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Neural circuits for coping with social defeat

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When resources, such as food, territory, and potential mates are limited, competition among animals of the same species is inevitable. Over bouts of agonistic interactions, winners and losers are determined. Losing is a traumatic experience, both physically and psychologically. Losers not only need to deploy a set of species-specific defensive behaviors to minimize the physical damage during defeat, but also adjust their behavior towards the winners to avoid future fights in which they are likely disadvantaged. The expression of defensive behaviors and the fast and long-lasting changes in behaviors accompanying defeat must be supported by a complex neural circuit. This review summarizes the brain regions that have been implicated in coping with social defeat, one centered on basolateral amygdala and the other on ventromedial hypothalamus. Gaps in our knowledge and hypotheses that may help guide future experiments are also discussed.

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In the wild, resources such as food, territory, and potential mates are limited. Consequently, animals often need to compete for obtaining and securing such resources and fighting is a major means to achieve that [1]. While animals of different species employ widely diverse tactics during aggressive encounters, nearly all attacks share the common goal of inflicting pain on the opponent. As a fight progresses, the animal with superior physical strength and fighting ability starts to dominate, initiating most of the offensive attacks and actively pursuing its opponent. Meanwhile, the losing animal starts to act more defensively, focusing on escaping from the opponent's attacks and minimizing physical damage [2•]. In solitary species, the losing animal will simply flee, leaving the winner and resources behind. However, animals living in a social group may be more reluctant to flee or disperse as an isolated animal can be vulnerable to predation and attacks from other groups. In contrast to natural open settings, in laboratory settings escaping is typically not an option as the fighting animals are confined to the small space of a test arena. In these cases, the losing animal starts to adopt strategies that minimize its interaction with the opponent and readily assumes submissive postures to reduce provocation of the aggressor [3•,4–6]. After fighting is terminated, either by the experimenter or the winner, the losing animal clearly remembers this traumatic experience and adjusts its behavior in future encounters with the winner. It continuously avoids close interaction with the winner and readily assumes submissive postures when confronted [6,7•]. Additionally, the loser learns to stay away from the area where the fights have occurred [8•,9]. This contextual avoidance could be particularly important for territorial species as intrusion into the winner's territory inevitably evokes attacks.

The series of adaptive behaviors exerted by a losing animal are crucial to its survival. Knowing when to lay low or flee, who to avoid, and where to forage (or not) reduces the risk of engaging in a disadvantageous conflict. What are the neural mechanisms that support these complex coping actions? Over the last several decades, studies that mainly use rodents as animal models have revealed several key brain regions essential for mediating these coping processes. The goal of this review is to provide an overview of our current knowledge regarding the neural circuits underlying the adaptive behaviors of a losing animal in coping with social defeat and discuss the knowledge gaps that remain to be filled.

Aggressive and defensive behaviors in rodents

In mice, hamsters, and rats, inter-male fighting can be readily observed in laboratory settings. When a single housed male mouse encounters a strange male intruder of the same species in its home cage, it quickly approaches the intruder and initiates attacks with a short latency ranging from seconds to minutes. In several recent reviews, brain regions relevant for the generation of aggressive behaviors have been described in detail [10–13]. Here, we will focus on a situation in which the intruder male is a highly capable fighter who manages to fight back against the resident and successfully delivers bites to inflict pain on the resident [14,15]. After several bouts of failed attacks, the resident animal typically gives up on its attacking

