Published in final edited form as:

Curr Opin Behav Sci. 2018 December ; 24: 104–112. doi:10.1016/j.cobeha.2018.06.011.

Functions of medial hypothalamic and mesolimbic dopamine circuitries in aggression

Takashi Yamaguchi^{1,2} and Dayu Lin^{2,3,4}

¹ Laboratory for Advanced Brain Functions, Institute for Protein Research, Osaka University, Osaka, Japan

² Neuroscience Institute, New York University School of Medicine, 522 First Avenue, New York, NY 10016, USA

³ Department of Psychiatry, New York University School of Medicine, 1 Park Avenue, New York, NY 10016, USA

⁴ Center for Neural Science, New York University, 4 Washington Place, New York, NY 10003, USA

Abstract

Aggression is a crucial survival behavior: it is employed to defend territory, compete for food and mating opportunities, protect kin, and resolve disputes. Although widely differing in its behavioral expression, aggression is observed across many species. The neural substrates of aggression have been investigated for nearly a century and two highly conserved circuitries emerge as critical substrates for generating and modulating aggression. One circuitry centers on the medial hypothalamus. Activity of the medial hypothalamic cells closely correlates with attacks and can bi-directionally modulate aggressive behaviors. The other aggression-related circuit involves the mesolimbic dopamine cells. Dopaminergic antagonists are the most commonly used treatment for suppressing human aggression in psychotic patients. Animal studies support essential roles of dopaminergic signaling in the nucleus accumbens in assessing the reward value of aggression and reinforcing the aggressive behaviors. In this review, we will provide an overview regarding the functions of medial hypothalamus and dopaminergic system in mediating aggressive behaviors and the potential interactions between these two circuitries.

Hypothalamic control of aggressive behaviors

The role of the hypothalamus in the generation of aggression is well-established through decades of work in many species. Since the initial work by Walter Hess demonstrating that aggression could be elicited by electrical stimulation in the cat hypothalamus [1], dozens of studies have replicated this result and demonstrated that hypothalamic stimulation is effective in inducing attack or other aggression-related behaviors [2–16] (Table 1). For

Correspondence to: Dayu Lin.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

example, in marmosets and macaques, electric stimulation of the ventromedial hypothalamus elicited threatening vocalization and short attacks [4,5], while in cats, electric stimulation of medial hypothalamus evoked immediate hissing, piloerection and paw strikes towards another cat (<https://www.youtube.com/watch?v=Kj2MqEMpj4U>) [6,10]. In rats, a large hypothalamic attack area (HAA) from which an attack could be artificially elicited was mapped using systematic micro-stimulation [2,7,17]. Pharmacological manipulation of the hypothalamus can also facilitate aggression. Ferris et. al. injected vasopressin into the anterior hypothalamus of the hamster and observed increased aggressive behaviors [9]. More recently, by capitalizing on advances in mouse genetics and cell-type specific manipulation, a series of studies from our lab and others identified a subnucleus in the medial hypothalamus, the ventrolateral part of the ventromedial hypothalamus (VMHvl), as an essential locus for aggression in both male and female mice [11–14]. Optogenetic activation of the VMHvl cells, especially those expressing estrogen receptor alpha/progesterone receptor (overlap nearly 100%), induced immediate attack whereas either pharmacogenetic or optogenetic inactivation of the VMHvl suppressed naturally occurring aggression [11–14,18]. *In vivo* electrophysiological recording revealed that single units in the VMHvl exhibit an acute activity increase both while animals investigate aggression-provoking olfactory cues and during inter-male aggression [11,19–22].

Recent experiments have also confirmed that the role of the hypothalamus during aggression extends beyond acute attack. Early microstimulation experiments demonstrated that that hypothalamic stimulation can promote approach towards a potential attack target [23], suggesting the involvement in the preparatory or appetitive aspects prior to aggression. To specifically test the role of VMHvl in promoting preparatory or aggression-seeking behaviors, our recent study adopted an operant responding task to temporally separate the seeking and action phases of aggression. During the task, the animal learns to nose poke to gain access to a weaker intruder. Over 60% of animals learned the task, exhibited repeated poking of the intruder-paired port and attacked intruder immediately upon its introduction. Inactivation of the VMHvl decreased the poking rate whereas optogenetic activation of the VMHvl during inter-poke-interval shortened the latency to the next poke. Furthermore, *in vivo* recording demonstrated that the VMHvl activity prior to and during poking gradually increased over the days of training as the animals learned the task [22]. These results suggest the involvement of the VMHvl in generating learned seeking or preparatory behaviors in addition to attack.

A neural circuits approach to research on social behavior has revealed that the VMHvl is embedded within a larger amygdalo-hypothalamic circuit whose nodes have distinct roles in aggression (Figure 1). Here we will summarize the roles of other nodes within this extended circuit that project to the VMHvl. (1) The medial amygdala is often referred to as the “olfactory” amygdala due to the massive converging inputs from the accessory and main olfactory systems [24,25]. It projects to the VMHvl both directly and indirectly via the bed nucleus of stria terminalis [26]. Optogenetic activation of GABAergic neurons but not glutamatergic neurons in the medial amygdala, is sufficient to driving attack in male mice [27]. Optogenetic inactivation of medial amygdala GABAergic cells or permanent ablation of a subpopulation of GABAergic cells expressing aromatase reduces inter-male aggression [27,28]. (2) The ventral premammillary nucleus (PMv) is situated posterior to the VMHvl

