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Sociobiology: Changing the Dominance Hierarchy

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One fundamental question is to understand what neural circuits are involved when social hierarchies are established, maintained and modified. Now, a new study shows that a previously subordinate animal can become dominant after optogenetic stimulation of the dorsomedial prefrontal cortex, demonstrating that this brain region is necessary and sufficient to quickly induce winning during social competitions.

Social hierarchies are ubiquitous in social species. Natural selection has favored individuals equipped with psychological mechanisms adapted to successfully navigate dominance relationships, leading to important fitness consequences associated with higher ranks, such as better access to food resources, sexual partners and better health. Understanding how social hierarchies are established can answer deep questions about the brain's general adaptation to its social milieu and about individual markers for mental health and brain plasticity. In most social species, dominance status is established after animals engage in repeated social contests [1]. The history of winning in such competitive interactions determines the respective ranks of individuals in the hierarchy. Theoretical biology has long predicted that the emergence and maintenance of a social hierarchy appear if winning a challenge boosts the chances of winning future contests [2]. This is known as the 'winner effect', where animals increase their probability of victory during social contests after prior winning.

In a new study published in *Science*, Zhou *et al.* [3] managed to transform subordinate mice into dominant individuals by optogenetically stimulating a group of neurons in the dorsomedial prefrontal cortex (dmPFC). This brain region has previously been implicated in learning social dominance relationships [4,5] and changes in mPFC synaptic efficacy modulate rank in social hierarchies [6]. First, the authors established the behavior of weight-matched mice in the dominance tube test, a classical social competition task. In this test, two mice are released at the opposite ends of a transparent, narrow tube and their behavior is monitored by video (Figure 1A). When the more dominant animal forces its opponent out of the tube, it is declared the winner of the contest. Winner mice initiated more pushes than loser mice, and also showed more push-backs, resistances and fewer retreats when being pushed. A linear dominance rank order measure based on the total numbers of wins against cagemates also showed that opponents with closer rank distances generated more pushes. Having established this behavior, the authors recorded neurons from the dmPFC using tetrodes targeting the anterior part of the anterior cingulate (ACC) and the prelimbic (PL) cortices (Figure 1B). These neurons included 90% putative pyramidal (pPyr) neurons and 10% putative fast-spiking interneurons (pIN). The mean firing rate of pPyr neurons was higher during 'effortful' phases (push and resistance), but not in the passive (retreat) phase, than during stillness. In contrast, the firing rate of pIN units increased during the retreat epoch. Moreover, a fraction of the pPyr units showed increased firing rates during push behaviors, and one-third of them also showed an increase in firing rate during resistance, establishing that both types of efforts engaged the same subset of dmPFC neurons during social competition. Then, the authors used designer receptors exclusively activated by designer drugs (DREADD) to show that inhibition of the dmPFC leads to more defeats in social contests.

Next, the authors used optogenetics, a technique which involves the use of light to control neurons that have been genetically modified to express light-sensitive ion channels. They showed that dmPFC activation was sufficient to induce instantaneous winning of social contests when photostimulating the originally subordinate mice (Figure 1C). This effect could not be attributed to changes in locomotion, muscle strength, anxiety or aggression levels alone. Interestingly, the laser intensity required to dominate the opponents correlated with the rank distance between mice, demonstrating a dosage-dependent relationship between the level of dmPFC activation and the amount of effort required to win the competition. Previously subordinate mice maintained their new rank after several days when dmPFC photostimulation was applied for at least six wins on day zero, whereas those receiving fewer than five photostimulated wins returned to their original rank (Figure 1D). Thus, the winner effect could be artificially induced by repeated dmPFC stimulation. Because the mPFC receives prominent projections from the mediodorsal thalamus (MDT) and the MDT–dmPFC circuit shows synaptic weakening during repeated defeat-induced social avoidance [7], the authors next investigated whether there was a causal relationship between activity of the MDT input to the dmPFC and induction of dominance behavior (Figure 1D). They hypothesized that this pathway undergoes long-lasting synaptic strengthening after repeated winning. This was indeed confirmed by (i) detecting enhanced synaptic strength in the MDT-dmPFC pathway after repeated winning,