attempts. In contrast, the aggressive intruder actively approaches and pursues the resident and initiates attacks. While being attacked, the resident actively defends itself by standing up facing the aggressor and boxing, or dashing away from the opponent (Figure 1) [3•,4]. Often, as the defending resident flees, the aggressive intruder bites the defender's back, a preferred target during attacks [3•,4]. After being attacked for several bouts, the resident starts to spend more time cornering, either freezing in a crouched position or an upright submissive posture, interleaved with occasional forceful jumping facing the cage wall, likely in an attempt to escape (Figure 1) [3•,4,16•,17•]. Thus, within minutes, the resident changes its behavior towards the intruder dramatically — from active approach and attack to active avoidance and defense. The avoidance towards the aggressor persists for at least three days and gradually diminishes over time (Figure 1) [18]. After one acute defeat, the avoidance behavior is specific to the defeated resident [19]. Chronic defeat, on the other hand, could induce broader behavioral and physiological changes including long-lasting and non-discriminative social avoidance and has been used to model stress related disorders, such as depression and post-traumatic stress disorder (PSTD). The behavioral and neural changes associated with chronic social defeat are described in detail in several recent reviews [20,21]. Here, we will focus on the neural processes that quickly alter the social behaviors during and after acute defeat.

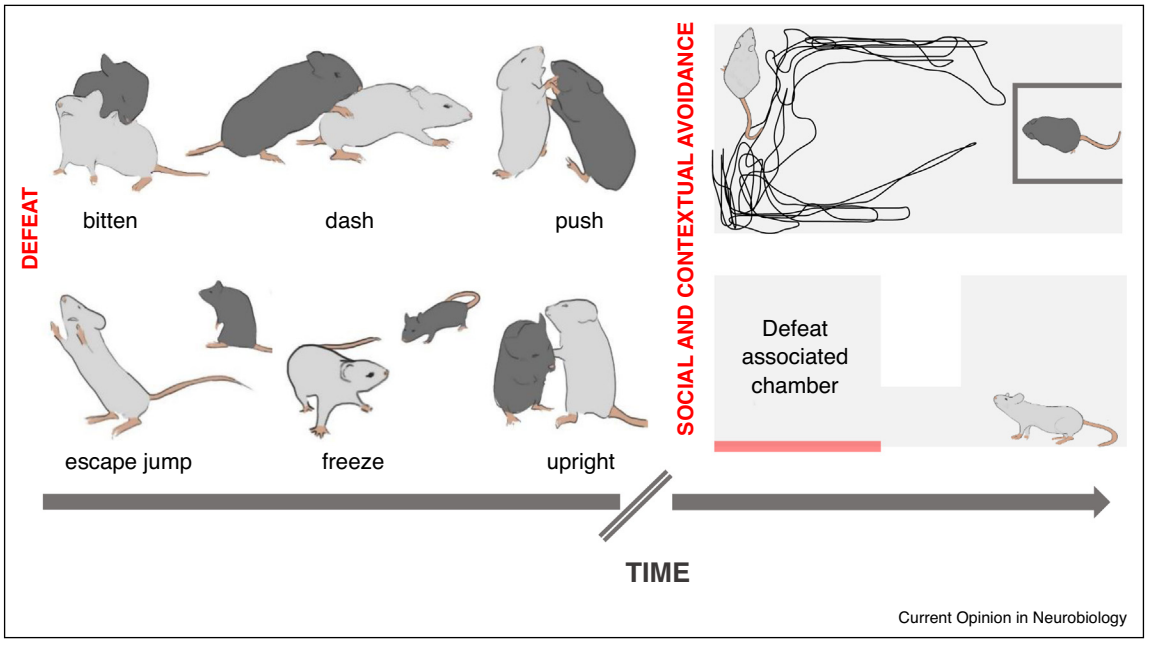
The role of basolateral amygdala associative learning circuit in defeat-induced social fear

In essence, defeat is an associative learning process during which aggressor cues become tightly associated with the painful experience of defeat. At the neural level, this association process likely induces synaptic plasticity that enables the aggressor cues to gain access to brain regions controlling avoidance and fearful behaviors. Associative learning during defeat is conceptually similar to classical fear conditioning – a process that pairs a neutral conditioned stimulus (CS, e.g. a tone or light) with a painful unconditioned stimulus (US, e.g. foot shock) [22,23]. After repeated CS-US pairing, the animal shows responses reminiscent of innate fear responses (e.g. freezing and avoidance) to the CS. During defeat, we may consider the intruder cue as a CS (although the conspecific cue is not neutral but innately attractive), and inflicted pain as a US. Repeated CS-US pairing transfers the negative valence of the US (bite) to the CS (intruder).

