HHS Public Access

Author manuscript

Curr Opin Neurobiol. Author manuscript; available in PMC 2022 June 01.

Published in final edited form as:

Curr Opin Neurobiol. 2021 June ; 68: 9–14. doi:10.1016/j.conb.2020.11.006.

Dissecting neural mechanisms of prosocial behaviors

Jessica J. Walsh, **Daniel J. Christoffel**, **Xiaoting Wu**, **Matthew B. Pomrenze**, **Robert C. Malenka**

Nancy Pritzker Laboratory, Dept. of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 265 Campus Drive, Stanford, CA 94305-5453, USA

Abstract

Prosocial behaviors are essential for group cooperation, which enrich life experience and enhance survival. These complex behaviors are governed by intricate interactions between numerous neural circuits functioning in concert. Impairments in prosocial interactions result from disruptions of this coordinated brain activity and are a prominent feature of several pathological conditions including autism spectrum disorder, depression and addiction. Here we highlight recent studies that use advanced techniques to anatomically map, monitor and manipulate neural circuits that influence prosocial behavior. These recent findings provide important clues to unravel the complexities of the neural mechanisms that mediate prosocial interactions and offer insights into new strategies for the treatment of aberrant social behavior.

Introduction

Prosocial behavior, often termed sociability, is a complex amalgamation of a variety of distinct types of social interactions. Positive prosocial interactions occur in many species ranging from insects to mammals and are critically important for development, survival, and reproduction. Thus, the neural mechanisms mediating prosocial, non-aggressive interactions have likely been evolutionarily conserved and involve circuits that play a role in a range of motivated behaviors that are critical for survival.

Pioneering studies in prairie voles demonstrated that the actions of the neuropeptide oxytocin (OXT) in the nucleus accumbens (NAc) were critical for pair bonding, providing one of the first hints of the neural circuit mechanisms regulating one particular form of sociability [1,2]. In the ensuing years, it became clear that other neuromodulators, including dopamine (DA) and serotonin (5-HT), are also important for adaptive social behaviors [3,4]. This body of work generated the hypothesis that these molecules regulate prosocial interactions by modulating neuronal activity in key nodes of the mesolimbic reward

Corresponding author: Malenka, Robert C. (malenka@stanford.edu).

Conflict of interest

R.C.M. is on the scientific advisory board (SAB) of MapLight Therapeutics, Cerevance, The Brave Neuroscience Co., Cognition Therapeutics, and AZ Therapies.

circuitry, perhaps by tuning intrinsic neuronal properties and filtering fast synaptic transmission [5,6]. However, progress in delineating more precisely the neural circuits governing prosocial behaviors did not occur until the arrival of now standard tools, which enable genetic access to discrete neuronal populations to monitor and precisely manipulate their activity patterns [7,8]. Here, we confine our discussion to recent findings on the brain regions, circuits and neuromodulators in mice implicated in non-aggressive, non-sexual prosocial interactions, which encompass social reward, social motivation, and social memory. In addition, we discuss the neural mechanisms underlying sociability impairments in rodent models of neuropsychiatric conditions.

Prosocial behaviors and social reward

The foundational investigations on the role of OXT in prairie vole pair bonding begged the question of its mechanism of action in the NAc. In mice, social reward was found to depend on OXT-induced release of 5-HT from dorsal raphe (DR) inputs in the NAc [9*]. The increase in NAc 5-HT induces long-term depression (LTD) of excitatory synaptic transmission in the NAc via activation of presynaptic 5-HT1b receptors, which are required for the development of a social conditioned place preference [9*]. While 5-HT had previously been implicated in regulating social behaviors [3,4,10,11], these findings [9*] generated the prediction that 5-HT release, specifically in the NAc would play a critical role in sociability. Recent experiments using a “circuits-first” approach have confirmed this prediction [12**]. Selective optogenetic activation of DR 5-HT inputs to the NAc enhanced prosocial behaviors while inhibiting these inputs decreased sociability. Furthermore, the prosocial action of activating DR 5-HT neurons was prevented by infusion of a 5-HT1b receptor antagonist into the NAc [12**].

