INTRODUCTION

Oxytocin (OXT) neurons of the hypothalamus are at the center of several physiological functions, including milk ejection, uterus contraction, and maternal and social behavior. In lactating females, OXT neurons show a pattern of burst firing and inter-neuron synchronization during suckling that leads to pulsatile release of surges of OXT into the bloodstream to stimulate milk ejection. This pattern of firing and population synchronization may be facilitated in part by hypothalamic glutamatergic circuits, as has been observed in vitro using brain slices obtained from male rats and neonates. However, it remains unknown how hypothalamic glutamatergic circuits influence OXT cell activity outside the context of lactation. In this review, we summarize the in vivo and in vitro studies that describe the synchronized burst firing pattern of OXT neurons and the implication of hypothalamic glutamate in this pattern of firing. We also make note of the few studies that have traced glutamatergic afferents to the hypothalamic paraventricular and supraoptic nuclei. Finally, we discuss the genetic findings implicating several glutamatergic genes in neurodevelopmental disorders, including autism spectrum disorder, thus underscoring the need for future studies to investigate the impact of these mutations on hypothalamic glutamatergic circuits and the OXT system.

KEYWORDS

glutamate, hypothalamus, lactation, neurodevelopmental disorders, oxytocin
the circulation to regulate peripheral functions, including milk ejection and parturition, a pathway that does not implicate parvocellular OXT neurons.7,12 Parvocellular neurons, in contrast, project to the midbrain, brain stem and spinal cord8,13 to modulate cardiovascular function, breathing, feeding behavior and nociception.14 Through their collateral axons, magnocellular neurons of both the PVN and SON also project to other brain targets, including the prefrontal cortex, anterior olfactory nucleus, lateral septum, medial and central amygdala, and nucleus accumbens, to modulate a variety of behaviors, including social behavior.4–6,19–21 Less is clear, however, about how somatosensory and social cues are transmitted to OXT neurons and which neural inputs play a role in regulating the activity of OXT neurons to modulate physiological functions, including behavior.

In this review, we discuss research highlighting the influence of glutamate on OXT neural activity in vivo during lactation and parturition in females and in vitro using hypothalamic slices primarily obtained from adult males and neonates. We also emphasize the need for future studies to investigate whether hypothalamic glutamatergic circuits contribute to physiological functions other than parturition and lactation in females and/or males in vivo. Furthermore, we speculate that investigating the impact of mutations in glutamatergic genes on these circuits, as well as on the OXT system, will be of significant relevance to neurodevelopmental disorders characterized by social behavior deficits, including autism spectrum disorder (ASD).

2 | ELECTROPHYSIOLOGICAL CHARACTERISTICS OF OXYTOCIN NEURONS IN VIVO

Much of our knowledge about the characteristics of OXT neurons is gleaned from in vivo electrophysiological experiments conducted in the 1970s and 1980s, which were performed on anesthetized lactating female rats.12 These studies were pioneered by Wakerley and Lincoln, who characterized the activity of antidromically-identified neurosecretory cells in the PVN and SON during lactation.22–24 They found that the majority of these neurosecretory cells engage in consistent, low frequency activity (“tonic” firing) (1–10 spikes s–1), whereas a small percentage of these cells display intermittent activity separated by periods of quiescence, which they described as a “phasic” pattern of discharge. Furthermore, they reported that 10–20 s prior to increases in intramammary pressure indicative of milk ejection, about half of the recorded neurosecretory cells accelerate to a high-frequency rate of discharge (30–80 spikes s–1). This high-frequency firing lasts for 2–4 s, occurs at regular intervals of 4–8 min with transient periods of inhibition, and is strongly influenced by the number of suckling pups. These findings led to the speculation that high-frequency or “burst” firing underlies the release of pulses of OXT into the bloodstream during lactation, when OXT action on the mammary gland is needed for milk let-down. This speculation was supported and further delineated by a subsequent study conducted in 1977 by Poulain and colleagues, who demonstrated that, in both the PVN and SON, there are at least two distinct sets of neurosecretory cells, one of which displays “burst” firing during milk ejection (OXT neurons) and the other that displays an asynchronous “phasic” pattern of firing in response to hemorrhage (vasopressin [AVP] neurons). The background firing rates of neurosecretory cells were also further differentiated as fast continuous (> 3 spikes s–1) or slow irregular (< 3 spikes s–1), the latter of which was more common.25 Importantly, the same firing pattern of OXT neurons prior to milk let-down was also observed in unanesthetized rats and further recorded in the expulsive phase of parturition, indicating that OXT burst activity is indeed associated with these naturally occurring conditions.26,27 It was later established that OXT concentration in the blood increases significantly during nursing and parturition,28 which aligned with the electrophysiological firing pattern of OXT neurons observed during these physiological conditions.

Following these findings, it was theorized that, for OXT to be released into the bloodstream at high levels during lactation, OXT neurons must fire bursts at the same time. To address this theory, Belin, Moos and Richard investigated the relationship of the firing patterns of multiple OXT neurons by carrying out paired extracellular recordings in bilateral SON nuclei or PVN/SON nuclei in lactating female rats.29,30 They found that peak activation of bursts in pairs of OXT neurons occurred coincidentally, with minor differences noted in the degree of synchronization between neurons (i.e., time to burst onset, maximum firing rate and amplitude). Furthermore, they observed that, throughout milk ejection, cells could become “recruited”, such that if one cell in a pair was engaged in burst firing when the other was not, over time, the non-bursting cell might begin to burst as well and, once it did, its peak activation was synchronized with that of the other bursting cell in the pair.31 They therefore concluded that burst activity of OXT neurons between nuclei is highly synchronized and thereby facilitates the pulsatile release of OXT.