Basolateral amygdala

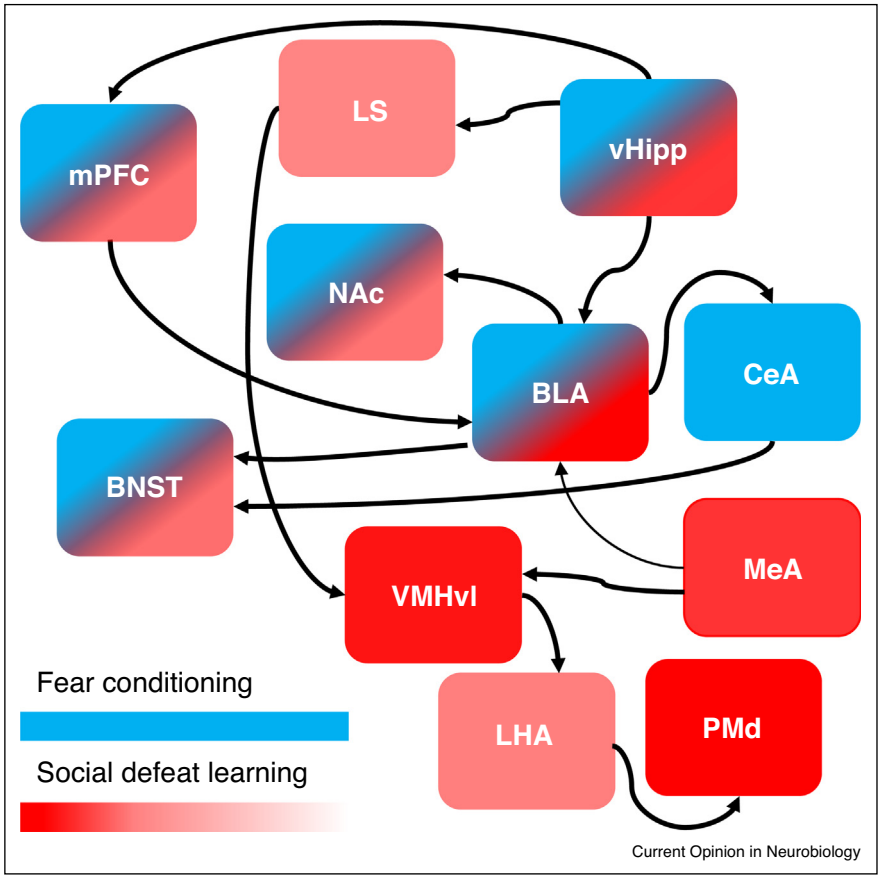
Given the conceptual similarity between defeat and fear conditioning, could these two processes recruit similar neural circuits? Basolateral amygdala (BLA) has been generally accepted as the core region for the CS-US association formation during fear conditioning based on a large body of lesion, pharmacological, and neurophysiological studies (Figure 2) [22–24]. BLA integrates cues of

Figure 1



Mouse behavior during defeat, followed by social and contextual avoidance. During an aggressor encounter, the aggressor will attack and bite the opponent, prompting escape and defensive behaviors including dashing, pushing, jumping, freezing, and assuming an upright posture. Post encounter, the defeated mouse avoids contact with the aggressor (trace represents mouse movement, notice confinement to corners and edges) and contexts associated with the defeat experience. The defeated mouse is shown in light gray and the aggressor is shown in dark gray.

