expression of subordination in future encounters [28]. The long-term facilitation of a recently acquired subordinate, but not dominant, status is also achieved by increasing post-encounter corticosterone levels following a first social encounter [29]. Furthermore, the potentiation of a social hierarchy by stress involves the engagement of the social neuropeptide system oxytocin in the medial amygdala [30], in line with a role of this system in social recognition [31] and social dominance [32].

The gonadotropin-releasing hormone (GnRH) has also been implicated in the plasticity of social hierarchy. In an interesting social opportunity paradigm, where removal of the alpha male from group-living mice leads to immediate aggression of subdominant mice toward subordinates, an elevated GnRH mRNA level in the medial preopic area (mPOA) of the hypothalamus is detected in these subdominant mice [33••].

Neural circuit mechanism

Recently, accumulating evidence has implied that social dominance might be regulated by the activity of specific neural circuits, especially circuits in the higher cortical areas of the central nervous system [34,35]. The prefrontal cortex (PFC), in particular, has been implicated in

coding several cognitive features that might be related to social hierarchy behavior, including social status recognition and representation [36,37], social norm compliance [38], cost-benefit analysis and effort-based decision making [39–42], as well as action planning in challenging or competitive situations [36,43,44]. The volume of PFC grey matter in monkeys and humans correlates with social success [45,46]. Consistently, lesions in PFC impair processing of social hierarchy information, reduce social interest and lower social rank [47–50]. Furthermore, viral-based molecular manipulations that increase or decrease the synaptic efficacy of dorsal mPFC (dmPFC) neurons in mice cause a gradual upward or downward shift in their social status, respectively [9]. However, although the effects of these viral experiments have a quicker onset (12–48 hours) than the lesion studies (days to weeks), it is still not fast enough to distinguish whether mPFC controls dominance behavior through neuronal activation directly, or indirectly by altering testosterone level.

Most recently, taking advantage of temporally precise optogenetic tools, Zhou *et al.* discovered that optogenetic excitation of dmPFC causes winning in an unexpectedly fast manner (<1 min). Furthermore, single-unit tetrodes recording and video analysis revealed that a population of dmPFC neurons are activated during the effortful (push or resist) behavioral epochs in the tube test [14••]. Importantly, dmPFC activation does not seem to enhance dominance by changing general locomotion, anxiety, social memory, basal aggression, muscle strength or testosterone level. Rather, dmPFC activation causes the initiation and maintenance of more effortful behaviors in social competition, suggesting that mPFC-based cognitive processes might provide a neurobiological foundation for dominance-associated traits, such as grit or competitive drive (Figure 2).

Which upstream brain region may feed relevant sensory information into the dmPFC for its cost-benefit analysis during social competition? The mediodorsal thalamus (MDT), as a higher order thalamic relay, shows strong reciprocal connections with the mPFC [51–53]. The MDT input into the mPFC is critical for the maintenance of working memory [54] and attentional control [55]. As an olfactory thalamus, the MDT processes olfactory information [56] and 40% of neurons in the MD are activated by social interaction [57], making it an ideal upstream input to convey sensory information with social content. Selective optogenetic activation of the synaptic input from the MDT to dmPFC is sufficient to induce tube test winning, highlighting the importance of this pathway in dominance behavior [14••].

Another brain area that is emerging as critically involved in social competitiveness and, consequently, in the early stages of social hierarchy formation, is the nucleus accumbens (NAc). Its role is supported by human neuroimaging data [37,58] and rodent studies involving a variety of approaches; that is, from lesion [59] and neurochemical [60] experiments to immediate early gene brain mapping and psychopharmacological inactivation [61]. Importantly, mitochondrial function in the NAc has been recently shown to play a crucial role in social hierarchy establishment, particularly in mediating the influence of anxiety on social competition [61]. Individuals high in trait anxiety show low social competitiveness [61,62] and impaired mitochondrial function mediates this effect [61]. Conversely, boosting NAc mitochondrial function either through intra-accumbal infusion of nicotinamide [61] or by systemic injections of the anxiolytic drug diazepam [63] improve social competitiveness. Dopamine receptor 1-containing medium spiny neurons were implicated in these effects [61,63]. In the future, it will be important to determine whether accumbal mitochondrial function is implicated not only in the establishment but also in the maintenance of social rank in long-lasting social groups. In support of this possibility is recent ^{1}H-NMR spectroscopy data indicating that subordinate mice in well-established colonies show lower levels of energy-related metabolites in the NAc than dominant ones [13••].