3 | ELECTROPHYSIOLOGICAL CHARACTERISTICS OF OXYTOCIN NEURONS IN VITRO

These ground-breaking studies performed in vivo were followed by several in vitro studies, which used acute hypothalamic slices and organotypic slice cultures to further inform the mechanisms of neuronal activity. In vitro studies offer the advantage of being able to control the extracellular environment and perform more stable intracellular recordings. Furthermore, the general pattern of activity of hypothalamic neurosecretory cells in vivo has also been observed in vitro, with the majority of cells engaging in spontaneous slow irregular firing, whereas some display fast continuous or burst firing patterns.22–26 However, it is important to note that key differences in the characteristics of neurosecretory cell activity in vivo and in vitro have been reported, particularly in relation to their interspike interval (ISI) distributions.37 It is assumed that the loss of synaptic input caused by deafferentiation during slice preparation led to these observed differences in ISI distribution between in vivo and in vitro data. Computational analysis with a Hodgkin–Huxley model derived from in vitro data confirmed that the ISI distributions of
in vitro and in vivo data could be similarly matched if the in vitro model was stimulated with tonic excitatory input. Thus, tonic excitatory synaptic input to the OXT neurons appears to play an important role in influencing specific aspects of the pattern of neurosecretory cell activity. Additionally, among studies using in vitro models, reports concerning the specific characteristics of firing patterns have varied greatly, which could be attributed to several other factors, including slice preparation and origin (adult males, lactating females, neonates), the region of recording (SON or PVN) and the type of neuron recorded (AVP or OXT). More targeted electrophysiological recordings of hypothalamic neurosecretory cells in vitro became possible with the development of specific antibodies to identify these cell types, which could be used in conjunction with dye-labeling of recorded neurons to differentiate between OXT and AVP neurons. Using this approach, groups targeted their intracellular recordings specifically to the OXT neural population and again found similarities as well as differences in the firing pattern of OXT neurons between previous recordings in lactating females in vivo and slices obtained from lactating rats, adult males or neonates in vitro. In vitro, OXT neuron bursting activity consisted of bursts of smaller amplitude, more variable duration and shorter inter-burst intervals compared to the typical pattern of bursting activity observed in vivo. It was also reported by Wang and Hatton, using paired extracellular recordings in vitro, that the bursting activity of OXT neurons was not synchronized in slices obtained from lactating rats as it is in vivo in lactating rats. Contrastingly, Israel and colleagues observed synchronized burst activity between pairs of OXT neurons using intracellular recordings in hypothalamic organotypic culture; however, considerable variability in the degree of burst synchronization was reported. As noted previously, these observed differences between in vitro and in vivo models are not entirely surprising because many inputs to the hypothalamus are severed in the process of slice preparation. Yet, providing proper stimulants in the media, such as phenylephrine, low Ca++, OXT and glutamate, can allow studies to parse out the relative influences of these substances and piece together the mechanism by which specific patterns of OXT neural activity occur. In this way, in vitro studies have led to critical advances in our knowledge of OXT neural activity, although limitations of the model should also be acknowledged with these findings.

4 | POSITIVE FEEDBACK REGULATION OF OXYTOCIN NEURONS BY OXYTOCIN

The idea of using OXT to stimulate the firing of OXT neurons was formulated based on early evidence suggesting that OXT neurons are capable of regulating their own activity and the paracrine release of OXT by a positive feedback mechanism. Intracerebroventricular administration of OXT in lactating female rats was found to cause an increase in the firing frequency and in the burst amplitude and frequency of OXT neurons. These increases were accompanied by a rise in intramammary pressure and milk ejection. Furthermore, administration of an OXT receptor antagonist inhibited both bursting activity and lactation. Interestingly, i.c.v. OXT administration was also capable of eliciting bursts in previously non-responsive neurons and OXT injected directly into the PVN or SON induced bursting activity in the contralateral nuclei, together indicating that local OXT is important for the recruitment of hypothalamic OXT neurons involved in the milk ejection reflex. To further examine whether local endogenous OXT acts on OXT neurons, microdialysis was performed in females during parturition and lactation, which confirmed that intranuclear concentrations of OXT were indeed increased in the PVN and SON during these processes. Importantly, the increase in OXT was attenuated following infusion of an OXT receptor antagonist into the hypothalamus, which also negatively impacted milk ejection and parturition. From these studies, it has been proposed that intrahypothalamic OXT, released from the soma and dendrites of OXT neurons, regulates OXT burst activity via positive feedback. Computational modeling has provided support for this theory, indicating that OXT exerts a local excitatory effect that, in conjunction with tonic afferent excitatory synaptic drive and phasic inhibitory effects of local endocannabinoid release, shapes the pattern of burst firing.

Similar mechanisms of OXT action on hypothalamic OXT neurons has also been observed in vitro. OXT administered through medium to slices of hypothalamus taken from adult male or lactating female rats led to an increase in OXT release, which could be blocked by an OXT antagonist. Extracellular recordings in hypothalamic slices of male rats further revealed that application of OXT excites putative OXT neurons, causing an increase in their firing rate. Addition of OXT or OXT receptor agonist to hypothalamic neonatal slice culture also led to increased bursting activity of both spontaneously bursting and non-bursting hypothalamic OXT neurons, which could be inhibited by an OXT antagonist. Interestingly, hyperpolarization/depolarization was unable to affect OXT-induced bursting activity, whereas application of the glutamate receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) was able to do so. These results led to the conclusion that synaptic input involving glutamate, coupled with OXT, is highly influential in the coordination of burst activity in hypothalamic OXT cells. However, as previously noted, the pattern of OXT activity observed in vitro differs from that observed in vivo. In vivo, OXT application stimulates bursting but does not increase background firing rate, as it does in vitro. Furthermore, a sucking stimulus is necessary to induce bursting in vivo. Therefore, although in vitro models provide important information concerning how OXT regulates the activity of OXT neurons, the underlying synchronous bursting mechanism may be more complicated as a result of intact intrinsic and extrinsic influences in vivo.