and provides strong glutamatergic inputs to the VMHvI [29,30]. It receives strong inputs from the medial amygdala and thus is highly responsive to conspecific olfactory cues [30–32]. Lesioning the ventral premammillary nucleus significantly reduces maternal aggression and intruder-induced Fos expression in the VMHvI [31]. Most recently, Stagkourakis et al. found that optogenetic activation of dopamine transporter (DAT) expressing cells in the PMv can elicit attack in spontaneously aggressive, but not non-aggressive, male mice, suggesting a role in enhancing aggressive behaviors [33]. (3) Neurons in the subparaventricular zone regulate aggressive behaviors through monosynaptic and disynaptic projections to the VMHvI [34]. It is a major postsynaptic target of the suprachiasmatic nucleus (SCN) which is an important brain region for controlling circadian rhythm [35]. Todd et. al. found that VMH-projecting subparaventricular zone GABAergic cells show low activity during early night when the aggression level is high and high activity during early day when the aggression level is low [34]. Pharmacogenetic inhibition of subparaventricular zone GABAergic cells increased aggression during early day but not early night. The subparaventricular zone GABAergic projection to the VMH is essential for controlling the daily rhythm of aggression. (4) The lateral septum is another source of inhibition to the VMHvI [36]. Lesions in the septum cause an increase in aggression, a phenomenon commonly referred to as “septal rage” [37]. Interestingly, we found that the lateral septum inhibited attack-excited cells while it activated attack-inhibited cells in the VMHvI, suggesting that lateral septum input has a net effect on suppressing VMHvI activation during aggression. When the pathway from the lateral septum to VMHvI was activated optogenetically, inter-male aggression was significantly reduced [36].

Decades of lesion and electric stimulation studies in a variety of species established an essential role of medial hypothalamus in generating aggressive behaviors. Recent circuit map studies in mice confirmed these earlier findings and provided a more detailed view regarding the medial hypothalamic aggression circuit. Altogether, these works have now established the VMHvI and its connected regions as key neural substrates for generating aggressive behaviors in mice and beyond.

Mesolimbic dopamine control of aggressive behaviors

A parallel set of studies strongly support an essential role of dopaminergic signaling in modulating aggression [38] (Figure 2). To begin, dopamine antagonists represent the most frequent and enduring treatment for suppressing human aggression. Haloperidol, a D2 receptor antagonist, has been used for decades to control aggressive behaviors associated with a wide range of psychotic conditions [39–45]. However, the effect of haloperidol in decreasing aggression is closely linked to the sedative effects caused by the drug, making it a less than ideal treatment. Other D2 receptor antagonist, such as risperidone, and D1/D2 combined antagonist, Zuclopenthixol, were also found to be effective in suppressing aggression in autistic adults, schizophrenia patients and children with bipolar disorders [46–48]. Consistent with effects in humans, systemic injection of dopamine receptor antagonists in rodents are effective in reducing attack [49,50]. However, the effect of dopamine receptor agonists on aggression varies from study to study [51–53] although methamphetamine, a drug that increases the dopamine release by reversing the DAT action, consistently facilitated aggression [54,55].

More region-specific manipulation of dopamine signaling has revealed that the mesolimbic dopamine pathway (the connection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc)) is the key circuit for controlling aggression. The most direct evidence comes from a recent study by Yu et al. In this study, they crossed DAT-Cre mouse line with a Cre-dependent channelrhodopsin reporter line and found that light activation of VTA in those mice significantly enhanced attack towards both male and female intruders [56]. It is worth noting that in Yu's study, the pulsed blue light was delivered continuously during the 10-minutes interaction between the test mouse and the intruder. Thus, it is possible that the VTA activation increases attack by enhancing the perceived rewarding value of aggression or in other words aggressive motivation instead of eliciting time-locked attacks as hypothalamic stimulation does.

The role of the mesolimbic dopaminergic pathway in the rewarding effect of aggression was specifically assessed using an operant learning paradigm. In a study by Couppis and Kennedy, they trained the male mice to nose poke to gain access to a weak male intruder using a variable ratio (VR-5) schedule [57]. Under this schedule, the animals were "rewarded" after 5 pokes on average although the exact number of pokes to trigger the reward varies from trial to trial. In well-trained animals, the authors injected D1 or D2 receptor antagonist into the NAc and found that both D1 and D2 receptor antagonists significantly reduced nose-poking rate at dosages that did not compromise locomotion. Under those dosages, the aggressive behaviors during intruder encounters were only mildly impaired (decrease biting events by 10%). Consistent with findings in mice, D2 receptor antagonist in the NAc suppressed aggression in hyper-aggressive low-anxiety rats [58]. These animal studies are well collaborated with human results, supporting a role of D2 antagonists in suppressing aggressive behaviors.