Recent findings on the mechanisms of action of the recreational drug (±)3,4-methylenedioxymethamphetamine (MDMA), which is known to have powerful prosocial effects in human subjects [13], provide further support for the critical role of 5-HT release in the NAc in sociability [14**]. Specifically, in rodents, direct NAc infusion of MDMA, which causes large increases in 5-HT levels due to its potent interaction with the 5-HT transporter (SERT) [15], promoted sociability in the three chamber task, while NAc infusion of a 5-HT1b receptor antagonist prevented the prosocial effect of parenteral MDMA administration. Furthermore, MDMA application generated LTD in the NAc due to activation of 5-HT1b receptors [14**; but see 16]. MDMA may also prolong a developmental critical period for social reward learning due to OXT release [16]. A challenging question that warrants further investigation is how 5-HT induced depression of excitatory transmission at some unknown population of NAc inputs leads to the enhancement of social reward and sociability.

Unlike DA release in the NAc, 5-HT release is not inherently rewarding [7,12**,17, but see 18], suggesting that 5-HT modulation of NAc activity must differ from the modulation caused by DA. Nevertheless, presumably because of its powerful role in influencing a range of appetitive behaviors, DA is also a critical regulator of social behavior [19]. Indeed, ventral tegmental area (VTA)-to-NAc DA neurons exhibit increased activity during social interactions and optogenetic activation of this circuit enhances sociability, due to activation

of D1 receptors in the NAc [20]. Consistent with a role for NAc DA release in social reward, OXT also acts in the VTA to promote social reward via enhancement of DA cell firing [21–23]. Thus, OXT plays a critical role in promoting social reward by influencing two key nodes of mesolimbic reward circuitry, the NAc and VTA.

The consequences of activating excitatory inputs to the NAc fit well with the putative role of depressing NAc excitatory synaptic transmission in promoting sociability. Activation of a subset of NAc projecting neurons in the prelimbic cortex (PL) decreased the preference for a social target, while their activity increased during social investigation, but only in specific locations [24**]. Activation of basolateral amygdala (BLA) inputs in the NAc also decreased sociability and increased social avoidance, but did not reduce palatable food seeking [25]. Collectively, these studies provide compelling evidence for a critical role of the NAc in social reward and prosocial behaviors. A major challenge will be to elucidate how the different sets of excitatory and modulatory NAc inputs modify NAc activity in a coordinated fashion to robustly and perhaps specifically influence the rewarding aspects of social interactions.

Social Memory

Social motivation is influenced by social cognition and social memory, the ability to recognize and remember conspecifics, respectively. Older studies revealed that OXT acting in the medial amygdala and septum is necessary for the social preference of a novel, rather than a familiar, conspecific [2,26,27]. More recently, via the use of transgenic mouse lines, specific sub-regions of the hippocampus have been implicated in the storing and processing of memories associated with social interactions. Selective inactivation of the dorsal CA2 (dCA2) region using the Amigo2-Cre driver line reduced social memory, but surprisingly did not influence sociability *per se* nor other hippocampal-dependent forms of memory [28*]. Similarly, excitotoxic lesion of the CA2 abolished social memory, but not olfactory memory [29]. Furthermore, single-unit recordings revealed that unlike CA1 neurons, CA2 neuron firing patterns remapped during social encounters and exhibited reduced response to spatial stimuli compared to CA1 neuron firing [30].

A heterosynaptic form of input-timing-dependent inhibitory LTD (iLTD) in CA2 parvalbumin-positive (PV+) interneurons provides one plausible physiological substrate for social learning and memory [31] in that blockade of this iLTD in PV+ interneurons impairs social memory [31,32]. Consistent with this proposal, 22q11.2 deletion mice exhibit social memory deficits associated with reduction of CA2 PV+ interneuron plasticity [29]. Modulation of CA2 pyramidal neuron firing by OXT and/or vasopressin may also be important for social memory. The CA2 region expresses a very high density of OXT receptors (OXTRs) [33–35] and vasopressin 1b receptors (Avpr1bRs) [36] compared to other hippocampal sub-regions. OXTR activation increases CA2 pyramidal neuron burst firing [33], while conditional deletion of OXTRs from the CA2 and CA3 sub-regions prevents social memory [34,35]. Furthermore, activating vasopressin inputs in the CA2 enhances social memory due to actions at Avpr1bRs [36].

Recent studies have also revealed the importance of the ventral CA1 (vCA1) in social memory [37**–40]. Leveraging the specificity of transgenic lines for vCA1 and dorsal CA1 (dCA1), selective inhibition of the two populations of pyramidal neurons demonstrated that only vCA1 neurons participate in encoding social memory [37**]. Projections from vCA1 to both the NAc and medial prefrontal cortex (mPFC) appear to be specifically important in regulating social memory as are inputs from dCA2 to vCA1 [37**–39]. Collectively, these studies suggest a circuit substrate that is critical for social memory, involving OXT and AVP modulatory inputs to dCA2, which relays social information to vCA1 that in turn influences extrahippocampal regions including the NAc and mPFC.