5 | GLUTAMATE REGULATES OXYTOCIN NEURONAL ACTIVITY IN THE HYPOTHALAMUS

5.1 | In vivo studies

The excitatory amino acid neurotransmitter glutamate has been shown to play an important role in stimulating OXT activity
within the hypothalamus, thereby regulating OXT release. In female rabbits, application of glutamate by microelectrophoresis in the PVN increased the firing rate of neurosecretory and non-neurosecretory cells. Microinjection of L-glutamate directly into the PVN of male rats also led to increased concentration of OXT in the blood, which was coupled with decreased heart rate. Similar results were obtained by Hattori and colleagues, showing decreased heartbeat following L-glutamate infusion. In their study, they also employed microdialysis to measure OXT concentration in the PVN following L-glutamate infusion, but reported no changes in central OXT levels. It is possible that the microdialysis and RIA approach was not sensitive enough to detect changes in PVN dialysate OXT, whereas changes in plasma OXT were of a high magnitude (seven-fold increase) and could be easily detected by these methods.

In an effort to further understand the role of glutamate receptor subtypes in regulating OXT neural activity, OXT release and its physiological relevance, the effect of specific excitatory amino acid agonists and antagonists on OXT release in lactating rats was assessed. Glutamate receptors can be ionotropic (fast) or metabotropic (slow), with the former consisting of NMDA receptors and non-NMDA receptors (AMPA and kainate). In their initial studies, Parker and Crowley found that AMPA and kainic acid injected into the SON led to increased concentration of OXT in the plasma. Furthermore, they found that the effects of AMPA were attenuated by the AMPA/kainate receptor antagonist CNQX. Interestingly, suckling-induced increases in OXT concentration were also inhibited by CNQX, indicating that glutamate may be important for the physiological regulation of OXT release during lactation. Notably, application of NMDA or the metabotropic receptor agonist (IS,3R)-1-amino-cyclopentane-1,3-dicarboxylic acid had no effect. However, further investigation revealed a partial role for NMDA receptors in OXT release, given that co-application of AMPA and NMDA agonists in the SON or PVN stimulated increases in plasma OXT that were then blocked by either AMPA or NMDA antagonists (CNQX and 3-[(2-carboxypiperazin-4-yl)propyl]1-phosphonic acid, respectively). A separate study by Moos and colleagues later identified a role for NMDA receptors in OXT cell activity in lactating rats. Injection of NMDA or the NMDA antagonist DL-2-amino-5-phosphonopentanoic acid (AP5) into the SON respectively increased or decreased the firing rate of OXT neurons and burst amplitude. However, it is critical to note that NMDA and AP5 did not affect the occurrence of bursts in non-bursting OXT neurons. Therefore, Moos and colleagues reported that, although both NMDA and AMPA receptors are implicated in the enhancement of OXT neural activity and the stimulation of OXT release in vivo, NMDA receptors alone do not facilitate burst occurrence.

### 5.2 In vitro studies

Electrophysiological studies in male hypothalamic acute slices and organotypic slice cultures have further supported a stimulatory role for glutamate. Application of glutamate and its agonists kainate and quisqualate elicited excitatory postsynaptic potentials (EPSPs) in hypothalamic neurons, whereas glutamate antagonists kynurenic acid and y-δ-glutamyglycine attenuated spontaneous and evoked EPSPs. Application of the non-NMDA receptor antagonist CNQX consistently blocked spontaneous and evoked EPSPs in several studies. The reported effects of NMDA receptors varied across studies employing different recording techniques in distinct in vitro preparations; however, most observed a modest effect of NMDA and its antagonist AP5 on postsynaptic activity compared to CNQX. Metabotropic glutamate receptors have also been shown to contribute to hypothalamic neurosecretory cell activity, through both presynaptic modulation of glutamate release and postsynaptic suppression of potassium currents. Therefore, it is likely that metabotropic and ionotropic receptor subtypes are all implicated in maintaining excitatory neurotransmission in hypothalamic OXT neurons. However, their particular roles and degree of influence may vary based on the physiological circumstances under which they are recruited.

Although outside the scope of this review, it should be noted that other key neurotransmitters, such as GABA, noradrenaline, dopamine, and acetylcholine, have been shown to modulate magnocellular neuron activity/release and likely work in conjunction with glutamate and OXT to facilitate activity in a circuit-specific, context-dependent manner. More thorough reviews on the effects of these neurotransmitters in the hypothalamus are available.

### 6 GLUTAMATERGIC CIRCUITS IN THE HYPOTHALAMIC PVN AND SON

Evidence for glutamatergic synaptic innervation of hypothalamic magnocellular neurosecretory cells has been supported by both structural and functional studies. Several ultrastructural immunocytochemistry studies conducted in male and female rodents have revealed that presynaptic axon terminals with glutamatergic immunoreactivity make contact with dendrites and cell bodies of AVP and OXT neurons. Approximately 20% of all presynaptic axon terminals on hypothalamic neurosecretory cells are glutamatergic, with many forming “shared” synapses in which terminals make contact with two or more postsynaptic cell bodies/dendrites. Furthermore, vesicular glutamate transporters (VGLUTs), specifically VGLUT-2 and VGLUT-3, are also detected within hypothalamic neurons. Functional evidence for glutamatergic circuits in magnocellular hypothalamic nuclei was established through in vitro recordings conducted in slices of adult male rat hypothalamus. These recordings demonstrated that extracellular electrical stimulation elicited EPSPs/excitatory postsynaptic currents (EPSCs) in magnocellular neurons that were characterized by both synchronous and asynchronous glutamate release, which prolongs the excitatory synaptic response and...
increases the probability of firing multiple action potentials with each synaptic activation.\textsuperscript{104,105} Together, these findings suggested that glutamatergic neurons input onto magnocellular neurosecretory cells in the PVN and SON, and that neurosecretory neurons in these nuclei are also glutamatergic themselves and may be capable of releasing both peptides and glutamate.