Several lines of evidences support a role of dopamine in reinforcing aggressive behaviors after winning experience. Systemic injection of either D1 or D2 receptor antagonists after winning blocked the winning induced increase in aggression [59]. Consistent with these functional data, the natural dopamine in NAc was found to reach its peak value 20–30 min following repeated aggression [60,61]. The winning induced change in aggression circuit may partly occur in the mesolimbic dopamine pathway itself. After the mice won contests for 20 consecutive days, the mesolimbic VTA tyrosine hydroxylase (TH) and DAT mRNA levels increased and this increase persisted up to 14 days following the last win [62]. The winning-induced increase in aggression could be mimicked by artificial increase in dopamine. Repeated systemic injections of methamphetamine, increased aggression 15 min and 20 h later [63]. The sustained increase in aggression 20 hours after the drug application is particularly interesting as it supports a role of high level of dopamine in altering the aggression circuit to cause long-term shift in aggressive behaviors. An additional line of evidence that supports a role of the VTA in mediating the rewarding effect of winning comes from studies of an upstream region of the VTA, the lateral habenula (LHb). LHb projects densely to the rostromedial tegmental nucleus (RMTg) which in turn inhibits the dopaminergic cells in the VTA [64,65]. Activation of the LHb terminals suppresses 90% of VTA dopamine neurons [66]. Golden et al. used a place preference conditioning paradigm to demonstrate the rewarding value of winning: after aggressive mice attacked and subordinated an intruder, they developed a preference for the intruder-paired chamber. When

the LHb was artificially activated by optogenetically silencing an inhibitory input to the LHb, the rewarding effect of winning was blocked [67]. Thus, reducing activity of the LHb which presumably increasing activity of VTA dopamine neurons is essential for the rewarding effect of winning.

The aforementioned results suggest that one major function of the mesolimbic dopamine is to signal the rewarding value of future or past aggressive behaviors. A decrease in reward expectancy of future attacks decreases actions leading to attack. A high reward after winning experience reinforces future aggressive behaviors. Whether the dopamine signaling in the NAc plays a role in acute execution of attack awaits to be investigated in future studies.

Interaction between the VTA and hypothalamic aggression circuit

The medial hypothalamus and mesolimbic dopamine systems are likely not operating independently. They are several routes for potential interaction, allowing these two circuits to work synergistically to mediate aggression (Figure 3). While the VMHvl projection to the VTA is relatively sparse, VMHvl projects densely to the medial preoptic area (MPOA) and lateral hypothalamus, which in turn project moderately to the VTA [71,72]. Our recent study in female mice found that cells in the MPOA provide inhibitory inputs to virtually 100% non-dopaminergic, presumably mainly GABAergic, cells in the VTA [73]. Since VTA GABAergic cells inhibit dopaminergic cells, inputs from the MPOA to the VTA is expected to disinhibit the dopaminergic cells [74]. Indeed, McHenry et al. showed that optogenetic activation of the MPOA neurotensin expressing cells result in time-locked release of dopamine in the nucleus accumbens [75]. Similarly, the lateral hypothalamus has also been shown to target VTA GABAergic cells and activation of lateral hypothalamic inputs to the VTA causes dopamine release in the VTA [76]. Thus, there are anatomical connections from the VMHvl to VTA to allow information transfer. Future studies combining simultaneous recordings at VTA and medial hypothalamus and pathway specific inhibition during aggressive behaviors will help address which aspects of aggression-related information may be relayed from the medial hypothalamus to the VTA.

Aggression related information may also be relayed to the VTA through structures upstream of the VMHvl, such as BNST [77]. BNST is a heterogeneous structure containing over 12 subnuclei [78]. While the anterior BNST has been mostly indicated in anxiety and strongly interconnected with central amygdala, a critical region for coping threat, the posterior BNST is strongly interconnected with medial amygdala and likely processes social information [79]. Both anterior and posterior BNST also have access to pheromone information via direct inputs from the accessory olfactory bulb [80]. When the BNST is impaired either by lesion or by gene knockout, the aggression level decreases [81,82]. So far, the function of the BNST to VTA projection has only been examined in the context of anxiety. It was found that BNST cells preferentially target the TH negative cells, presumably GABAergic interneurons in the VTA. The glutamatergic projection from the BNST to the VTA is anxiogenic while the GABAergic BNST projection to the VTA is anxiolytic [83]. The role of BNST in relaying aggression related information to the VTA remain to be investigated in future studies.

The dopamine release, possibly promoted by the hypothalamic neuron activation, can in turn facilitate the excitation of the hypothalamic neurons that drive attack. In a series of electric stimulation studies, it was found that systemic administration of methamphetamine or apomorphine (D2/D1 receptor agonist) decreases the thresholds for hypothalamically elicited rage responses in cats whereas haloperidol (D2 receptor antagonist) elevated the defensive rage threshold [84,85]. When D2 receptor antagonist, but not D1 receptor antagonist, is injected prior to apomorphine, the facilitating effect of apomorphine was blocked, suggesting that the facilitating effect of dopamine on aggression is through D2 receptor [86]. In a follow-up study with more targeted manipulation, apomorphine or a D2 agonist injection into the anterior hypothalamus facilitates hypothalamically evoked rage responses whereas microinjections of D2 antagonist, but not a D1 antagonist, elevated current thresholds to evoke rage responses [87]. These results suggest that the dopamine can facilitate attack through its action in the hypothalamus, possibly by acting onto the very hypothalamic cells that drive attacks. Notably, the source of dopaminergic inputs to the hypothalamic attack neurons remain unknown, but likely originated from both within and outside of the hypothalamus, including the VTA [88,89].

Future directions

Decades of research has established essential roles of medial hypothalamus and mesolimbic dopaminergic circuit in aggression. Specifically, the medial hypothalamus appears to be mostly involved in driving both preparatory and consummatory actions related to attack whereas the mesolimbic dopamine system may encode the rewarding value of aggression, either expected or experienced, and modifies the aggression circuit based on winning or losing experience. The medial hypothalamic and mesolimbic dopamine circuit can positively influence each other and several neural pathways have been identified to allow potential interaction. Future studies using pathway specific manipulation and large scale *in vivo* recording will address the pathways, timing and functional roles of the cross-talk between these two systems in more details.

