Journal Club

Editor's Note: These short reviews of recent *JNeurosci* articles, written exclusively by students or postdoctoral fellows, summarize the important findings of the paper and provide additional insight and commentary. If the authors of the highlighted article have written a response to the Journal Club, the response can be found by viewing the Journal Club at www.jneurosci.org. For more information on the format, review process, and purpose of Journal Club articles, please see https://www.jneurosci.org/content/jneurosci-journal-club.

Oxytocin-Sensitive Neurons in Prefrontal Cortex Gate Social Recognition Memory

Tara Raam
Department of Neurobiology, David Geffen School of Medicine at UCLA, Los Angeles, California 90095
Review of Tan et al.

Social memory, the ability to recognize familiar conspecifics, is a complex biological process that enables stability of social interactions over time. It requires integration of multimodal sensory information with output from limbic circuits and those that encode memory of prior social experiences (Chen and Hong, 2018). Oxytocin and its corresponding receptor (OXTR) have long been known to regulate social recognition memory (Ferguson et al., 2000; Lee et al., 2008; Macbeth et al., 2009). However, how oxytocin acts on specific neural circuits to influence social memory remains incompletely understood. For example, the medial prefrontal cortex (mPFC) receives direct input from oxytocin-releasing neurons (Knobloch et al., 2012) and supports a broad range of social behaviors, including social memory (Bicks et al., 2015). Yet, little is known about which mPFC-dependent circuits oxytocin acts on to regulate these behaviors.

In a recent study, Tan et al. (2019) used electrophysiology, functional magnetic resonance imaging (fMRI), *in vivo* optogenetics, and behavioral assays to examine the role of a population of OXTR-expressing cells in mPFC in social memory (Tan et al., 2019). Although previous studies have reported that the OXTR is mainly expressed in somatostatin-positive interneurons in mPFC (Nakajima et al., 2014; Li et al., 2016), Tan et al. (2019) found that OXTR is expressed in a mixed population of GABAergic interneurons (32.6%) and glutamatergic pyramidal-like neurons (46.5%). These results were confirmed with slice electrophysiology experiments, which showed that OXTR-expressing mPFC cells can have electrophysiological properties of either cell type. Moreover, optical stimulation of channelrhodopsin-2 (ChR2)-expressing OXTR neurons in mPFC induced both inhibitory and excitatory postsynaptic responses in neighboring neurons.

Next, using *in vivo* optogenetic stimulation combined with whole-brain fMRI, the authors found that activation of mPFC OXTR-expressing neurons increased activity in three subcortical targets of mPFC: the nucleus accumbens (NAc), the basolateral amygdala (BLA), and the bed nucleus of the stria terminals (BNST). Increased activity was also reported in the ventral tegmental area (VTA) and dorsal raphe nucleus (DRN), although data were not shown. Consistent with these results, slice electrophysiological recordings showed that stimulating axon terminals of OXTR-expressing mPFC neurons in NAc, BLA, or BNST induced robust excitatory responses, suggesting that OXTR-expressing mPFC neurons make functional glutamatergic synapses in these downstream regions. No evidence of long-range inhibitory projections emerging from OXTR-expressing mPFC neurons was found in these regions, although such projections may be sparse and therefore hard to identify. Additionally, although not examined in these experiments, OXTR-expressing mPFC neurons may target local interneurons in BLA, and may lead to inhibition of BLA under some conditions, depending on the relative proportion of excitatory versus inhibitory neurons that are targeted.

The authors next asked how OXTR-expressing mPFC neurons contribute to social and nonsocial behaviors. To answer this question, they expressed ChR2 selectively in OXTR-expressing mPFC neurons and stimulated the neurons during four behavioral tasks, which assayed sociability, social recognition memory, novel object recognition, or anxiety-like behavior. Remarkably, the activation of OXTR-expressing mPFC neurons selectively impaired social recognition memory. Specifically, when presented with the choice to interact with a familiar versus unfamiliar conspecific, mice in which OXTR-expressing neurons were activated did not show the stereotypical preference for unfamiliar conspecifics. Notably, these animals do not show any abnormalities in the two-chamber sociability task that measures the preference of the animal to investigate a conspecific versus an empty

Received June 11, 2019; revised Dec. 13, 2019; accepted Dec. 14, 2019.
I thank Dr. Weizhe Hong for thoughtful feedback and suggestions.
The authors declare no competing financial interests.
Correspondence should be addressed to Tara Raam at tararaam@ucla.edu.
https://doi.org/10.1523/JNEUROSCI.1348-19.2019

chamber. Furthermore, activating OXTR-expressing mPFC neurons did not affect the amount of time spent in the open arm of an elevated plus maze. These data suggest that the deficit in social memory is not a consequence of general changes in sociability or anxiety-like behavior that affect the motivation of the animal to explore stimuli in the environment. Additionally, animals in which OXTR-expressing mPFC neurons were activated showed a normal preference for novel objects over familiar objects, indicating that the effects on social memory are not due to a general deficit in memory function. These results suggest that, although the mPFC is important for sociability (Yizhar et al., 2011; Felix-Ortiz et al., 2016; Murugan et al., 2017), novel object recognition (Spanswick and Dyck 2012), and innate anxiety (Li et al., 2016; Padilla-Coreano et al., 2016), OXTR-expressing mPFC neurons specifically regulate functioning related to social recognition.