Figure 2



Neural circuitry involved in fear conditioning and social defeat learning. Blue highlights regions with potential roles in Pavlovian fear conditioning. Red indicates regions relevant for coping with social defeat, including social defense, defeat induced social avoidance, and defeat induced contextual avoidance. Shade indicates the strength of the supporting evidence. Brighter color corresponds to stronger evidence. Abbreviations: lateral septum (LS), medial prefrontal cortex (mPFC), nucleus accumbens (NAc), ventral hippocampus (vHipp), central amygdala (CeA), basolateral amygdala (BLA), medial amygdala (MeA), ventrolateral part of the ventromedial hypothalamus (VMHvl), lateral hypothalamic area (LHA), dorsal part of the premammillary nucleus (PMd) and bed nucleus of the stria terminalis (BNST).

various sensory modalities, for example, auditory information from auditory thalamus and pain related information from periaqueductal gray (PAG), and drives fear expression through its projection to central amygdala (CeA) [25]. Aversive stimuli, such as foot shocks, evoke spiking activity in BLA cells. When a CS is repeatedly paired with the aversive stimulus, synapses that carry CS information to the BLA are potentiated and, consequently, CS input alone effectively drives BLA cells to elicit fear [25]. Consistent with a role of the BLA in social defeat, BLA is among the regions that shows strong increase in c-Fos expression after defeat [26,27]. A series of functional experiments have further established a causal role of BLA in defeat-induced social avoidance in hamsters. Inactivation, blocking protein synthesis, or blocking NMDA receptors in the BLA before defeat all reduced defeat-induced conspecific avoidance 24 hours later [28,29,30•,31]. Conversely, increasing the expression of cAMP-responsive element binding protein (CREB, a transcription factor that regulates synaptic plasticity and memory formation) in the BLA enhances avoidance towards the aggressor [32]. Inhibiting the BLA immediately before the social preference avoidance test 24-hours after defeat also reduces avoidant behaviors, supporting a role of the BLA in both in social fear acquisition and expression [30•]. More recently, findings in hamsters were corroborated by loss-of-function experiments in mice, supporting a necessary role of the BLA in defeat-induced social avoidance [18].

Medial prefrontal cortex

Medial prefrontal cortex (mPFC) is another key region involved in fear conditioning (Figure 2). Specifically, prelimibic cortex (PL) is required for fear acquisition and expression whereas infralimibic cortex (IL) is necessary for fear extinction — both through their projections

to the BLA [33,34]. A role of the mPFC in defeat-induced social avoidance has been investigated, although contradictory results were reported. In hamsters, it was found that inactivation of the mPFC using muscimol, a GABAA receptor agonist, significantly enhanced the acquisition of subsequent social avoidance [35]. In contrast, studies in mice found that temporal inactivation or lesion of the dorsomedial PFC (dmPFC) abolished social fear induced by defeat [36,37]. It is possible that these inconsistent results reflect differences in the specific target region or species. Future studies with more precise PL and IL targeting will help elucidate the roles of mPFC in defeat-induced social fear and its extinction.

Ventral hippocampus

Ventral hippocampus (vHipp) projects densely to the BLA and mPFC and is a part of the intricate network for mediating fear expression and extinction (Figure 2) [33]. Temporary inactivation of the vHipp using muscimol disrupted the acquisition of social fear after defeat, whereas blocking protein synthesis in this area has no effect [29], suggesting that vHipp is likely not the site for memory storage but may participate in relaying CS or US related information during associative learning. In particular, vHipp may be important in relaying contextual information as lesioning vHipp consistently impaired contextual fear memory [38,39]. After defeat, the loser animal avoids the context in which it was defeated and performs careful exploration of the environment through risk assessment behaviors, suggesting that contextual fear learning has taken place [9,40]. To date, the function of vHipp in defeat-induced contextual fear learning remains unknown and awaits to be elucidated in future studies.

Central amygdala and bed nucleus of stria terminalis

The most studied region downstream of the BLA in driving fear response is central amygdala (CEA) (Figure 2). BLA projects to the lateral part of CEA, which in turn projects to medial part of CEA and ultimately drives freezing through its projection to the ventrolateral PAG [41–43]. Although CEA is among the regions that show elevated c-Fos after social defeat, a role of CEA in driving defeat-induced social fear remains debatable. While electrical lesion of the CEA in hamsters significantly reduces submissive and defensive behaviors towards a conspecific, bilateral lesion of CEA in rats do not change defeat-induced immobility towards a dominant rat [44,45].