Acknowledgement

This research was supported by a JSPS oversea fellowship (T.Y.), a Uehara postdoctoral fellowship (T.Y.), NIH 1R01MH101377, 1R21MH105774–01A1 and 1R21HD090563–01A1 (D.L.), the Mathers Foundation (D.L.) and Irma T. Hirschl Career Scientist Award (D.L.).

References

1. Hess WR: Stammganglien-reizversuche. *Berichte der gesamten. Physiologie* (1928) 42(554– 555.
 2. Siegel A, Roeling TAP, Gregg TR, Kruk MR: Neuropharmacology of brain-stimulation-evoked aggression. *Neurosci Biobehav R* (1999) 23(3):359–389.
- This paper provides an overview of the hypothalamic stimulation induced attack in cats and rats and how various neuromodulators affect the hypothalamic evoked aggression responses.
3. Kruk MR: Hypothalamic attack: A wonderful artifact or a useful perspective on escalation and pathology in aggression? A viewpoint. *Curr Top Behav Neurosci* (2014).
 4. Robinson BW: Vocalization evoked from forebrain in macaca mulatta. *Physiology & Behavior* (1967) 2(4):345–&.

5. Lipp HP, Hunsperger RW: Threat, attack and flight elicited by electrical stimulation of the ventromedial hypothalamus of the marmoset monkey *callithrix jacchus*. *Brain Behav Evol* (1978) 15(4):260–293. [PubMed: 100172]
6. Egger MD, Flynn JP: Effects of electrical stimulation of the amygdala on hypothalamically elicited attack behavior in cats. *J Neurophysiol* (1963) 26(705–720. [PubMed: 14065322]
7. Kruk MR, Vanderpoel AM, Meelis W, Hermans J, Mostert PG, Mos J, Lohman AHM: Discriminant-analysis of the localization of aggression-inducing electrode placements in the hypothalamus of male-rats. *Brain Res* (1983) 260(1):61–79. [PubMed: 6681724]
8. Roberts WW, Steinber MI, Means LW: Hypothalamic mechanisms for sexual aggressive and other motivational behaviors in opossum *didelphis virginiana*. *J Comp Physiol Psych* (1967) 64(1):1–&.
9. Ferris CF, Melloni RH, Jr., Koppel G, Perry KW, Fuller RW, Delville Y: Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. *J Neurosci* (1997) 17(11):4331–4340. [PubMed: 9151749]
10. Siegel A, Pott CB: Neural substrates of aggression and flight in the cat. *Prog Neurobiol* (1988) 31(4):261–283. [PubMed: 3045882]
- 11•. Lin D, Boyle MP, Dollar P, Lee H, Lein ES, Perona P, Anderson DJ: Functional identification of an aggression locus in the mouse hypothalamus. *Nature* (2011) 470(7333):221–226.
This paper identified the VMHvI as the locus that controls aggressive behaviors in male mice using a combination of optogenetic and pharmacogenetic manipulations and in vivo single unit recording.
[PubMed: 21307935]
- 12•. Yang CF, Chiang MC, Gray DC, Prabhakaran M, Alvarado M, Juntti SA, Unger EK, Wells JA, Shah NM: Sexually dimorphic neurons in the ventromedial hypothalamus govern mating in both sexes and aggression in males. *Cell* (2013) 153(4):896–909.
This paper identified the VMHvI cells that express progesterone receptor as the key population for aggressive behaviors in male mice with cell-type specific ablation.
[PubMed: 23663785]
- 13•. Lee H, Kim DW, Remedios R, Anthony TE, Chang A, Madisen L, Zeng H, Anderson DJ: Scalable control of mounting and attack by *esr1+* neurons in the ventromedial hypothalamus. *Nature* (2014) 509(7502):627–632.
This paper demonstrated that optogenetic activation of VMHvI cells that express estrogen receptor alpha can acutely evoke aggressive behaviors in male mice.
[PubMed: 24739975]
- 14•. Hashikawa K, Hashikawa Y, Tremblay R, Zhang J, Feng JE, Sabol A, Piper WT, Lee H, Rudy B, Lin D: *Esr1+* cells in the ventromedial hypothalamus control female aggression. *Nat Neurosci* (2017).
Using optogenetic and pharmacogenetic manipulations and in vivo recordings, this paper demonstrates that VMHvI cells that express estrogen receptor alpha are essential for aggressive behaviors not only in male mice, but also in female mice.
15. Lammers JH, Kruk MR, Meelis W, van der Poel AM: Hypothalamic substrates for brain stimulation-induced attack, teeth-chattering and social grooming in the rat. *Brain Res* (1988) 449(1–2):311–327. [PubMed: 3395851]
16. Renfrew JW: Intensity function and reinforcing properties of brain stimulation that elicits attack. *Physiology & Behavior* (1969) 4(4):509–&.
17. Kruk MR, Van der Laan CE, Mos J, Van der Poel AM, Meelis W, Olivier B: Comparison of aggressive behaviour induced by electrical stimulation in the hypothalamus of male and female rats. *Prog Brain Res* (1984) 61(303–314. [PubMed: 6543251]
18. Yang T, Yang CF, Chizari MD, Maheswaranathan N, Burke KJ, Jr., Borius M, Inoue S, Chiang MC, Bender KJ, Ganguli S, Shah NM: Social control of hypothalamus-mediated male aggression. *Neuron* (2017).