These discoveries coupled with observations concerning the effects of glutamate on OXT neuron activity brought the attention of the field to the potential role of local glutamatergic synaptic circuits in synchronizing the firing of OXT neurons. Activation of local circuits with glutamate microdrop application was shown to cause an increase in the frequency of EPSPs/EPSCs in some neurons,\textsuperscript{102} and EPSPs induced by noradrenaline were shown to be mediated by glutamate, given that bath application of both 6,7-dinitroquinoxaline-2,3-dione (DNQX) and APS blocked these excitatory responses.\textsuperscript{80} The noradrenaline-induced increase in EPSPs was retained in brain slices in which tissue surrounding the PVN had been trimmed away, suggesting that the presynaptic noradrenaline-sensitive glutamatergic circuits are intrinsic to the PVN. Notably, EPSP/EPSCs in the PVN could also be generated by microdrop stimulation of the ipsilateral SON or contralateral PVN, which were also blocked by DNQX and APS.\textsuperscript{101} Together, these ex vivo findings suggested the existence of local glutamatergic circuits and showed that synchronization between neurons in the PVN and SON could be achieved, at least in principal, by local glutamatergic circuits.

Direct evidence for synchronous synaptic inputs to OXT neurons from local glutamate circuits came from electrophysiological recordings in organotypic slice cultures of the hypothalamus. These slice cultures retain a certain number of cells intrinsic to the slice section and maintain the gross synaptic organization of the original tissue after several weeks in culture.\textsuperscript{44} Using this approach, Poullain and colleagues were able to record synchronized bursts of glutamatergic EPSPs in identified OXT neurons that drove synchronous high frequency bursts of action potentials among pairs of OXT neurons.\textsuperscript{43,48,106} This, therefore, provided direct evidence for synchronized bursting in OXT neurons coordinated in part by the activation of local hypothalamic glutamatergic circuits (Figure 1). Although excitatory synaptic connections generated by the slice culture conditions which are not normally present in native hypothalamic tissue may have contributed to synchronization of the OXT bursts in these studies, this finding nevertheless indicated that intrinsic glutamate circuits were present at the time the hypothalamus was isolated. These same regenerative properties of the slice culture preparation may have also contributed to synchronized synaptic inputs and action potentials in this preparation that have not been observed in acute slices or in vivo.

7 | EXTRAHYPOTHALAMIC GLUTAMATERGIC INPUTS TO THE PVN AND SON

Although studies conducted in vitro have greatly informed our understanding of the patterns of OXT neural activity and the release of OXT peptide in response to glutamate, the question of how sensory stimuli in the environment translate to neural signals to affect the pattern of hypothalamic OXT neurons remains of interest. Some insight on this matter emerged from studies in female rats where somatosensory information from the uterus, during parturition, or the nipples, during suckling, has been shown to trigger OXT release via the activity of A2 adrenergic afferents from the nucleus tractus solitarius of the brainstem to the PVN and SON.\textsuperscript{107-112} A2 adrenergic afferents release noradrenaline, which acts on local glutamatergic circuits within the PVN and SON, leading to changes in the firing pattern of OXT neurons and to the release of the OXT peptide.\textsuperscript{75,80,113,114} Furthermore, several in vitro experiments have shown that noradrenaline depolarizes magnocellular neurons by direct ionic mechanisms.\textsuperscript{114,115} Finally, noradrenergic neurons have also been shown to produce and release glutamate, suggesting that glutamate and noradrenaline are likely to be co-released from hypothalamic neurons.\textsuperscript{116-119} More work needs to be done to achieve a better understanding of how external sensory stimulation, such as baby vocalizations, suckling, social interaction and social transmission of maternal behavior, which was recently shown to be mediated by OXT,\textsuperscript{120} lead to activation of OXT neurons and to the release of OXT peptide, as well as which inputs on OXT neurons play a role in this process.

To identify glutamatergic/aspartatergic inputs to the PVN and SON, Csáki and colleagues used the retrograde tracer [H]D-aspartate coupled with autoradiography in male rats.\textsuperscript{121,122} They found that both the PVN and SON receive excitatory inputs from the thalamus, septum, bed nucleus of the stria terminals and amygdala. They also found that cell bodies within several hypothalamic nuclei, including the PVN and SON, were labelled with [3H]d-aspartate, indicating that these nuclei are interconnected by glutamatergic neurons. It is important to note that, although the approach applied in these studies provided important information on the origins of excitatory inputs to the hypothalamus, it lacked specificity because it is not selective for inputs to OXT neurons; therefore, the definite identity of these inputs could not be accurately determined. Recently, Tang and colleagues applied a retrograde tracing approach in females which allowed for the detection of afferents that specifically innervate OXT neurons. Using a viral system based on a retrograde trans-synaptic EnvA-pseudotyped G deletion-mutant rabies virus in combination with a helper adeno-associated virus expressed under the OXT promoter,\textsuperscript{123} they found that OXT neurons of the PVN receive afferents from several brain structures including the septum, medial preoptic area, insula, habenula, paraventricular nucleus of the thalamus, amygdala and substantia nigra. Although the identity of these inputs was not determined in their study, these findings in conjunction with those from Csáki and colleagues\textsuperscript{121,122} suggest that some of these afferents may be glutamatergic, and the question remains as to whether these glutamatergic inputs from extrahypothalamic brain regions play a role in the regulation of OXT neural firing and, if so, what behavioral or physiological mechanisms engage these circuits (Figure 1).
PHYSIOLOGICAL RELEVANCE OF GLUTAMATERGIC CIRCUITS