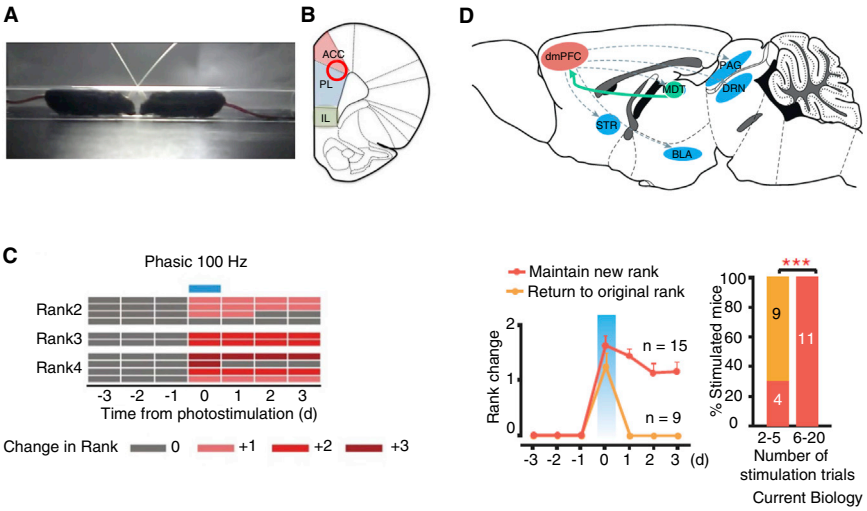

Figure 1. Optogenetic activation of dmPFC induces instantaneous winning in the tube test.
(A) Two mice with implanted optic fibers confronted each other in the dominance tube test (reprinted with permission from AAAS [3]). (B) dmPFC location of the injection of the AAV2 virus expressing light-sensitive channelrhodopsin and of the optic fiber implantation (red circle). (Modified from [20].) (C) Optogenetic activation of the dmPFC induces winning in the tube test. Rank change of each manipulated mouse with CAG::ChR2 expressed in dmPFC and received phasic 100 Hz. Each line indicates the tube-test dynamics of one manipulated animal. Rank numbers at the left indicate the initial rank position of each animal (reprinted with permission from AAAS [3]). (D) (Top) Synaptic strength of the mediodorsal thalamic–dmPFC circuit underlies the winner effect in the tube test (modified from Wang, F., *et al.* (2014) The mouse that roared: neural mechanisms of social hierarchy. Trends Neurosci. *37*, 674–682.) (Bottom) Mice either maintain their new rank or return to their original rank position after dmPFC photostimulation, depending on the number of stimulated-win trials. d, day. Numbers on the graphs indicate the number of mice (reprinted with permission from AAAS [3]).

(ii) eliminating the sustained winning by introducing long-term depression (LTD) to reverse the synaptic strengthening in the MDT-mPFC circuit, and (iii) directly causing sustained winning in the tube test after inducing long-term potentiation (LTP) in the MDT–mPFC synapses while mice were freely moving in their home cage.

Winning social competitions is not only influenced by the history of success/defeats but also by personality traits, such as susceptibility to stress. In another recent study reported in *Current Biology*, Larrieu *et al.* [8] focused on the behavioral and neural consequences of a similar social-confrontation tube test in mice (Figure 2A), to test vulnerability to chronic social defeat stress. To do this, they first housed four mice in the same home cage for several weeks, and then tested them in a pairwise fashion, considering social rank as stable only when mice adopted the same rank position for four consecutive days. They showed that dominant mice, but not subordinates, were the ones susceptible to developing social avoidance and depression-like behavior after social defeats (Figure 2B, top). The authors interpreted this finding as reflecting that subordinate animals are used to being defeated during social hierarchy establishment, making them more resilient to subsequent social stress, while dominant mice may respond more strongly to unpredicted defeats. Moreover, risk factors predictive of vulnerability to stress and metabolic changes were identified with spectroscopy. The authors focused on the mPFC–nucleus accumbens (NAc) circuit, known to be engaged in reward/motivation and in flexible behavioral responses to social events, such as social defeats [6,7,9,10]. Subordinates showed lower levels of energy-related metabolites in the NAc, but not in the mPFC, compared to dominants. After exposure to the chronic social defeat stress test, subordinates, but not dominants, showed increased levels of these metabolites, possibly reflecting NAc integrity in subordinate but not in dominant mice (Figure 2B, bottom). Together, these two studies indicate that the mPFC and the NAC respond differentially to the history of success and to susceptibility to stress. The fact that individual susceptibility to develop social avoidance after chronic social defeat stress results from preexisting dominance hierarchies may have clinical implications. Specifically, the findings may suggest a vulnerability to neuropsychiatric disorders mediated by the experience of iterated social defeats, such as depression.