19. Falkner AL, Dollar P, Perona P, Anderson DJ, Lin D: Decoding ventromedial hypothalamic neural activity during male mouse aggression. *J Neurosci* (2014) 34(17):5971–5984. [PubMed: 24760856]
20. Hashikawa K, Hashikawa Y, Falkner A, Lin D: The neural circuits of mating and fighting in male mice. *Curr Opin Neurobiol* (2016) 38(27–37). [PubMed: 26849838]
21. Hashikawa Y, Hashikawa K, Falkner AL, Lin D: Ventromedial hypothalamus and the generation of aggression. *Front Syst Neurosci* (2017) 11(94). [PubMed: 29375329]
- 22••. Falkner AL, Lin D: Recent advances in understanding the role of the hypothalamic circuit during aggression. *Front Syst Neurosci* (2014) 8(168)

This paper used a self-initiated aggression seeking task to separate the seeking and action phases of aggression. By using a variety of recording and functional manipulation tools, it demonstrates that VMHvl drives both aggression seeking and attack.

[PubMed: 25309351]

23. Falkner AL, Grosenick L, Davidson TJ, Deisseroth K, Lin D: Hypothalamic control of male aggression-seeking behavior. *Nat Neurosci* (2016) 19(4):596–604. [PubMed: 26950005]
24. Roberts WW, Kiess HO: Motivational properties of hypothalamic aggression in cats. *J Comp Physiol Psychol* (1964) 58(187–193). [PubMed: 14215388]
25. Keshavarzi S, Power JM, Albers EH, Sullivan RK, Sah P: Dendritic organization of olfactory inputs to medial amygdala neurons. *J Neurosci* (2015) 35(38):13020–13028. [PubMed: 26400933]
26. Bergan JF, Ben-Shaul Y, Dulac C: Sex-specific processing of social cues in the medial amygdala. *eLife* (2014) 3(e02743). [PubMed: 24894465]
27. Canteras NS, Simerly RB, Swanson LW: Organization of projections from the medial nucleus of the amygdala: A phal study in the rat. *J Comp Neurol* (1995) 360(2):213–245. [PubMed: 8522644]
28. Hong W, Kim DW, Anderson DJ: Antagonistic control of social versus repetitive self-grooming behaviors by separable amygdala neuronal subsets. *Cell* (2014) 158(6):1348–1361. [PubMed: 25215491]
29. Unger EK, Burke KJ, Yang CF, Bender KJ, Fuller PM, Shah NM: Medial amygdalar aromatase neurons regulate aggression in both sexes. *Cell Rep* (2015) 10(4):453–462. [PubMed: 25620703]
30. Canteras NS, Simerly RB, Swanson LW: Projections of the ventral premammillary nucleus. *J Comp Neurol* (1992) 324(2):195–212. [PubMed: 1430329]
31. Soden ME, Miller SM, Burgeno LM, Phillips PE, Hnasko TS, Zweifel LS: Genetic isolation of hypothalamic neurons that regulate context-specific male social behavior. *Cell reports* (2016) 16(2):304–313. [PubMed: 27346361]
32. Motta SC, Guimaraes CC, Furigo IC, Sukikara MH, Baldo MVC, Lonstein JS, Canteras NS: Ventral premammillary nucleus as a critical sensory relay to the maternal aggression network. *P Natl Acad Sci USA* (2013) 110(35):14438–14443.
33. Cavalcante JC, Bittencourt JC, Elias CF: Distribution of the neuronal inputs to the ventral premammillary nucleus of male and female rats. *Brain Res* (2014) 1582(77–90). [PubMed: 25084037]
34. Stagkourakis AS, Spigolon G, Williams P, Prozman J, Fisone G, Broberger C: The role of the ventral premammillary nucleus in intermale mouse aggression and hierarchy
35. Todd WD, Fenselau H, Wang JL, Zhang R, Machado NL, Venner A, Broadhurst RY, Kaur S, Lynagh T, Olson DP, Lowell BB et al.: A hypothalamic circuit for the circadian control of aggression. *Nat Neurosci* (2018).
36. Klein DC, Moore RY, Reppert SM: *Suprachiasmatic nucleus : The mind's clock*. Oxford University Press, New York (1991).
37. Wong LC, Wang L, D'Amour JA, Yumita T, Chen G, Yamaguchi T, Chang BC, Bernstein H, You X, Feng JE, Froenke RC et al.: Effective modulation of male aggression through lateral septum to medial hypothalamus projection. *Curr Biol* (2016) 26(5):593–604. [PubMed: 26877081]
38. Schnurr R: Localization of the septal rage syndrome in long-evans rats. *J Comp Physiol Psychol* (1972) 81(2):291–296. [PubMed: 4563588]