Our enhanced understanding of the role that glutamate plays in regulating OXT neural activity and the presumption, based on independent observations that OXT neurons are innervated by glutamatergic afferents, raises new questions about the physiological relevance of the hypothalamic glutamate-OXT circuits. It has been demonstrated, based on several in vivo studies, that intrahypothalamic glutamate may contribute to OXT neuron activity and release during lactation in vivo and synchronized burst firing in vitro, but interpretation of these data together is complicated by key differences in the model systems utilized in these studies. Originally, it was assumed that OXT cell burst activity is exclusive to females during parturition and lactation, given that evidence of synaptic remodeling has been reported in hypothalamic OXT neurons under these physiological conditions. However, in vitro studies examining this mechanism have primarily used hypothalamic tissue obtained from adult males or neonates and it is unknown whether this activity occurs naturally in vivo in these populations and, if so, under what circumstances. Glutamate has been implicated in stimulating OXT release to regulate cardiovascular activity and during dehydration. Although the function of glutamate-OXT circuits in the context of social behaviors remains unknown, both glutamate and OXT have been separately implicated in neurodevelopmental disorders characterized by deficits in social behavior.
Glutamatergic signaling plays a pivotal role in early brain development by regulating the proliferation and differentiation of neural progenitor cells. Neuronal migration and synaptic plasticity are critical processes that are affected by abnormalities in glutamatergic circuits and OXT neurons. The role of the hypothalamic OXT system in ASD and other NDDs has been extensively studied, with evidence suggesting that perturbations in the OXT system could be linked to the development of these disorders. The causality between OXT and ASD has been extensively discussed in the last two decades, and research findings suggest that the OXT system may play a role in the pathophysiology of these disorders.
behaviors will enhance our understanding of the mechanisms of function of the OXT system, and that investigating the impact of NDD-associated mutation on the OXT system has the potential to uncover new pathophysiology that could be underlying social behavior deficits.

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The authors declare that they have no conflicts of interest.

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Amanda Leithead: Conceptualization; Writing – original draft; Writing – review & editing. Jeffrey G. Tasker: Supervision; Writing - original draft; Writing - review & editing. Hala Harony-Nicolás: Conceptualization; Funding acquisition; Resources; Supervision; Writing – original draft; Writing – review & editing.

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REFERENCES
1. Jurek B, Neumann ID. The oxytocin receptor: from intracellular signaling to behavior. Physiol Rev. 2018;98(3):1805-1908.
2. Adams MM, Shah RA, Jansen WG, Morrison JH. Different modes of hippocampal plasticity in response to estrogen in young and aged female rats. Proc Natl Acad Sci USA. 2001;98(14):8071-8076.
3. Armstrong WE, Warach S, Hatton GL, McNeill TH. Subnuclei in the rat hypothalamic paraventricular nucleus: a cytoarchitectural, horseradish peroxidase and immunocytochemical analysis. Neuroscience. 1980;5(11):1931-1958.
4. Grinevich V, Knobloch-Bollmann HS, Eliava M, Busnelli M, Chini B. Assembling the puzzle: pathways of oxytocin signaling in the brain. Biol Psychiatry. 2016;79(3):155-164.
5. Grinevich V, Neumann ID. Brain oxytocin: how puzzle stones from animal studies translate into psychiatry. Mol Psychiatry. 2020;25(1):265-279.
6. Sofroniew MV. Morphology of vasopressin and oxytocin neurons and their central and vascular projections. Prog Brain Res. 1983;60:101-114.
7. Swanson LW, Kuypers HG. The paraventricular nucleus of the hypothalamus: cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex, and spinal cord as demonstrated by retrograde fluorescence double-labeling methods. J Comp Neurol. 1980;194(3):555-570.
8. Swanson LW, Sawchenko PE. Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. Annu Rev Neurosci. 1983;6:269-324.
9. Swanson LW, Sawchenko PE, Wiegand SJ, Price JL. Separate neurons in the paraventricular nucleus project to the median eminence and to the medulla or spinal cord. Brain Res. 1980;198(1):190-195.
10. Liao P-Y, Chiu Y-M, Yu J-H, Chen S-K. Mapping central projection of oxytocin neurons in unmated mice using Cre and alkaline phosphatase reporter. Front Neuroanat. 2020;14:559402.
11. Zhang B, Qiu L, Xiao W, et al. Reconstruction of the hypothalamo-neurohypophysial system and functional dissection of magnocellular oxytocin neurons in the brain. Neuron. 2021;109(2):331-346.
12. Poulain DA, Wakerley JB. Electrophysiology of hypothalamic magnocellular neurons secreting oxytocin and vasopressin. Neuroscience. 1982;7(4):773-808.
13. Sawchenko PE, Swanson LW. Immunohistochemical identification of neurons in the paraventricular nucleus of the hypothalamus that project to the medulla or to the spinal cord in the rat. J Comp Neurol. 1982;205(3):260-272.
14. Atasoy D, Betley JN, Su HH, Sternson SM. Deconstruction of a neural circuit for hunger. Nature. 2012;488(7410):172-177.
15. Condes-Lara M, Gonzalez NM, Martinez-Lorencana G, Delgado OL, Freund-Mercier MJ. Actions of oxytocin and interactions with glutamate on spontaneous and evoked dorsal spinal cord neuronal activities. Brain Res. 2003;976(1):75-81.
16. Mack SO, Kc P, Wu M, Coleman BR, Tolentino-Silva FP, Haxhiu MA. Paraventricular oxytocin neurons are involved in neural modulation of breathing. J Appl Physiol (1985). 2002;92(2):826-834.
17. Petersson M. Cardiovascular effects of oxytocin. Proc Brain Res. 2002;129:281-288.
18. Eliava M, Melchior M, Knobloch-Bollmann HS, et al. A new population of parvocellular oxytocin neurons controlling magnocellular neuron activity and inflammatory pain processing. Neuron. 2016;89(6):1291-1304.
19. Dolen G, Darvishzadeh A, Huang KW, Malenka RC. Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature. 2013;501(7466):179-184.
20. Knobloch HS, Charlet A, Hoffmann LC, et al. Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron. 2012;73(3):553-566.
21. Menon R, Grund T, Zoicas I, et al. Oxytocin signaling in the lateral septum prevents social fear during lactation. Curr Biol. 2018;28(7):1066-1078 e1066.
22. Lincoln DW, Wakerley JB. Electrophysiological evidence for the activation of supraoptic neurons during the release of oxytocin. J Physiol. 1974;242(2):533-554.
23. Lincoln DW, Wakerley JB. Factors governing the periodic activation of supraoptic nad paraventricular neurosecretory cells during suckling in the rat. J Physiol. 1975;250(2):443-461.
24. Wakerley JB, Lincoln DW. The milk-ejection reflex of the rat: a 20- to 40-fold acceleration in the firing of paraventricular neurons during oxytocin release. J Neuroendocrinol. 1973;57(3):477-493.
25. Poulain DA, Wakerley JB, Dyball REJ. Electrophysiological differentiation of oxytocin-and vasopressin-secreting neurons. Royal Society. 1977;196(1125):367-384.
26. Summerlee AJS, Lincoln DW. Electrophysiological recordings from oxytocinergic neurons during suckling in the unanesthetized lactating rat. J Neuroendocrinol. 1981;90:255-265.
27. Summerlee AJS. Extracellular recordings from oxytocin neurons during the expulsive phase of birth in unanesthetized rats. J Physiol. 1981;321:1-9.
28. Higuchi T, Honda K, Fukuoka T, Negoro H, Wakabayashi K. Release of oxytocin during suckling and parturition in the rat. J Endocrinol. 1985;105(3):339-346.