CEA is densely connected with the anterior part of the bed nucleus of stria terminalis (BNST), which also receives moderate input directly from the BLA (Figure 2) [46]. A large number of studies using fear conditioning paradigm suggest that BNST is dispensable for rapid-onset, short-duration behaviors (e.g. freezing) in response to a conditioned threat, but it is important for persistent behavioral changes after removing the threat, that is, anxiety [47]. In the context of social defeat, inhibiting BNST before defeat has no impact on social avoidance 24 hours later, arguing against its role in associative learning during defeat. However, injecting muscimol or a CRF receptor antagonist into the BSNT immediately before the social test suppresses avoidance towards a conspecific [44,48]. In the rodent species *Peromyscus californicus*, also known as California mice, administration of an oxytocin receptor antagonist into the BNST modulates social avoidance after defeat, but interestingly, exerts opposite effects in males and females [49]. Altogether, BNST may play a role in increasing social anxiety after defeat.

Nucleus accumbens

The other major downstream of the BLA is nucleus accumbens (NAc) (Figure 2). In contrast to the BLA to CEA projection that mediates freezing after fear conditioning, the BLA to NAc shell projection is important for active avoidance, that is, running to a safe box upon the presentation of a danger-predicting cue [50]. After defeat, the loser shows clear active avoidance, for example, runs away from an approaching aggressor. Does the BLA to NAc projection mediate active aggressor avoidance in defeated animals? Answers to this question remain unknown although some clues suggest this might be the case. Infusion of muscimol into the NAc of defeated hamsters restores attacks towards the opponent [51]. As attack is proceeded by approach, this result suggests that NAc inhibition reduces active avoidance of a conspecific. It is worth noting that the behavioral change induced by NAc inhibition differs from other above-mentioned regions, including BLA, mPFC and vHipp. In the paper, the authors wrote: 'this (NAc) is the first component of the putative conditioned defeat neural circuit wherein we have found the pharmacological manipulations are effective in restoring the territorial aggressive response in previously defeated hamsters' [51]. Later, the same group reported that injecting nonspecific dopamine receptor antagonist cis-(Z)-flupenthixol in the NAc also promotes aggression in defeated animals [52]. Together, these results suggest NAc may play role in active avoidance post defeat via a dopaminergic mechanism.

Lateral septum

Lateral septum (LS) is a major efferent target of the ventral hippocampus, and has been recognized for decades as a key player in modulating aggression (Figure 2). Early lesion and inactivation studies implicating the LS in 'sham rage' [53], and more recently our studies, suggest that LS can suppress ongoing aggression through its projection to the ventrolateral part of the ventromedial hypothalamus (VMHvl), a key region for driving aggressive behaviors [54]. The function of the LS in defeat-induced social avoidance has also been examined in hamsters. Similar to the NAc inactivation, LS inactivated animals show increased aggression towards an opponent [55]. However, unlike NAc inactivation effects, LS inactivation induces hyper-aggression in defeated as well as

non-defeated animals, consistent with a role of the LS in exerting general suppression on aggression [55]. Additionally, a series of studies have revealed a role for oxytocin signaling in the LS in modulating animals' emotional state after social defeat. Microdialysis experiments first demonstrated that oxytocin is released in the LS during acute social defeat [56]. However, initial effort to antagonize the oxytocin receptor in the LS, either during defeat or after 24 hours, failed to induce any change in social fear [56]. Later, it was found that antagonizing oxytocin receptors in the LS abolished defeat-induced exaggeration of conditioned fear response. Interestingly, the same manipulation also diminished the social buffering-induced dampening of conditioned fear responses [57•]. Thus, LS may play a role in changing the emotional state of the animal after both positive and negative social experiences.