Pathological social motivation

Impairments in adaptive prosocial behaviors (e.g. social amotivation or avoidance) are common debilitating features of many neuropsychiatric conditions, including autism spectrum disorder (ASD), depression, and addiction [4]. Here, we briefly review recent findings on some of the neural mechanisms that contribute to sociability impairments in rodent models of these disorders.

Autism Spectrum Disorders

Rodent models of ASDs based on causal genetic variants have been invaluable tools for advancing the understanding of ASD pathophysiology. One common cause of ASD is a copy number variation on chromosome 16p11.2. Selective deletion of the syntenic region of chromosome 16p11.2 from DR 5-HT neurons caused significant deficits in prosocial behaviors, which were associated with reductions in the activity of these neurons during social interactions, as well as decreases in their intrinsic excitability [12**]. Optogenetic activation of DR 5-HT inputs in the NAc restored sociability in these mutant mice to normal levels and this rescue was dependent upon 5-HT1b receptors [12**]. Impaired social interactions were also observed in mice expressing a gain-of-function SERT variant that decreased 5-HT levels [41]. Collectively, these findings provide further support for the hypothesis that 5-HT release in the NAc is critical for sociability.

Alterations in the balance of excitatory and inhibitory synaptic transmission, so called E/I balance, in specific brain regions are found in several genetic ASD models. In the CNTNAP2 deletion mouse, correction of E/I imbalance by optogenetic activation of inhibitory PV neurons in mPFC rescued social deficits [42*]. Similarly, in a 16p11.2 duplication mouse model, restoring mPFC inhibitory synapse function reversed social and cognitive impairments [43*]. Surprisingly, E/I imbalance in the anterior cingulate cortex, but not the adjacent mPFC, contributes to social deficits in Shank3 deletion mice [44*]. These mice also exhibit aberrant BLA-to-NAc activity, modulation of which via endocannabinoids [25] restored adaptive social interaction, as did activation of DR 5-HT neurons [45].

Direct modulation of GABA receptors may serve as an alternative strategy to remedy deficits in E/I balance as evidenced by the finding that systemic administration of the $GABA_B$ receptor agonist, R-Baclofen, reversed social deficits in two different variants of the 16p11.2 deletion model [46]. However, altered E/I balance in the somatosensory cortex was observed in four different genetic ASD mouse models without any corresponding changes in

overall circuit excitability, suggesting that altered E/I balance may be a homeostatic compensation rather than a mechanism for impaired sociability [47**].

Major Depressive Disorder

Sociability deficits are a key symptom of major depressive disorder and have been attributed to abnormalities in the mesolimbic DA system [48]. The specific form of stress used to generate depression symptoms appears to influence the pathophysiological mechanisms that mediate the sociability deficits. Chronic mild stress may influence subpopulations of VTA DA neurons differentially with a reduction in DA release in target regions presumably contributing to the behavioral deficits [48]. In contrast, the sociability deficits observed in susceptible mice following chronic social defeat stress (CSDS) appear to require the release of brain-derived neurotrophic factor (BDNF) from VTA DA terminals in the NAc [48]. Early life stress, on the other hand, induces social impairments, at least in part by altering the transcriptional profile of VTA DA neurons [49*] and reducing DA receptor 3 signaling in the lateral septum [50,51].

Changes in inputs to the VTA also regulate CSDS-induced social deficits. Specifically, blocking the stress-induced increase in ventral pallidum (VP)-to-VTA inhibitory transmission reverses social avoidance, whereas a distinct population of VP inputs to the lateral habenula (LHb), a potent regulator of DA neuron activity, mediate passive coping [52**]. Interestingly, a di-synaptic inhibitory circuit from the retina to the LHb mediates the antidepressant and prosocial effects of light therapy in the CSDS model [53].

As a key node of mesolimbic reward circuitry, modulation of NAc function has long been thought to play a critical role in depression [54]. Recent work suggests that CSDS differentially alters excitatory inputs onto NAc medium spiny neuron subtypes with enhanced synaptic transmission for one thalamic input being critical for social avoidance [54]. NAc cholinergic interneuron activity is also impacted by stress and modulation of ion channels in this cell population normalized stress-induced decreases in social behavior [55].