29. Belin V, Moos F. Paired recordings from supraoptic and paraventricular oxytocin cells in suckled rats: recruitment and synchronization. J Physiol. 1986;377:369-390.

30. Belin V, Moos F, Richard P. Synchronization of oxytocin cells in the hypothalamic paraventricular and supraoptic nuclei in suckled rats: direct proof with paired extracellular recordings. Exp Brain Res. 1984;57:201-203.

31. Moos F, Richard P. Characteristics of early- and late-recruited oxytocin bursting cells at the beginning of suckling in rats. J Physiol. 1988;399(1):11-12.

32. Armstrong WE, Smith BN, Tian M. Electrophysiological characteristics of immunocytochemically identified rat oxytocin and vasopressin neurons in vitro. J Physiol. 1994;475(1):115-128.

33. Dudek FE, Hatton GI, Macvicar BA. Intracellular recordings from the paraventricular nucleus in slices of rat hypothalamus. J Physiol. 1980;301(1):101-114.

34. Haller E, Wakerley J. Electrophysiological studies of paraventricular and supraoptic neurons recorded in vitro from slices of rat hypothalamus. J Physiol. 1980;302(1):347-362.

35. Hatton GI, Armstrong WE, Gregory WA. Spontaneous and osmotically-stimulated activity in slices of rat hypothalamus. Brain Res Bull. 1978;3(5):497-508.

36. Stern JE, Armstrong WE. Electrophysiological differences between oxytocin and vasopressin neurons recorded from female rats in vitro. J Physiol. 1995;488(3):701-708.

37. Sabatier N, Brown CH, Ludwig M, Leng G. Phasic spike pattern in rat supraoptic neurons in vivo and in vitro. J Physiol. 2004;558(1):161-180.

38. Leng T, Leng G, MacGregor DJ. Spike patterning in oxytocin neurons: capturing physiological behaviour with Hodgkin-Huxley and integrate-and-fire models. PLoS One. 2017;12(7):e0180368.

39. Cobbett P, Smithson KG, Hatton GI. Immunoreactivity to vasopressin-but not oxytocin-associated neurophysin antisera in phasic neurons of rat hypothalamic paraventricular nucleus. Brain Res. 1986;362(1):7-16.

40. Yamashita H, Inenaga K, Kawata M, Sano Y. Phasically firing neurons in the supraoptic nucleus of the rat hypothalamus: immunocytochemical and electrophysiological studies. Neurosci Lett. 1983;37(1):87-92.

41. Bourque C, Renaud L. Membrane properties of rat magnocellular neuroendocrine cells in vivo. Brain Res. 1991;540(1-2):349-352.

42. Dyball R, Way S, Leng G. Modulation of oxytocin release at the secretory terminal by endogenous opioids following systemic administration of cholecystokinin in the rat. J Physiol. 1991;434:83P.

43. Israel JM, Le Masson G, Theodosis DT, Poullain DA. Glutamatergic input governs periodicity and synchronization of bursting activity in oxytocin neurons in hypothalamic organotypic cultures. Eur J Neurosci. 2003;17(12):2619-2629.

44. Jourdain P, Poullain D, Theodosis DT, Israel JM. Electrical properties of oxytocin neurons in organotypic cultures from postnatal rat hypothalamus. J Neurophysiol. 1996;76(4):2772-2785.

45. Wang F, Hatton GI. Milk ejection burst-like electrical activity evoked in supraoptic oxytocin neurons in slices from lactating rats. J Neurophysiol. 2004;91:2312-2321.

46. Wang YF, Hatton GI. Burst firing of oxytocin neurons in male rat hypothalamic slices. Brain Res. 2005;1032(1-2):36-43.

47. Hatton G, Wang Y. Neural mechanisms underlying the milk ejection burst and reflex. In: Neumann ID, Landgraf R, (eds.) Advances in Vasopressin and Oxytocin: From Genes to Behaviour to Disease. Progress in Brain Research. Vol 170. Elsevier; 2008:155-166.
coactivation through Non-NMDA glutamate receptors or the glycine coagonist site. *Neuroendocrinology*. 1995;62(5):467-478.

67. Moos F, Rossi K, Richard P. Activation of N-methyl-D-aspartate receptors regulates basal electrical activity of oxytocin and vasopressin neurons in lactating rats. *Neuroscience*. 1997;77(4):993-1002.

68. Hu B, Bourque CW. Functional N-methyl-D-aspartate and non-N-methyl-D-aspartate receptors are expressed by rat supraoptic neurosecretory cells in vitro. *J Neuroendocrinol*. 1991;3(5):509-514.

69. van den Pol A. Glutamate and aspartate immunoreactivity in hypothalamic presynaptic axons. *J Neurosci*. 1991;11(11):2087-2101.

70. van den Pol A, Wuarin J, Dudek F. Glutamate, the dominant excitatory transmitter in neuroendocrine regulation. Science. 1990;250:1276-1278.

71. Gribkoff VK, Dudek FE. Effects of excitatory amino acid antagonists on synaptic responses of supraoptic neurons in slices of rat hypothalamus. *J Neurophysiol*. 1990;63(1):60-71.