The role of medial hypothalamus in social defense and social fear

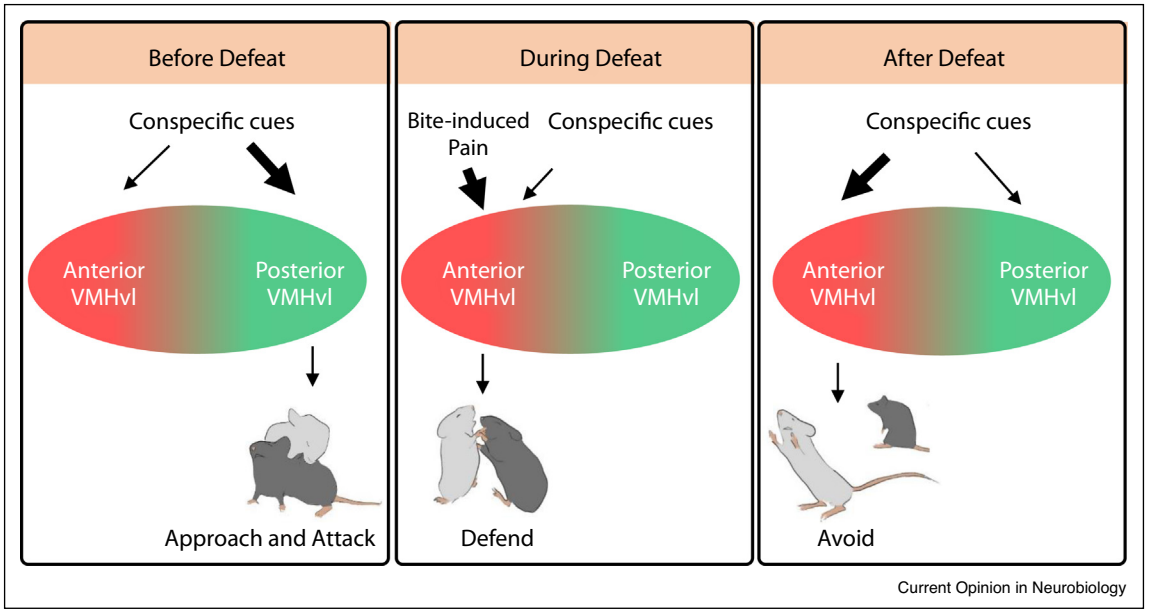
Medial amygdala

Thus far, defeat and classical fear conditioning recruit many of the same brain regions to mediate behavioral changes towards the aggressor or a conditioned cue. Social defeat, however, differs from the classical fear conditioning in that the latter uses simple auditory and visual cues as conditioned stimuli whereas the conditioned stimulus during defeat is a combination of cues associated with the conspecific, involving multiple sensory modalities. For rodents, among all the sensory cues associated with a conspecific, olfactory cues are particularly important and detected by both the main olfactory system (for general volatiles) and accessory olfactory system (for pheromones) [58]. Those olfactory cues converge onto the medial amygdala (MEA) through a massive direct projection from the accessory olfactory bulb and indirect projection from the main olfactory bulb via cortical amygdala [58]. Immediate early gene studies consistently found a high level of activity in the MEA after defeat [59–61]. Lesioning the MEA impairs both the acquisition and expression of defeat-induced social fear while blocking protein synthesis in the MEA has no effect [31]. Thus, the MEA appears to be an important sensory relay of aggressor-related information but is not a site of plasticity that supports defeat-induced behavior change. Does the MEA relay aggressor-related sensory information to the BLA for memory formation? Answers to this question remain ambiguous. While the MEA provides a sparse to moderate input to the BLA, depending on the subregion, the vast majority of the MEA fibers end in the medial hypothalamus [62].