One limitation of the two studies discussed above is that, although they measured slow changes in testosterone after photostimulation or stress, they did not measure testosterone pulses during specific phases of the competitive interactions. Yet, this hormone is important for increasing and maintaining social status [11–13] and preclinical findings, including neuroendocrinological manipulations in rodents, have demonstrated a causal link between post-victory testosterone *pulses* and the winner effect [14]. Winning a territorial fight, but not fighting itself [15], causes a surge in testosterone which could enhance an individual's ability to win future encounters by increasing aggression [14,16]. The mechanisms by which testosterone pulses increase future ability to win include long-term plasticity in the neurobiological circuits that control aggression [14] and higher sensitivity of the dopaminergic reward system to testosterone [17,18]. Future studies will need to measure the rapid time course of testosterone surge during social contests.

Another important question is how these results obtained in mice can help to understand the mechanisms engaged in social dominance behaviors in humans. One approach to bridge this gap between species is to establish links between fundamental computational principles of social dominance processes and the brain system level. In particular, the fact that learning social hierarchies may rely on similar principles as learning stimuli–reward associations by reinforcement has been underappreciated [4,5,19]. Using a model-based approach combining fMRI and tDCS in humans, we recently showed that the rostromedial part of the PFC (rmPFC) is necessary for learning social dominance relationships during competitive interactions [18]. This study

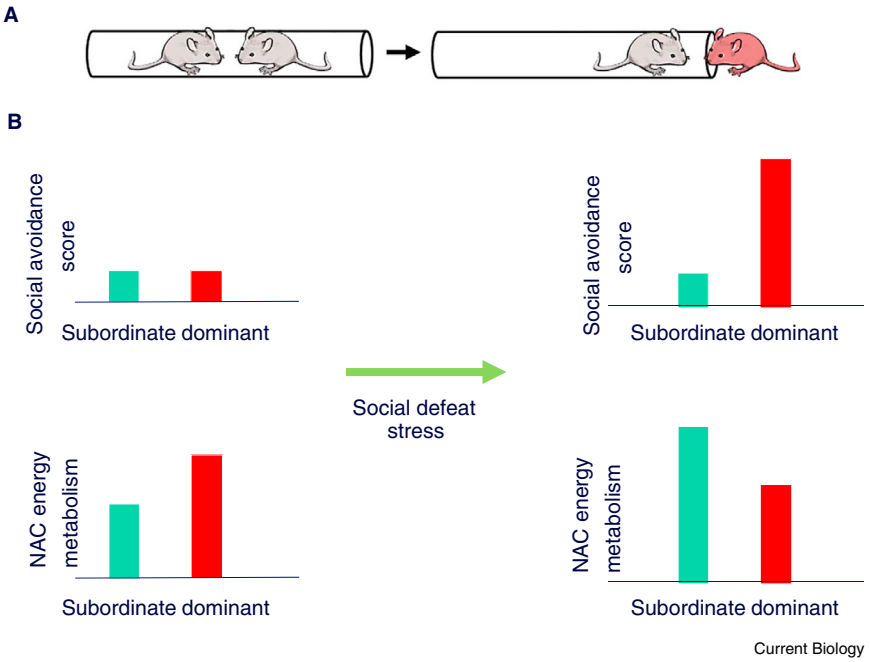

Figure 2. Hierarchical status predicts vulnerability to stress and NAC metabolic profile after chronic social defeat stress.
(A) Schematic of the social defeat stress test administrated for 10 days (from [8]). (B) After the social defeat stress, dominant mice exhibited the susceptible phenotype (higher social dominance score) and the Nucleus Accumbens (NAC) metabolism was differentially modulated by social rank.

focused on learning processes using a cognitive paradigm and did not require motor effort to win the social competition. Future studies investigating social dominance in humans will need to decipher whether social ranks learned by contests requiring a real effort also engage the rmPFC.

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