72. Wuarin J-P, Dudek FE. Excitatory amino acid antagonists inhibit synaptic responses in the guinea pig hypophysial paraventricular nucleus. *J Neurophysiol*. 1991;65(4):946-951.

73. Schrader L, Tasker J. Presynaptic modulation by metabotropic glutamate receptors of excitatory and inhibitory synaptic inputs to hypothalamic magnocellular neurons. *J Neurophysiol*. 1997;77(2):527.

74. Schrader L, Tasker J. Modulation of multiple potassium currents by metabotropic glutamate receptors in neurons of the hypothalamic supraoptic nucleus. *J Neurophysiol*. 1997;78(6):3428-3437.

75. Randle J, Day T, Jhamandas J, Bourque C, Renaud L. Neuropharmacology of supraoptic nucleus neurons: norepinephrine and gamma-aminobutyric acid receptors. Paper presented at: Federation proceedings1986.

76. Randle J, Renaud L. Actions of gamma-aminobutyric acid on rat supraoptic nucleus neurosecretory neurons in vitro. *J Physiol*. 1987;387(1):629-647.

77. Jhamandas JH, Renaud L. A gamma-aminobutyric-acid-activated baroreceptor input to supraoptic vasopressin neurons in the rat. *J Physiol*. 1986;381(1):595-606.

78. Theodosis D, Paut L, Tappaz M. Immunocytochemical analysis of the GABAergic innervation of oxytocin-and vasopressin-secreting neurons in the rat supraoptic nucleus. *Neuroscience*. 1986;19(1):207-222.

79. Decavel C, van den Pol AN. Converging GABA-and glutamate-immunoreactive axons make synaptic contact with identified hypothalamic neurosecretory neurons. *J Comp Neurol*. 1992;316(1):104-116.

80. Daftary S, Boudaba C, Szabo K, Tasker J. Noradrenergic excitation of magnocellular neurons in the rat hypothalamic paraventricular nucleus via intranuclear glutamatergic circuits. *J Neurosci*. 1998;18(24):10619-10628.

81. Daftary S, Boudaba C, Tasker J. Noradrenergic regulation of parvocellular neurons in the rat hypothalamic paraventricular nucleus. *Neuroscience*. 2000;96(4):743-751.

82. Moos F, Richard P. Excitatory effect of dopamine on oxytocin and vasopressin reflex releases in the rat. *Brain Res*. 1982;241(2):249-260.

83. Baskerville T, Allard J, Wayman C, Douglas A. Dopamine-oxytocin interactions in penile erection. *Eur J Neurosci*. 2009;30(11):2151-2164.

84. Baskerville TA, Douglas AJ. Dopamine and oxytocin interactions underlying behaviors: potential contributions to behavioral disorders. *CNS Neurosci Ther*. 2010;16(3):e92-e123.

85. Zaninetti M, Tribollet E, Bertrand D, Raggenbass M. Nicotinic cholinergic activation of magnocellular neurons of the hypothalamic paraventricular nucleus. *Neuroscience*. 2002;110(2):287-299.

86. Gribkoff V, Christian E, Robinson J, Deadwyler S, Dudek F. Cholinergic excitation of supraoptic neurons in hypothalamic slices of rat. *Neuropharmacology*. 1988;27(7):721-727.

87. Li D-P, Pan H-L. Potentiation of glutamatergic synaptic input to supraoptic neurons by presynaptic nicotinic receptors. *Am J Physiol Regul Integr Comp Physiol*. 2001;281(4):R1105-R1113.

88. Renaud L, Bourque C. Neurophysiology and neuropharmacology of hypothalamic magnocellular neurons secreting vasopressin and oxytocin. *Prog Neurobiol*. 1991;36:131-169.

89. Brown CH, Bains JS, Ludwig M, Stern JE. Physiological regulation of magnocellular neurosecretory cell activity: integration of intrinsic, local and afferent mechanisms. *J Neuroendocrinol*. 2013;25(8):678-710.

90. Iovino M, Giagulli VA, Lichelli B, Iovino E, Guastamacchia E, Triggiani V. Synaptic inputs of neural afferent pathways to vasopressin- and oxytocin-secreting neurons of supraoptic and paraventricular hypothalamic nuclei. *Endocr Metab Immune Disord Drug Targets*. 2016;16(4):276-287.

91. Augustine RA, Seymour AJ, Campbell RE, Grattan DR, Brown CH. Integrative neuro-humoral regulation of oxytocin neuron activity in pregnancy and lactation. *J Neuroendocrinol*. 2018;30(8):e12569.

92. Leng G, Caquineau C, Sabatier N. Regulation of oxytocin secretion. *Vitam Horm*. 2005;71:27-58.

93. Seider SL, Armstrong WE, Crowley WR. Oxytocin release in magnocellular nuclei: neurochemical mediators and functional significance during gestation. *Am J Physiol Regul Integr Comp Physiol*. 2010;299(2):R452-R458.

94. El Majdoubi M, Poulain D, Theodosis D. Lactation-induced plasticity in the supraoptic nucleus augments axodendritic and axosomatic GABAergic and glutamatergic synapses: an ultrastructural analysis using the disector method. *Neuroscience*. 1997;80(4):1137-1147.

95. El Majdoubi M, Poulain DA, Theodosis DT. The glutamatergic innervation of oxytocin- and vasopressin-secreting neurons in the rat supraoptic nucleus and its contribution to lactation-induced synaptic plasticity. *Eur J Neurosci*. 1996;8:1377-1389.

96. Meeker R, Swanson D, Greenwood R, Hayward J. Quantitative mapping of glutamate presynaptic terminals in the supraoptic nucleus and surrounding hypothalamus. *Brain Res*. 1993;600(1):112-122.

97. Meeker R, Swanson D, Hayward J. Light and electron microscopic localization of glutamate immunoreactivity in the supraoptic nucleus of the rat hypothalamus. *Neuroscience*. 1989;33(1):157-167.