Ventromedial hypothalamus, ventrolateral part

Consistent with the strong projection from the MEA to the medial hypothalamus, immediate early gene mapping and *in vivo* recordings have shown that cells in several medial hypothalamic nuclei, such as the medial preoptic nucleus, ventromedial hypothalamus ventrolateral part (VMHvl), and premammillary nucleus strongly respond to conspecific olfactory cues [63–69]. Among those regions, the ventromedial hypothalamus (VMH) also receives ascending pain signals from the lateral parabrachial nucleus (lPBN) [70]. Thus, it is well positioned to integrate defeat-associated CS (aggressor-related olfactory cues) and US (biting-induced pain) information, two key ingredients for associative learning. Does synaptic plasticity occur in the VMH to support a CS-US association that ultimately results in social avoidance towards the CS? Answers to this question remain unknown although several lines of evidence suggest that VMHvl is capable of driving social fear and avoidance. Using an innovative method named CANE (capturing activated neural ensembles), Sakurai *et al.* captured VMHvl cells that are activated during defeat and found that re-activation of the captured cells elicited fear responses towards a benign conspecific [71•]. This result is similar to findings in the BLA — when the shock-induced c-Fos expressing cells in the BLA were reactivated, animals showed increased fear-like behavior, for example, immobility [72]. Thus, both VMHvl and BLA contain the neural substrates sufficient to drive fear-like behaviors. Furthermore, inactivation of the VMHvl and its surrounding area reduces social avoidance towards the aggressor one day after defeat [8•], suggesting that the VMHvl activity is necessary for defeat-induced social fear. Our recent study further revealed functional heterogeneity of the VMHvl cells — anterior VMHvl estrogen receptor alpha (Esr1) expressing cells are preferentially activated during defeat while the posterior VMHvl Esr1 cells are most activated during attack [17•]. Optogenetic activation of the anterior VMHvl Esr1 cells elicits cornering, upright postures, and avoidance of a conspecific, while optogenetic activation of the posterior VMHvl Esr1 cells elicits approach, close investigation, and attack of a social target [17•]. Thus, we speculate that conspecific cues could be directed to either the anterior VMHvl cells to drive social avoidance or posterior VMHvl cells to drive approach and attack (Figure 3). During defeat, VMHvl anterior cells may undergo long-term potentiation, which results in preferential activation of the 'social avoidance' cells by conspecific cues during future encounters. It is worth noting that two functionally distinct and topographically organized neural populations also exist in the BLA. Kim *et al.* found that BLA cells expressing *Rspo2*+ are concentrated in the anterior region and represent negative experience (e.g. foot shock), and activating those cells elicits negative behaviors (e.g. immobility), whereas *Ppplr1b*+ cells are concentrated in the posterior region, are activated by positive experience (e.g. eating peanut oil), and elicit positive behaviors (e.g. self-stimulation) [73]. The similar Ying-Yang organization pattern in the BLA and VMHvl is intriguing and may suggest this as a common and efficient way to assign values to neutral sensory inputs. Interestingly, Rspo2+ and Ppp1r1b+ cells establish reciprocal inhibition [73], which may be an important mechanism to ensure CS evoke either approach or avoidance at any given time. It will be

Figure 3



Defeat learning hypothesis at the VMHvl. Before defeat, conspecific cues preferentially activate posterior VMHvl, eliciting approach and attack. During defeat, anterior VMHvl cells are activated by painful bites, driving defensive behaviors. Repeated pairing of pain during defeat and multimodal inputs from the aggressor leads to potentiation of synapses carrying aggressor cues. Consequently, aggressor cues become sufficient to preferentially drive avoidance behaviors in future aggressor encounters. The test mouse is shown in light gray.

interesting to investigate whether similar reciprocal inhibition exists between the anterior and posterior VMHvl cells.