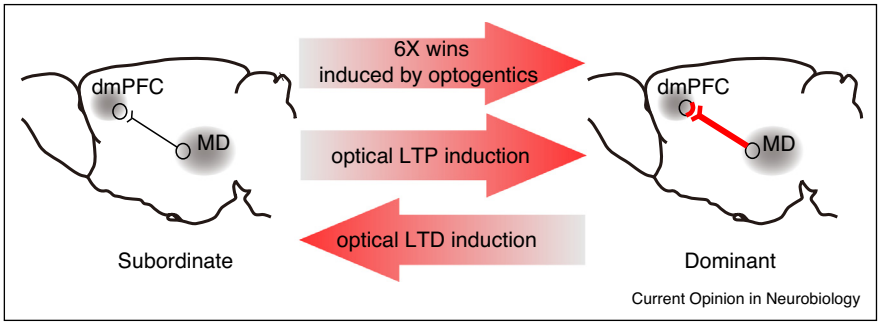
Neural mechanism mediating the external regulation of social dominance — the 'winner effect'

Among the external factors that can regulate social dominance, prior history of winning or losing can influence an animal's self-assessment and is an important parameter for the cost-benefit computation in a social competition. The 'winner/loser effect', by which winners or losers in previous competitions are more likely to keep winning or losing in future contests [64], exists across a wide range of animal taxa, ranging from insects [65,66•], crayfish [67], fish [68], birds [69] to humans [70]. The reinforcement generated through the 'winner effect' can have a long-lasting impact on social hierarchy [71].

Neural mechanism of the winner effect

Earlier work dissecting the neural mechanisms of 'winner effect' focused on changes in the neuroendocrine system including corticosteroid, androgen, testosterone and serotonin, after repeated winning [72–75]. Recent studies have begun to look into the plasticity of specific neural pathways. In zebra fish, Chou *et al.* found that silencing of the lateral subregion of the dorsal habenula (dHbL) eliminates the 'winner effect' [76••]. The synaptic transmission in the dHbL-dorsal/intermediate interpeduncular nucleus (d/iIPN) circuit is weakened by losing experience but remains unchanged by winning [76••]. In mice, inspired by the finding that the MDT-dmPFC circuit shows synaptic weakening after repeated social defeats [77••], Zhou *et al.* tested whether the same MDT-dmPFC pathway might mediate the 'winner effect'. They found that the synaptic strength in the MDT-dmPFC pathway

Figure 3



Plasticity of the MDT to dmPFC synapses mediates the winner effect. Repeated winning potentiates the synapses of the MDT to dmPFC pathway. Optical LTP or LTD induction in these MDT-dmPFC synapses converts subordinate mice into dominants, and vice versa, respectively.

is enhanced after repeated winning. Importantly, optogenetic induction of long-term potentiation (LTP) in the MDT-mPFC synapses directly causes sustained tube test winning, whereas optogenetic long-term depression (LTD) in the MDT-mPFC pathway eliminates the winner effect (Figure 3).

Generalized 'winner effect'

Animals encounter different forms of competition, over food, water, territory, or mates, in establishing social hierarchy. Earlier studies of the 'winner effect' were restricted to the impact of winning on the same behavioral paradigm [64], which might not capture the full complexity of social confrontations in the real world. A generalized form of the 'winner effect', where dominance transfers from one type of contest (tube test) to another (warm spot test), was recently described [14••]. Specifically, repeated tube test winning induced by optogenetic activation of dmPFC causes rank elevation in the warm spot test. It is proposed that this transferability of the 'winner effect' might reciprocally reinforce the dominance status in differential social contests, facilitating the formation and stabilization of dominance hierarchy.

Concluding remarks and future directions

It is an exciting time to be studying the neural mechanisms of social hierarchy. The field is emerging and many key issues remain to be addressed.

First a series of questions need to be addressed at the neural circuit level. As the dmPFC contains heterogeneous neural populations, it will be important to determine how cells of different types or with different projections within the dmPFC microcircuit differentially contribute to the control of social dominance. To understand how dmPFC regulates social dominance through top-down control of different subcortical nuclei, different downstream pathways need to be deconstructed. As one of the downstream targets of dmPFC, and given its involvement in reward and effort, the role of the NAc in social hierarchy needs to be further dissected. Furthermore, as the experience of winning or losing is rewarding or aversive, respectively, and can change the endocrine system, it will be interesting to figure out how hormones or reward-related neuromodulators interplay with the synaptic plasticity mechanism to mediate the winner effect.

Second, the organization of complex social structure and maintenance of social hierarchy rely on individual recognition, social memory and reinforcement learning process [78–81,82••,83]. It will be very interesting to resolve the role of these processes in the construction of social hierarchy.

Third, the trait of dominance can be genetically selected [81,84]. Yet isogenic mice with almost identical genetic background still establish robust transitive linear social hierarchy [9]. Thus both genetic and epigenetic factors can be instrumental in the establishment of social hierarchy and need to be identified.

Last, but not least, as seen in Table 1, most studies on social dominance in rodents have been conducted in male animals. Dominance hierarchy is thought to be established through aggressive interactions during initial encounters, which is apparent in male mice but not females. It remains an outstanding question how female mice establish social hierarchy without overt aggression.

Conflict of interest statement

Nothing declared.

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