39. de Almeida RM, Ferrari PF, Parmigiani S, Miczek KA: Escalated aggressive behavior: Dopamine, serotonin and gaba. *Eur J Pharmacol* (2005) 526(1–3):51–64. [PubMed: 16325649]
 40. Ostinelli EG, Brooke-Powney MJ, Li X, Adams CE: Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation). *Cochrane Database Syst Rev* (2017) 7(CD009377. [PubMed: 28758203]
 41. Calver L, Drinkwater V, Gupta R, Page CB, Isbister GK: Droperidol v. Haloperidol for sedation of aggressive behaviour in acute mental health: Randomised controlled trial. *Br J Psychiatry* (2015) 206(3):223–228. [PubMed: 25395689]
 42. Carlyle W, Ancill RJ, Sheldon L: Aggression in the demented patient: A double-blind study of loxapine versus haloperidol. *Int Clin Psychopharmacol* (1993) 8(2):103–108. [PubMed: 8345158]
 43. Khushu A, Powney MJ: Haloperidol for long-term aggression in psychosis. *Cochrane Database Syst Rev* (2016) 11(CD009830. [PubMed: 27889922]
 44. Chandler A, Freeze-Ramsey R, Seupaul RA: Is the use of haloperidol a safe and effective method of tranquilization for patients with psychosis-induced aggression or agitation? *Ann Emerg Med* (2014) 63(6):757–758. [PubMed: 24275570]
 45. Huf G, Alexander J, Allen MH, Raveendran NS: Haloperidol plus promethazine for psychosis-induced aggression. *Cochrane Database Syst Rev* (2009) 3:CD005146.
 46. Huf G, Alexander J, Gandhi P, Allen MH: Haloperidol plus promethazine for psychosis-induced aggression. *Cochrane Database Syst Rev* (2016) 11(CD005146. [PubMed: 27885664]
 47. McDougale CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH: A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Archives of general psychiatry* (1998) 55(7):633–641. [PubMed: 9672054]
 48. Grinshpoon A, Moskowitz M, Valevski A, Kreizman A, Palei L, Mar M, Weizman A: Zuclopenthixol, d(1)/d(2) antagonist, for treatment of chronic aggressive schizophrenia and psychotic oligophrenic patients. *Eur Psychiatry* (1998) 13(5):273–275. [PubMed: 19698639]
 49. Ercan ES, Ardic UA, Kandulu R, Yektas C: Zuclopenthixol acetate treatment in children with bipolar disorder and severe aggression. *J Clin Psychopharmacol* (2011) 31(3):397–398. [PubMed: 21532374]
 50. Fragoso VM, Hoppe LY, de Araujo-Jorge TC, de Azevedo MJ, Campos JD, Cortez CM, de Oliveira GM: Use of haloperidol and risperidone in highly aggressive swiss webster mice by applying the model of spontaneous aggression (msa). *Behav Brain Res* (2016) 301(110–118. [PubMed: 26698401]
 51. Kudryavtseva NN, Lipina TV, Koryakina LA: Effects of haloperidol on communicative and aggressive behavior in male mice with different experiences of aggression. *Pharmacol Biochem Behav* (1999) 63(2):229–236. [PubMed: 10371651]
 52. Tidey JW, Miczek KA: Morphine withdrawal aggression: Modification with d1 and d2 receptor agonists. *Psychopharmacology (Berl)* (1992) 108(1–2):177–184. [PubMed: 1357705]
 53. Smith AN, Kabelik D: The effects of dopamine receptor 1 and 2 agonists and antagonists on sexual and aggressive behaviors in male green anoles. *PLoS One* (2017) 12(2):e0172041. [PubMed: 28187160]
 54. Baggio G, Ferrari F: Role of brain dopaminergic mechanisms in rodent aggressive behavior: Influence of (+/-)n-n-propyl-norapomorphine on three experimental models. *Psychopharmacology (Berl)* (1980) 70(1):63–68. [PubMed: 6775337]
 55. Crowley TJ: Dose-dependent facilitation or suppression of rat fighting by methamphetamine, phenobarbital, or imipramine. *Psychopharmacologia* (1972) 27(3):213–222. [PubMed: 4674515]
 56. Miczek KA: Intraspecies aggression in rats: Effects of d-amphetamine and chlordiazepoxide. *Psychopharmacologia* (1974) 39(4):275–301. [PubMed: 4476082]
 - 57•. Yu Q, Teixeira CM, Mahadevia D, Huang Y, Balsam D, Mann JJ, Gingrich JA, Ansorge MS: Dopamine and serotonin signaling during two sensitive developmental periods differentially impact adult aggressive and affective behaviors in mice. *Mol Psychiatry* (2014) 19(6):688–698.
- This paper is the first demonstration that optogenetic activation of dopamine neurons in the VTA increased aggressive behaviors in male mice.
- [PubMed: 24589889]

- 58•. Couppis MH, Kennedy CH: Therewarding effect of aggression is reduced by nucleus accumbens dopamine receptor antagonism in mice. *Psychopharmacology* (2008) 197(3):449–456.

This paper used operant learning task to demonstrate that the reward effect of aggression is reduced after pharmacologically antagonizing the dopamine receptors in the nucleus accumbens. Note that in this paradigm, the reduced nose poking could be interpreted as a decrease in rewarding effect of aggression or a decrease in aggressive motivation.

[PubMed: 18193405]

59. Di Beiderbeck, Reber SO, Havasi A, Bredewold R, Veenema AH, Neumann ID: High and abnormal forms of aggression in rats with extremes in trait anxiety--involvement of the dopamine system in the nucleus accumbens. *Psychoneuroendocrinology* (2012) 37(12): 1969–1980.

[PubMed: 22608548]

60. Becker EA, Marler CA: Postcontest blockade of dopamine receptors inhibits development of the winner effect in the California mouse (*Peromyscus californicus*). *Behav Neurosci* (2015) 129(2): 205–213. [PubMed: 25798633]

- 61•. Ferrari PF, van Erp AM, Tornatzky W, Miczek KA: Accumbal dopamine and serotonin in anticipation of the next aggressive episode in rats. *Eur J Neurosci* (2003) 17(2):371–378.

Using microdialysis, the authors found that the dopamine level in the nucleus accumbens increases when the animals anticipate a fight during a specific time of a day.

[PubMed: 12542674]

- 62•. van Erp AM, Miczek KA: Aggressive behavior, increased accumbal dopamine, and decreased cortical serotonin in rats. *J Neurosci* (2000) 20(24):9320–9325.