Finally, the authors sought to determine how information related to social memory is relayed from mPFC to downstream targets. Optogenetically stimulating OXTR-expressing mPFC neuron terminals in the BLA recapitulated the effects of stimulating OXTR-expressing mPFC cell bodies—the stimulation impaired social memory without affecting sociability or novel object recognition. Because bath application of oxytocin activated mPFC pyramidal neurons that release glutamate in the BLA, Tan et al. (2019) concluded that social memory is mediated by glutamatergic OXTR-expressing mPFC neurons that project to the BLA. These results are consistent with previous studies, which found that knocking out OXTR in CaMKII-expressing excitatory forebrain neurons impaired social memory (Macbeth et al., 2009). Importantly, however, other targets of OXTR-expressing mPFC neurons, including NAc, BNST, VTA, and DRN, were not examined, so whether the projection to the BLA is uniquely responsible for the behavioral phenotype remains unclear.

Although there are notable technical benefits of cell type-specific optogenetic manipulations, complementary experiments that manipulate OXTRs, rather than OXTR-expressing neurons, may provide further insight into how the mPFC is involved in social memory. For example, OXTR-expressing mPFC neurons may also express receptors for other neurotransmitters, such as glutamate, vasopressin, or dopamine, and the release of these other neurotransmitters in mPFC may depolarize OXTR-expressing neurons to promote social memory. While optogenetic manipulation of OXTR-expressing neurons provides important temporal and cell type-specific advantages to causally assess the role of the OXTR-expressing neurons, it leaves an open question of how the receptor itself, rather than the neurons, contributes to the behavior. To better understand the role of the OXTR itself in mPFC, complementary studies using Cre-dependent OXTR conditional knock-out mouse lines (Lee et al., 2008) may clarify how the oxytocin pathway contributes to this behavior.

Nevertheless, the study by Tan et al. (2019) fills a critical gap in our understanding of how OXTR-expressing mPFC neurons influence circuits that control social behaviors. It also opens new avenues of inquiry. For example, given that previous studies found that knockout of OXTR in the forebrain impairs social memory and it is thought that oxytocin enhances social recognition memory (Lee et al., 2008; Macbeth et al., 2009), it is unexpected that optogenetic stimulation of OXTR-expressing mPFC neurons and their projections to the BLA diminished, rather than enhanced, social memory in the experiments by Tan et al. (2019). One possible explanation for this apparent contradiction is that mPFC OXTR-expressing neurons must be activated in an optimal range to enhance social memory, and both increasing or decreasing their activity outside this range impairs social memory. Alternatively, because balanced excitation and inhibition in mPFC is critical for normal social behaviors (Yizhar et al., 2011), it is possible that gross optogenetic stimulation of OXTR-expressing mPFC neuron cell bodies or their axon terminals in BLA hyperactivates these neurons in a manner unnatural to their endogenous firing pattern, leading to a deficit. A third possibility is that optogenetic stimulation disrupts coding schemes in mPFC that may be required for social memory. Discriminating two social stimuli at the behavioral level requires an underlying neural mechanism that differentiates them. One common mechanism used by neural circuits is mapping representations of similar stimuli into distinct populations of neurons, minimizing their overlap. Previous studies in the hippocampus and amygdala have shown that blocking the actions of oxytocin or OXTR disrupts these coding mechanisms, leading to greater overlap between different social stimuli (Li et al., 2017; Raam et al., 2017). It is possible that one function of OXTR-expressing mPFC neurons is to segregate representation of the familiar and novel social stimuli into distinct populations of neurons. Optogenetically stimulating them may therefore increase neural responses of both stimuli in mPFC or downstream in the BLA in a nonspecific manner that leads to mnemonic interference. Further experiments may clarify these possibilities—for example, optogenetic inhibition to probe the necessity of OXTR-expressing mPFC neurons in social memory, as well as *in vivo* calcium imaging or electrophysiology to determine the response properties of these neurons during social memory.