Of course, the symptoms of depression including sociability deficits involve circuit modifications beyond those occurring in reward circuitry. Interrogation of network activity using multi-circuit *in vivo* recordings coupled with machine learning revealed that chronic stress disrupts synchronous activity in the mPFC, amygdala, and VTA mesocorticolimbic network. Restoration of mPFC activity normalized network dynamics and sociability in susceptible mice [56]. Additionally, pharmacological manipulations of the mPFC, via the novel antidepressant ketamine, improves social behavior in part by stimulating descending PFC inputs to the dorsal periaqueductal gray [57].

Addiction

Drug addiction and withdrawal are commonly associated with impaired sociability. While little is known about the precise neural mechanisms governing these impairments, recent work implicates alterations in cytokine signaling in the LHb and changes in opioid receptor activity [58,59]. Furthermore, the notion that increasing social support could be a means for attenuating addictive behaviors is supported by recent findings where rats reduced drug intake when provided with the choice to socialize [60*]. Socializing also reduced drug

craving which was mediated by a discrete micro-circuit in the central amygdala [61*]. These recent studies suggest that, similar to depression, maladaptive changes in corticostriatal circuitry and key modulatory inputs to the NAc contribute to abnormal social motivation in addiction.

Conclusions

What is more important in today's world than developing interventions that will promote empathic and compassionate positive, prosocial interactions? As neuroscientists, we can hopefully contribute to this effort by delineating the complex neural mechanisms underlying social reward and social motivation. Given that sociability deficits are present in a range of neuropsychiatric conditions, a more sophisticated and comprehensive understanding of the pathophysiological circuit activity that generates these deficits will also aid in the development of improved treatments. To date, much of the research focus on these topics has appropriately been on specific circuits and cell types known to play a role in many different types of motivated behaviors. Future studies will need to assess how social cues engage these separate circuits in a manner to modify social interactions and how they work in concert to regulate and promote prosocial interactions. Perhaps with sufficient knowledge of neural mechanisms, we can help our species promote prosocial behaviors and simultaneously reduce the aggressive, self-destructive social behaviors that threaten our very survival.

Acknowledgement

Funding: Work in the authors' laboratory was supported by grants from the NIH (P50 DA042012 to R.C.M.; F32 MH103949 to J.J.W.; F32 MH106206 and K99 DK115985 to D.J.C.; T32DA035165 to M.B.P.).

References and recommended reading

1. Insel TR: The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior. Neuron 2010, 65:768–779. [PubMed: 20346754]
2. Lee HJ, Macbeth AH, Pagani JH, Young WS 3rd: Oxytocin: the great facilitator of life. Prog Neurobiol 2009, 88:127–151. [PubMed: 19482229]
3. Brown S-L, Praag HMv: The role of serotonin in psychiatric disorders. New York: Brunner/Mazel; 1991.
4. Charney DS, Sklar PB, Buxbaum JD, Nestler EJ: Charney & Nestler's neurobiology of mental illness Fifth edition. New York, NY: Oxford University Press; 2018.
5. Tritsch NX, Sabatini BL: Dopaminergic modulation of synaptic transmission in cortex and striatum. Neuron 2012, 76:33–50. [PubMed: 23040805]
6. Müller CP, Cunningham KA: Handbook of the behavioral neurobiology of serotonin.: Elsevier; 2020.
7. Steinberg EE, Christoffel DJ, Deisseroth K, Malenka RC: Illuminating circuitry relevant to psychiatric disorders with optogenetics. Curr Opin Neurobiol 2015, 30:9–16. [PubMed: 25215625]
8. Lerner TN, Ye L, Deisseroth K: Communication in neural circuits: tools, opportunities, and challenges. Cell 2016, 164:1136–1150. [PubMed: 26967281]
9. Dolen G, Darvishzadeh A, Huang KW, Malenka RC: Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature 2013, 501:179–184. [PubMed: 24025838] *This study demonstrates that oxytocin release in the NAc is required for social conditioned place preference, an assay for social reward. Oxytocin acts by causing the release of 5-HT, which in turn

acts on presynaptic 5-HT1b receptors to induce a long-term depression of excitatory synaptic transmission.