Using microdialysis, the authors found that the dopamine level in the nucleus accumbens peaks 20 minutes after repeated aggressive behaviors.

[PubMed: 11125011]

63. Bondar NP, Boyarskikh UA, Kovalenko IL, Filipenko ML, Kudryavtseva NN: Molecular implications of repeated aggression: Th, *dat1*, *snca* and *bdnf* gene expression in the vta of victorious male mice. *PLoS One* (2009) 4(1):e4190. [PubMed: 19142237]

64. Sokolov BP, Cadet JL: Methamphetamine causes alterations in the map kinase-related pathways in the brains of mice that display increased aggressiveness. *Neuropsychopharmacology* (2006) 31(5): 956–966. [PubMed: 16192988]

65. Quina LA, Tempest L, Ng L, Harris JA, Ferguson S, Jhou TC, Turner EE: Efferent pathways of the mouse lateral habenula. *J Comp Neurol* (2015) 523(1):32–60. [PubMed: 25099741]

66. Bourdy R, Barrot M: A new control center for dopaminergic systems: Pulling the vta by the tail. *Trends Neurosci* (2012) 35(11):681–690. [PubMed: 22824232]

67. Brown PL, Palacorolla H, Brady D, Riegger K, Elmer GI, Shepard PD: Habenula-induced inhibition of midbrain dopamine neurons is diminished by lesions of the rostromedial tegmental nucleus. *J Neurosci* (2017) 37(1):217–225. [PubMed: 28053043]

- 68••. Golden SA, Heshmati M, Flanigan M, Christoffel DJ, Guise K, Pfau ML, Aleyasin H, Menard C, Zhang H, Hodes GE, Bregman D et al.: Basal forebrain projections to the lateral habenula modulate aggression reward. *Nature* (2016) 534(7609):688–692.

Authors developed a conditional place preference task to test the rewarding value of winning in male mice. They demonstrated that the basal forebrain projection to the lateral habenula is essential for the aggression related reinforcement learning.

[PubMed: 27357796]

69. Tidey JW, Miczek KA: Social defeat stress selectively alters mesocorticolimbic dopamine release: An in vivo microdialysis study. *Brain Res* (1996) 721(1–2):140–149. [PubMed: 8793094]

70. Anstrom KK, Miczek KA, Budygin EA: Increased phasic dopamine signaling in the mesolimbic pathway during social defeat in rats. *Neuroscience* (2009) 161(1):3–12. [PubMed: 19298844]

71. Puglisialleggra S, Cabib S: Effects of defeat experiences on dopamine metabolism in different brain-areas of the mouse. *Aggressive Behavior* (1990) 16(3–4):271–284.
72. Beier KT, Steinberg EE, DeLoach KE, Xie S, Miyamichi K, Schwarz L, Gao XJ, Kremer EJ, Malenka RC, Luo L: Circuit architecture of vta dopamine neurons revealed by systematic input-output mapping. *Cell* (2015) 162(3):622–634. [PubMed: 26232228]
73. Watabe-Uchida M, Zhu L, Ogawa SK, Vamanrao A, Uchida N: Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* (2012) 74(5):858–873. [PubMed: 22681690]
74. Fang YY, Yamaguchi T, Song SC, Tritsch NX, Lin D: A hypothalamic midbrain pathway essential for driving maternal behaviors. *Neuron* (2018) 98(1):192–207 e110. [PubMed: 29621487]
75. Tan KR, Yvon C, Turiault M, Mirzabekov JJ, Doeberner J, Labouebe G, Deisseroth K, Tye KM, Luscher C: Gaba neurons of the vta drive conditioned place aversion. *Neuron* (2012) 73(6):1173–1183. [PubMed: 22445344]
76. McHenry JA, Otis JM, Rossi MA, Robinson JE, Kosyk O, Miller NW, McElligott ZA, Budygin EA, Rubinow DR, Stüber GD: Hormonal gain control of a medial preoptic area social reward circuit. *Nat Neurosci* (2017) 20(3):449–458. [PubMed: 28135243]
77. Nieh EH, Vander Weele CM, Matthews GA, Presbrey KN, Wichmann R, Leppla CA, Izadmehr EM, Tye KM: Inhibitory input from the lateral hypothalamus to the ventral tegmental area disinhibits dopamine neurons and promotes behavioral activation. *Neuron* (2016) 90(6):1286–1298. [PubMed: 27238864]
78. Dong HW, Swanson LW: Projections from bed nuclei of the stria terminalis, posterior division: Implications for cerebral hemisphere regulation of defensive and reproductive behaviors. *J Comp Neurol* (2004) 471(4):396–433. [PubMed: 15022261]
79. Lebow MA, Chen A: Overshadowed by the amygdala: The bed nucleus of the stria terminalis emerges as key to psychiatric disorders. *Mol Psychiatry* (2016) 21(4):450–463. [PubMed: 26878891]
80. Dong HW, Petrovich GD, Swanson LW: Topography of projections from amygdala to bed nuclei of the stria terminalis. *Brain Res Brain Res Rev* (2001) 38(1–2):192–246. [PubMed: 11750933]
81. Barber PC, Field PM: Autoradiographic demonstration of afferent connections of the accessory olfactory bulb in the mouse. *Brain Res* (1975) 85(2):201–203. [PubMed: 46162]
82. Masugi-Tokita M, Flor PJ, Kawata M: Metabotropic glutamate receptor subtype 7 in the bed nucleus of the stria terminalis is essential for intermale aggression. *Neuropsychopharmacology* (2016) 41(3):726–735. [PubMed: 26149357]
83. Miczek KA, Brykczynski T, Grossman SP: Differential effects of lesions in the amygdala, periamygdaloid cortex, and stria terminalis on aggressive behaviors in rats. *J Comp Physiol Psychol* (1974) 87(4):760–771. [PubMed: 4473467]
84. Jennings JH, Sparta DR, Stamatakis AM, Ung RL, Pleil KE, Kash TL, Stuber GD: Distinct extended amygdala circuits for divergent motivational states. *Nature* (2013) 496(7444):224–228. [PubMed: 23515155]
85. Maeda H, Sato T, Maki S: Effects of dopamine agonists on hypothalamic defensive attack in cats. *Physiol Behav* (1985) 35(1):89–92. [PubMed: 4059404]
86. Maeda H, Maki S: Dopaminergic facilitation of recovery from amygdaloid lesions which affect hypothalamic defensive attack in cats. *Brain Res* (1986) 363(1):135–140. [PubMed: 3004640]
87. Sweidan S, Edinger H, Siegel A: The role of d1 and d2 receptors in dopamine agonist-induced modulation of affective defense behavior in the cat. *Pharmacol Biochem Behav* (1990) 36(3):491–499. [PubMed: 1974065]
88. Sweidan S, Edinger H, Siegel A: D2 dopamine receptor-mediated mechanisms in the medial preoptic-anterior hypothalamus regulate effective defense behavior in the cat. *Brain Res* (1991) 549(1):127–137. [PubMed: 1680019]
89. Miller SM, Lonstein JS: Dopaminergic projections to the medial preoptic area of postpartum rats. *Neuroscience* (2009) 159(4):1384–1396. [PubMed: 19409227]
90. Bjorklund A, Lindvall O, Nobin A: Evidence of an incerto-hypothalamic dopamine neurone system in the rat. *Brain Res* (1975) 89(1):29–42. [PubMed: 238718]