A remaining intriguing question is how OXTR-expressing mPFC neurons influence other social behaviors regulated by the mPFC, such as sociability (Yizhar et al., 2011; Felix-Ortiz et al., 2016; Murugan et al., 2017), sociosexual approach (Nakajima et al., 2014; Li et al., 2016), parenting (Sabihi et al., 2014), encoding of social place (Murugan et al., 2017), and social dominance (Zhou et al., 2017; Kingsbury et al., 2019). Given that the stimulation of OXTR-expressing mPFC neurons activates several subcortical targets, how might oxytocin release in mPFC engage unique circuits for distinct types of social cues? How might the mechanisms underlying these different social behaviors converge or diverge with one another? To what extent do individual OXTR-expressing mPFC projection neurons collateralize to multiple subcortical targets, and to what extent are these projection neurons nonoverlapping? Future studies that combine circuit dissection with pharmacology, optogenetics, physiology, and detailed behavioral analyses may shed light on how OXTR-expressing mPFC circuits modulate social behaviors in both health and disease.

References

Bicks LK, Koike H, Akbarian S, Morishita H (2015) Prefrontal cortex and social cognition in mouse and man. Front Psychol 6:1805.

Chen P, Hong W (2018) Neural circuit mechanisms of social behavior. Neuron 98:16–30.

Felix-Ortiz AC, Burgos-Robles A, Bhagat ND, Leppla CA, Tye KM (2016) Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex. Neuroscience 321:197–209.

Ferguson JN, Young LJ, Hearn EF, Matzuk MM, Insel TR, Winslow JT (2000) Social amnesia in mice lacking the oxytocin gene. Nat Genet 25:284–288.

Kingsbury L, Huang S, Wang J, Gu K, Golshani P, Wu YE, Hong W (2019) Correlated Neural Activity and Encoding of Behavior across Brains of Socially Interacting Animals. Cell 178: 429–446.e416.

Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, Osten P, Schwarz MK, Seeburg PH, Stoop R, Grinevich V (2012)

Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron 73:553–566.

Lee HJ, Caldwell HK, Macbeth AH, Tolu SG, Young WS 3rd (2008) A conditional knockout mouse line of the oxytocin receptor. Endocrinology 149:3256–3263.

Li K, Nakajima M, Ibañez-Tallon I, Heintz N (2016) A Cortical circuit for sexually dimorphic oxytocin-dependent anxiety behaviors. Cell 167:60–72.e11.

Li Y, Mathis A, Grewe BF, Osterhout JA, Ahanonu B, Schnitzer MJ, Murthy VN, Dulac C (2017) Neuronal representation of social information in the medial amygdala of awake behaving mice. Cell 171:1176–1190.e17.

Macbeth AH, Lee HJ, Edds J, Young WS 3rd (2009) Oxytocin and the oxytocin receptor underlie intrastrain, but not interstrain, social recognition. Genes Brain Behav 8:558–567.

Murugan M, Jang HJ, Park M, Miller EM, Cox J, Taliaferro JP, Parker NF, Bhave V, Hur H, Liang Y, Nectow AR, Pillow JW, Witten IB (2017) Combined social and spatial coding in a descending projection from the prefrontal cortex. Cell 171:1663–1677.e16.

Nakajima M, Görlich A, Heintz N (2014) Oxytocin modulates female sociosexual behavior through a specific class of prefrontal cortical interneurons. Cell 159:295–305.

Padilla-Coreano N, Bolkan SS, Pierce GM, Blackman DR, Hardin WD, Garcia-Garcia AL, Spellman TJ, Gordon JA (2016) Direct ventral hippocampal-prefrontal input is required for anxiety-related neural activity and behavior. Neuron 89:857–866.

Raam T, McAvoy KM, Besnard A, Veenema AH, Sahay A (2017) Hippocampal oxytocin receptors are necessary for discrimination of social stimuli. Nat Commun 8:2001.

Sabihi S, Dong SM, Durosko NE, Leuner B (2014) Oxytocin in the medial prefrontal cortex regulates maternal care, maternal aggression and anxiety during the postpartum period. Front Behav Neurosci 8:258.

Spanswick SC, Dyck RH (2012) Object/context specific memory deficits following medial frontal cortex damage in mice. PLoS One 7:e43698.

Tan Y, Singhal SM, Harden SW, Cahill KM, Nguyen DM, Colon-Perez LM, Sahagian TJ, Thinschmidt JS, de Kloet AD, Febo M, Frazier CJ, Krause EG (2019) Oxytocin receptors are expressed by glutamatergic prefrontal cortical neurons that selectively modulate social recognition. J Neurosci 39:3249–3263.

Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, Sohal VS, Goshen I, Finkelstein J, Paz JT, Stehfest K, Fudim R, Ramakrishnan C, Huguenard JR, Hegemann P, Deisseroth K (2011) Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature 477:171–178.

Zhou T, Zhu H, Fan Z, Wang F, Chen Y, Liang H, Yang Z, Zhang L, Lin L, Zhan Y, Wang Z, Hu H (2017) History of winning remodels thalamo-PFC circuit to reinforce social dominance. Science 357:162–168.