10. Kiser D, Steemers B, Branchi I, Homberg JR: The reciprocal interaction between serotonin and social behaviour. Neurosci Biobehav Rev 2012, 36:786–798. [PubMed: 22206901]
11. Muller CL, Anacker AMJ, Veenstra-VanderWeele J: The serotonin system in autism spectrum disorder: from biomarker to animal models. Neuroscience 2016, 321:24–41. [PubMed: 26577932]
12. Walsh JJ, Christoffel DJ, Heifets BD, Ben-Dor GA, Selimbeyoglu A, Hung LW, Deisseroth K, Malenka RC: 5-HT release in nucleus accumbens rescues social deficits in mouse autism model. Nature 2018, 560:589–594. [PubMed: 30089910]
13. Kamilar-Britt P, Bedi G: The prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA): Controlled studies in humans and laboratory animals. Neurosci Biobehav Rev 2015, 57:433–446. [PubMed: 26408071]
14. Heifets BD, Salgado JS, Taylor MD, Hoerbelt P, Cardozo Pinto DF, Steinberg EE, Walsh JJ, Sze JY, Malenka RC: Distinct neural mechanisms for the prosocial and rewarding properties of MDMA. Sci Transl Med 2019, 11: eaaw6435. [PubMed: 31826983] **Together (12, 14) these studies present evidence that the release of 5-HT in the NAc promotes sociability via activation of presynaptic 5-HT1b receptors. Ref. 12 also demonstrates that in rodents, genetic deletion of the syntenic region of 16p11.2 from DR 5-HT neurons causes sociability deficits that can be rescued by release of 5-HT in the NAc.
15. Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI: The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev 2003, 55:463–508. [PubMed: 12869661]
16. Nardou R, Lewis EM, Rothhaas R, Xu R, Yang A, Boyden E, Dolen G: Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature 2019, 569:116–120. [PubMed: 30944474]
17. Klawonn AM, Malenka RC: Nucleus accumbens modulation in reward and aversion. Cold Spring Harb Symp Quant Biol 2018, 83:119–129. [PubMed: 30674650]
18. Liu Z, Lin R, Luo M: Reward contributions to serotonergic functions. Annu Rev Neurosci 2020, 43:141–162. [PubMed: 32640931]
19. Young LJ, Wang Z: The neurobiology of pair bonding. Nat Neurosci 2004, 7:1048–1054. [PubMed: 15452576]
20. Gunaydin LA, Grosenick L, Finkelstein JC, Kauvar IV, Fenno LE, Adhikari A, Lammel S, Mirzabekov JJ, Airan RD, Zalocusky KA, et al.: Natural neural projection dynamics underlying social behavior. Cell 2014, 157:1535–1551. [PubMed: 24949967]
21. Hung LW, Neuner S, Polepalli JS, Beier KT, Wright M, Walsh JJ, Lewis EM, Luo L, Deisseroth K, Dolen G, et al.: Gating of social reward by oxytocin in the ventral tegmental area. Science 2017, 357:1406–1411. [PubMed: 28963257]
22. Xiao L, Priest MF, Nasenbeny J, Lu T, Kozorovitskiy Y: Biased oxytocinergic modulation of midbrain dopamine systems. Neuron 2017, 95:368–384. [PubMed: 28669546]
23. Song Z, Borland JM, Larkin TE, O'Malley M, Albers HE: Activation of oxytocin receptors, but not arginine-vasopressin V1a receptors, in the ventral tegmental area of male Syrian hamsters is essential for the reward-like properties of social interactions. Psychoneuroendocrinology 2016, 74:164–172. [PubMed: 27632574]
24. Murugan M, Jang HJ, Park M, Miller EM, Cox J, Taliaferro JP, Parker NF, Bhave V, Hur H, Liang Y, et al.: Combined social and spatial coding in a descending projection from the prefrontal cortex. Cell 2017, 171:1663–1677. [PubMed: 29224779] **This study defines three different populations of neurons in the prelimbic cortex (PL) distinguished by their projection targets. Activation of NAc-projecting PL neurons, but not amgydala- or VTA-projecting PL neurons, decreases preference for a social target. Miniscope recordings reveal that NAc-projecting PL neurons encode both social and spatial information and play a role in social-spatial learning.
25. Folkes OM, Baldi R, Kondev V, Marcus DJ, Hartley ND, Turner BD, Ayers JK, Baechle JJ, Misra MP, Altemus M, et al.: An endocannabinoid-regulated basolateral amygdala-nucleus accumbens circuit modulates sociability. J Clin Invest 2020, 130:1728–1742. [PubMed: 31874107]