Highlights

- The VMHvl and its extended circuit is essential for generating aggressive behaviors.
- Mesolimbic dopamine circuit may signal the rewarding value of attacks and reinforce winning experience.
- The VMHvl can potentially drive the VTA dopaminergic cells through the LH and MPOA.
- Dopamine can modulate aggression through its action in the medial hypothalamus.

Figure 1. The upstream regions of the VMHvl and their influences on aggressive behaviors.

(A) Brain regions that provide inputs to the VMHvl. (B) A summary of functional manipulations of the upstream areas of the VMHvl during aggressive behaviors. BNST, bed nucleus of stria terminalis; MeA, medial amygdala; PMv, ventral premammillary nucleus; VMHvl, ventromedial hypothalamus ventrolateral part; LS, lateral septum; SPZ, subparaventricular zone. DAT, dopamine transporter; mGluR7, metabotropic glutamate receptor 7; Vgat, Vesicular GABA Transporter.

Figure 2. The mesolimbic dopamine system controls the rewarding effect of aggression.

(A) The potential neural circuit modulates aggressive behaviors through mesolimbic DA signaling. (B) A summary of functional manipulation and recording of mesolimbic and relevant areas during aggressive behaviors. DBN, diagonal band nucleus; LHb, lateral habenula; LS, lateral septum; NAc, nucleus accumbens; RMTg, rostromedial tegmental nucleus; VTA, ventral tegmental area. D1, dopamine 1 receptor; D2, dopamine 2 receptor; GABA, GABAergic; Glu, glutamatergic; DA: dopaminergic cells

Figure 3. The hypothalamus and BNST can potentially activate the DA neurons in the VTA through a disynaptic disinhibition mechanism.

The VMHvl projects heavily to the MPOA and LH which are all enriched in GABAergic cells and preferentially target onto the GABAergic cells in the VTA. Activation of the VMHvl glutamatergic cells (~95%) presumably activate the LH and MPOA cells which in turn inhibit the GABAergic cells and then activate the DA neurons in the VTA. BNST also receives aggression-related information and may relay the signal to the VTA dopamine neurons through a similar dis-inhibition mechanism. BNST, bed nucleus of stria terminalis; LH, lateral hypothalamus; MPOA, medial preoptic area; NAc, nucleus accumbens; VMHvl, ventromedial hypothalamus ventrolateral part. VTA: ventral tegmental area. GABA: GABAergic cells. DA: dopaminergic cells.

Table 1

A summary of hypothalamic activation induced aggressive behaviors in various mammalian species.

Species	Manipulation	Effect	Reference
Rat	Electrical stimulation	Increase attack	Kruk et al., 1983, Lammers et al., 1988, Siegel, Roeling et al., 1999
Opossum	Electrical stimulation	Biting attack	Roberts et al., 1967
Cat	Electrical stimulation	Threat, biting attack	Hess, 1928, Egger and Flynn, 1963, Siegel and Pott, 1988
Marmoset	Electrical stimulation	Vocal threat and short attacks	Lipp and Hunsperger, 1978
Squirrel monkeys	Electrical stimulation	Biting attack	Renfrew, 1969
Macaque	Electrical stimulation	Aggressive vocalization	Robinson, 1967
Hamster	arginine vasopressin	Increase attack	Ferris et al., 1997
Mouse	Optogenetic stimulation(ChR2)	Increase attack	Lin et al., 2011, Lee et al., 2014, Hashikawa et al., 2017
	Pharmacogenetic stimulation(Gq-DREADD)	Increase attack	Yang et al., 2017