In addition to a role in mediating social fear after defeat, VMHvl is also critical for active defense against an acute attack. *In vivo* recordings revealed that anterior VMHvl increases activity acutely when the animal actively defends against an attack [17•]. Strikingly, when the VMHvl Esr1 cells were optogenetically inhibited, the animals were compromised in their ability to defend effectively to terminate an attack. As a result, the VMHvl inhibited animals received much longer attacks than control animals as the attack often ended with the aggressor voluntarily walking away instead of the defender fleeing [17•]. According to these results, we would like to propose a defeat-learning hypothesis operating at the level of the aVMHvl. In this hypothesis, aVMHvl cells are activated by painful bites during defeat and consequently drive active defense, such as flight, upright posture and push, likely in part through their projection to the PAG [17•]. During defeat, anterior VMHvl cells simultaneously receive inputs carrying aggressor related sensory information and due to its repeated paring with the VMHvl spiking, driven by the painful bites, the synapses carrying the aggressor cues undergo long-term potentiation. As a result, sensory cues from the aggressor become effective in driving aVMHvl cells and inducing social defense in future encounters (Figure 3). Future studies using various circuit dissection and *in vivo* and *in vitro* recording tools will help to test this hypothesis.

Dorsal part of the premammillary nucleus

Other regions showing strong c-Fos activation after defeat include the dorsal part of the premammillary nucleus (PMd) [16•]. PMd is unique in that it is activated only after defeat and not after attack, suggesting that it specifically mediates aggressor-coping behaviors [16•]. In accordance with this observation, Canteras's group performed a series of experiments to investigate the function of the PMd during aggressor encounters. They found that excitotoxic PMd lesions in rats caused a dramatic decrease in fear responses towards the aggressor [16•]. The lesioned animals showed significant decrease in freezing and submissive postures (e.g. lying on their back), and continuously approached the aggressor even though they received comparable amount of attacks from the aggressor as the control animals [16•]. Additionally, PMd also shows elevated c-Fos expression when the animal is exposed to a defeat-associated context [9]. Pharmacological blockade of the PMd reduced the fear responses towards the defeat-associated context [9]. Tracing studies revealed that PMd projects densely to the dorsomedial and lateral PAG [74]. Lesion of these PAG areas similarly reduces fear responses towards the defeat-associated context [9]. Whether the PMd is merely a relay for fear expression or is a storage site

for fear memory towards the aggressor after defeat remains to be investigated.

Other hypothalamic areas

VMHvl and PMd are not directly connected, but VMHvl could potentially pass information to PMd via the lateral hypothalamic area juxtadorsomedial region (LHAjd) [75]. When the LHAdj is lesioned, defeated animals show a trend of decrease in social fear towards the aggressor [76]. Besides the VMHvl and PMd, several other medial hypothalamus nuclei also show elevated c-Fos after defeat, including lateral preoptic nucleus, anterior hypothalamic nucleus and dorsomedial hypothalamus [16•,27,59,60,77–79]. Indeed, there are generally many more cells showing c-Fos expression in defeated animals in comparison to the winning animals [60], suggesting that an extensive network of brain regions are recruited to cope with acute assaults as well as adjust behaviors in the future. The precise functions of each of these activated regions await to be elucidated.

Concluding remarks

When an animal encounters a social threat, multiple neural circuits swing into action to allow the animal to defend, run, and learn to avoid the threat in the future. On the one hand, decades of research suggest the BLA-centered associative fear learning circuit is recruited during defeat to associate the aggressor with the traumatic experience and drive subsequent fear responses towards the aggressor. On the other hand, recent studies point towards an important role of the medial hypothalamus, including VMHvl and PMd, in expressing social fear and active defense against the aggressor. This is interesting as the BLA-CEA circuit and VMHvl-PMd circuit are generally considered as distinct circuits for mediating learned versus innate fear [80]. How do the BLA and medial hypothalamus circuits interact? Do they function in series or in parallel, that is, do they play redundant or complementary roles during social defeat? Is the social fear memory stored primarily in the BLA or also in the medial hypothalamic circuit? Future studies combining well-designed behavioral paradigms that isolate various aspects of aggressor coping (e.g. active defense, social fear formation and expression) and temporally and molecularly precise functional manipulation and recording tools will advance our understanding regarding the neural coping of social defeat and its potential malfunction in psychiatric conditions.

Conflict of interest statement

Nothing declared.

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