26. Ferguson JN, Aldag JM, Insel TR, Young LJ: Oxytocin in the medial amygdala is essential for social recognition in the mouse. J Neurosci 2001, 21:8278–8285. [PubMed: 11588199]
27. Lukas M, Toth I, Veenema AH, Neumann ID: Oxytocin mediates rodent social memory within the lateral septum and the medial amygdala depending on the relevance of the social stimulus: male juvenile versus female adult conspecifics. Psychoneuroendocrinology 2013, 38:916–926. [PubMed: 23102690]
28. Hitti FL, Siegelbaum SA: The hippocampal CA2 region is essential for social memory. Nature 2014, 508:88–92. [PubMed: 24572357] *The authors generate the Amigo2-Cre mouse line, which allows genetic access specifically to CA2 pyramidal neurons. Inhibition of these cells strongly reduced social memory with no change in sociability or other forms of hippocampus-dependent memory. These results provide compelling evidence that the CA2 region plays a specific and critical role in the abilty to remember prior social interactions.
29. Piskorowski RA, Nasrallah K, Diamantopoulou A, Mukai J, Hassan SI, Siegelbaum SA, Gogos JA, Chevaleyre V: Age-dependent specific changes in area CA2 of the hippocampus and social memory deficit in a mouse model of the 22q11.2 deletion syndrome. Neuron 2016, 89:163–176. [PubMed: 26748091]
30. Alexander GM, Farris S, Pirone JR, Zheng C, Colgin LL, Dudek SM: Social and novel contexts modify hippocampal CA2 representations of space. Nat Commun 2016, 7:10300. [PubMed: 26806606]
31. Leroy F, Brann DH, Meira T, Siegelbaum SA: Input-timing-dependent plasticity in the hippocampal CA2 region and its potential role in social memory. Neuron 2017, 95:1089–1102. [PubMed: 28823730]
32. Dominguez S, Rey CC, Therreau L, Fanton A, Massotte D, Verret L, Piskorowski RA, Chevaleyre V: Maturation of PNN and ErbB4 signaling in area CA2 during adolescence anderlies the emergence of PV interneuron plasticity and social memory. Cell Rep 2019, 29:1099–1112. [PubMed: 31665627]
33. Tirko NN, Eyring KW, Carcea I, Mitre M, Chao MV, Froemke RC, Tsien RW: Oxytocin transforms firing mode of CA2 hippocampal neurons. Neuron 2018, 100:593–608. [PubMed: 30293821]
34. Raam T, McAvoy KM, Besnard A, Veenema AH, Sahay A: Hippocampal oxytocin receptors are necessary for discrimination of social stimuli. Nat Commun 2017, 8:2001. [PubMed: 29222469]
35. Lin YT, Hsieh TY, Tsai TC, Chen CC, Huang CC, Hsu KS: Conditional deletion of hippocampal CA2/CA3a oxytocin receptors impairs the persistence of long-term social recognition memory in mice. J Neurosci 2018, 38:1218–1231. [PubMed: 29279308]
36. Smith AS, Williams Avram SK, Cymerblit-Sabba A, Song J, Young WS: Targeted activation of the hippocampal CA2 area strongly enhances social memory. Mol Psychiatry 2016, 21:1137–1144. [PubMed: 26728562]
37. Okuyama T, Kitamura T, Roy DS, Itohara S, Tonegawa S: Ventral CA1 neurons store social memory. Science 2016, 353:1536–1541. [PubMed: 27708103] **Using an elegant combination of techniques including a CA1 pyramidal cell-specific Cre mouse line, the authors demonstrate that ventral CA1 neurons and their projections to NAc shell are critical for social memory. Miniscope recordings, as well as cFos labelling, show that distinct groups of cells are activated after encountering different conspecifics. The authors propose that a dCA2-to-vCA1-to-NAc shell circuit importantly contributes to social memory engrams.
38. Meira T, Leroy F, Buss EW, Oliva A, Park J, Siegelbaum SA: A hippocampal circuit linking dorsal CA2 to ventral CA1 critical for social memory dynamics. Nat Commun 2018, 9:4163. [PubMed: 30301899]
39. Phillips ML, Robinson HA, Pozzo-Miller L: Ventral hippocampal projections to the medial prefrontal cortex regulate social memory. Elife 2019, 8: e44182. [PubMed: 31112129]
40. Deng X, Gu L, Sui N, Guo J, Liang J: Parvalbumin interneuron in the ventral hippocampus functions as a discriminator in social memory. Proc Natl Acad Sci U S A 2019, 116:16583–16592. [PubMed: 31358646]
41. O'Reilly KC, Anacker AMJ, Rogers TD, Forsberg CG, Wang J, Zhang B, Blakely RD, Veenstra-VanderWeele J: A social encounter drives gene expression changes linked to neuronal function,

brain development, and related disorders in mice expressing the serotonin transporter Ala56 variant. Neurosci Lett 2020, 730:135027. [PubMed: 32437898]

42. Selimbeyoglu A, Kim CK, Inoue M, Lee SY, Hong ASO, Kauvar I, Ramakrishnan C, Fenno LE, Davidson TJ, Wright M, et al.: Modulation of prefrontal cortex excitation/inhibition balance rescues social behavior in CNTNAP2-deficient mice. Sci Transl Med 2017, 9: eaah6733. [PubMed: 28768803]
43. Rein B, Tan T, Yang F, Wang W, Williams J, Zhang F, Mills A, Yan Z: Reversal of synaptic and behavioral deficits in a 16p11.2 duplication mouse model via restoration of the GABA synapse regulator Npas4. Mol Psychiatry 2020.
44. Guo B, Chen J, Chen Q, Ren K, Feng D, Mao H, Yao H, Yang J, Liu H, Liu Y, et al.: Anterior cingulate cortex dysfunction underlies social deficits in Shank3 mutant mice. Nat Neurosci 2019, 22:1223–1234. [PubMed: 31332372] * These papers (42–44) demonstrate that alterations in cortical E/I balance contribute to social deficits in three different genetic ASD mouse models. Increasing PFC inhibition in CNTNAP2-deficient mice (42) or 16p11.2 duplication mice (43) ameliorated their sociability deficits, whereas increasing activity of anterior cingulate cortex pyramidal neurons in Shank3 mutants generated the same rescue (44). These papers suggest that despite E/I imbalance being a common endophenotype in ASD mouse models, the detailed neural manifestations can be different.
45. Luo J, Feng Q, Wei L, Luo M: Optogenetic activation of dorsal raphe neurons rescues the autistic-like social deficits in Shank3 knockout mice. Cell Res 2017, 27:950–953. [PubMed: 28374752]
46. Stoppel LJ, Kazdoba TM, Schaffler MD, Preza AR, Heynen A, Crawley JN, Bear MF: R-baclofen reverses cognitive deficits and improves social interactions in two lines of 16p11.2 deletion mice. Neuropsychopharmacology 2018, 43:513–524. [PubMed: 28984295]
47. Antoine MW, Langberg T, Schnepel P, Feldman DE: Increased excitation-inhibition ratio stabilizes synapse and circuit excitability in four autism mouse models. Neuron 2019, 101:648–661. [PubMed: 30679017] **By studying 4 different genetic ASD mouse models using a combination of *in vitro* and *in vivo* electrophysiology, the authors identified increases in E/I balance in somatosensory cortex as a common circuit phenotype. However, modeling revealed that the observed changes in E and I conductance were sufficiently matched to stabilize synaptic depolarization and explain the normal sensory-evoked spiking in all four models. The authors propose that elevated E/I balance in the cortex of these ASD models reflects homeostatic compensatory mechanisms to stabilize overall excitatory synaptic drive.
48. Koo JW, Chaudhury D, Han MH, Nestler EJ: Role of mesolimbic brain-derived neurotrophic factor in depression. Biol Psychiatry 2019, 86:738–748. [PubMed: 31327473]
49. Pena CJ, Kronman HG, Walker DM, Cates HM, Bagot RC, Purushothaman I, Issler O, Loh YE, Leong T, Kiraly DD, et al.: Early life stress confers lifelong stress susceptibility in mice via ventral tegmental area OTX2. Science 2017, 356:1185–1188. [PubMed: 28619944] *The authors find that early life stress in mouse pups causes enhanced susceptibility to the effects of social defeat stress, including decreased sociability. Gene expression profiling revealed long-lasting transcriptional alterations in the VTA, which were mediated by transient downregulation of the transcription factor OTX2. Transient overexpression of OTX2 in the VTA of juvenile mice normalized stress-induced changes in gene expression and prevented the emergence of depression-like behaviors in adulthood.
50. Shin S, Pribiag H, Lilascharoen V, Knowland D, Wang XY, Lim BK: Drd3 signaling in the lateral septum mediates early life stress-induced social dysfunction. Neuron 2018, 97:195–208 e196. [PubMed: 29276054]
51. Hultman R, Mague SD, Li Q, Katz BM, Michel N, Lin L, Wang J, David LK, Blount C, Chandy R, et al.: Dysregulation of prefrontal cortex-mediated slow-evolving limbic dynamics drives stress-induced emotional pathology. Neuron 2016, 91:439–452. [PubMed: 27346529]
52. Knowland D, Lilascharoen V, Pacia CP, Shin S, Wang EH, Lim BK: Distinct ventral pallidal neural populations mediate separate symptoms of depression. Cell 2017, 170:284–297. [PubMed: 28689640] ** This paper present a comprehensive analysis of reward circuits involved in distinct aspects of depressive behaviors. The authors identified discrete ventral pallidum outputs to the LHb and VTA, which mediate behavioral despair or sociability deficits, respectively. Optogenetic inhibition of pallidal projections to the VTA selectively improved social deficits after stress,

whereas inhibition of outputs to the LHb reduced despair behavior. This study demonstrates that discrete reward circuit components can mediate distinct features of depression, including sociability deficits.

53. Huang L, Xi Y, Peng Y, Yang Y, Huang X, Fu Y, Tao Q, Xiao J, Yuan T, An K, et al.: A visual circuit related to habenula underlies the antidepressive effects of light therapy. Neuron 2019, 102:128–142 e128. [PubMed: 30795900]
54. Fox ME, Lobo MK: The molecular and cellular mechanisms of depression: a focus on reward circuitry. Mol Psychiatry 2019, 24:1798–1815. [PubMed: 30967681]
55. Cheng J, Umschweif G, Leung J, Sagi Y, Greengard P: HCN2 channels in cholinergic interneurons of nucleus accumbens shell regulate depressive behaviorst Neuron 2019, 101:662–672. [PubMed: 30638901]
56. Hultman R, Ulrich K, Sachs BD, Blount C, Carlson DE, Ndubuizu N, Bagot RC, Parise EM, Vu MT, Gallagher NM, et al.: Brain-wide electrical spatiotemporal dynamics encode depression vulnerability. Cell 2018, 173:166–180. [PubMed: 29502969]
57. Franklin TB, Silva BA, Perova Z, Marrone L, Masferrer ME, Zhan Y, Kaplan A, Greetham L, Verrechia V, Halman A, et al.: Prefrontal cortical control of a brainstem social behavior circuit. Nat Neurosci 2017, 20:260–270. [PubMed: 28067904]
58. Valentinova K, Tchenio A, Trusel M, Clerke JA, Lalive AL, Tzanoulinou S, Matera A, Moutkine I, Maroteaux L, Paolicelli RC, et al.: Morphine withdrawal recruits lateral habenula cytokine signaling to reduce synaptic excitation and sociability. Nat Neurosci 2019, 22:1053–1056. [PubMed: 31209376]
59. Lalanne L, Ayranci G, Filliol D, Gaveriaux-Ruff C, Befort K, Kieffer BL, Lutz PE: Kappa opioid receptor antagonism and chronic antidepressant treatment have beneficial activities on social interactions and grooming deficits during heroin abstinence. Addict Biol 2017, 22:1010–1021. [PubMed: 27001273]
60. Venniro M, Zhang M, Caprioli D, Hoots JK, Golden SA, Heins C, Morales M, Epstein DH, Shaham Y: Volitional social interaction prevents drug addiction in rat models. Nat Neurosci 2018, 21:1520–1529. [PubMed: 30323276]
61. Venniro M, Russell TI, Ramsey LA, Richie CT, Lesscher HMB, Giovanetti SM, Messing RO, Shaham Y: Abstinence-dependent dissociable central amygdala microcircuits control drug craving. Proc Natl Acad Sci U S A 2020, 117:8126–8134. [PubMed: 32205443] *In these studies (60–61), the authors create a new operant model to study addictive behavior and understand “social choice-induced abstinence”. Importantly, this model allows for an animal to choose between two rewards, a social interaction or drug infusion. The opportunity to socialize reduced drug-seeking and “craving” behavior (60), an adaptive response mediated by amygdala inhibitory microcircuits (61).

Highlights

- Neural circuits mediating prosocial behaviors are being defined using modern methods
- Modulation of mesolimbic reward circuitry plays a key role in promoting sociability
- Social memory involves specific subregions of the hippocampus
- Prosocial behavior is deficient in rodent models of autism, depression, and addiction