98. Lin W, McKinney K, Liu L, Lakhlani S, Jennes L. Distribution of vesicular glutamate transporter-2 messenger ribonucleic acid and protein in the septum-hypothalamus of the rat. *Endocrinology*. 2003;144(2):662-670.

99. Ponzo TA, Ni Y, Montana V, Parpura V, Hatton Gl. Vesicular glutamate transporter expression in supraoptic neurons suggests a glutamatergic phenotype. *J Neuroendocrinol*. 2006;18(4):253-265.

100. Xu S, Yang H, Menon V, et al. Behavioral state coding by molecularly defined paraventricular hypothalamic cell type ensembles. *Science*. 2020;370(6514):eabb2494.

101. Boudaba C, Tasker JG. Intranuclear coupling of hypothalamic magnocellular nuclei by glutamate synaptic circuits. *Am J Physiol Regul Integr Comp Physiol*. 2006;291(1):R102-R111.

102. Boudaba C, Schrader LA, Tasker JG. Physiological evidence for local excitatory synaptic circuits in the rat hypothalamus. *J Physiol*. 1997;77(6):3396-3400.

103. Tasker JG, Boudaba C, Schrader LA. Local glutamatergic and gabaergic synaptic circuits and metabotropic glutamate receptors in the hypothalamic paraventricular and supraoptic nuclei. *Vasopressin and Oxytocin*. 1998;449:117-121.

104. Iremonger KJ, Bains JS. Integration of asynchronously released quanta prolongs the postsynaptic spike window. *J Neurosci*. 2007;27(25):6684-6691.

105. Iremonger KJ, Bains JS. Asynchronous presynaptic glutamate release enhances neuronal excitability during the post-spike refractory period. *J Physiol*. 2016;594(4):1005-1015.
106. Jourdain P, Dupouy B, Bonhomme R, Theodosit DS, Poulin DA, Israel JM. Electrophysiological studies of oxytocin neurons in organotypic slice cultures. In: Zingg H.H., Bourque C.W., Bichet D.G. (eds.) Vasopressin and Oxytocin. Advances in Experimental Medicine and Biology. Vol 449. Springer; 1998:135-145.

107. Cunningham E Jr, Sawchenko P. Anatomical specificity of noradrenergic inputs to the paraventricular and supraoptic nuclei of the rat hypothalamus. J Comp Neurol. 1988;274(1):60-76.

108. Douglas A, Scullion S, Antonijevic I, Brown D, Russell J, Leng G. Uterine contractile activity stimulates supraoptic neurons in term pregnant rats via a noradrenergic pathway. Endocrinology. 2001;142(2):633-644.

109. Meddle S, Leng G, Selvarajah J, Bicknell R, Russell J. Direct pathways to the supraoptic nucleus from the brainstem and the main olfactory bulb are activated at parturition in the rat. Neuroscience. 2000;101(4):1013-1021.

110. Onaka T, Luckman S, Antonijevic I, Palmer J, Leng G. Involvement of the noradrenergic afferents from the nucleus tractus solitarii to the supraoptic nucleus in oxytocin release after peripher al cholecystokinin octapeptide in the rat. Neuroscience. 1995;66(2):403-412.

111. Raby WN, Renaud L. Dorsomedial medulla stimulation activates rat supraoptic oxytocin and vasopressin neurons through different pathways. J Physiol. 1989;417(1):279-294.

112. Valtcheva S, Froemke RC. Neuromodulation of maternal circuits by LEITHEAD ET AL.

113. Boudaba C, Di S, Tasker J. Presynaptic noradrenergic regulation of glutamate inputs to hypothalamic magnocellular neurons. J Neuroendocrinol. 2003;15(8):803-810.

114. Yamashita H, Inenaga K, Kannan H. Depolarizing effect of noradrenaline on neurons of the rat supraoptic nucleus in vitro. Brain Res. 1987;405(2):348-352.

115. Randle J, Mazurek M, Kneifel D, Dufresne J, Renaud L. α1-adrenergic receptor activation releases vasopressin and oxytocin from perfused rat hypothalamic explants. Neurosci Lett. 1986;65(2):219-223.

116. Johnson CS, Bains JS, Watts AG. Neurotransmitter diversity in pre-synaptic terminals located in the parvicellular neuroendocrine paraventricular nucleus of the rat and mouse hypothalamus. J Comp Neurol. 2018;526(8):1287-1306.

117. Roman CW, Derkach VA, Palmiter RD. Genetically and functionally defined NTS to PBN brain circuits mediating anoxia. Nat Commun. 2016;7(1):1-11.

118. Stornetta RL, Sevigny CP, Guyenet PG. Visceral glutamate transporter DNPI/VGLUT2 mRNA is present in C1 and several other groups of brainstem catecholaminergic neurons. J Comp Neurol. 2002;444(3):191-206.

119. Chen C, Jiang Z, Fu X, Yu D, Huang H, Tasker JG. Astrocytes amplify neuronal dendritic volume transmission stimulated by norepinephrine. Cell Rep. 2019;29(13):4349-4361.e4344.

120. Carcea I, Caraballo NL, Marlin BJ, et al. Oxytocin neurons enable social transmission of maternal behaviour. Nature. 2021;596(7873):553-557.

121. Csakí A, Kocsis K, Halasz B, Kiss J. Localization of glutamatergic/aspartergic neurons projecting to the hypothalamic paraventricular nucleus studied by retrograde transport of [3H]D-aspartate autoradiography. Neuroscience. 2000;101(3):637-655.

122. Csakí A, Kocsis K, Kiss J, Halasz B. Localization of putative glutamatergic/aspartergic neurons projecting to the supraoptic nucleus area of the rat hypothalamus. Eur J Neurol. 2002;16:55-68.

123. Tang Y, Benusiglio D, Lefevre A, et al. Social touch promotes interfemale communication via activation of parvocellular oxytocin neurons. Nat Neurosci. 2020;23(9):1125-1137.

124. Theodosit DS. Oxytocin-secreting neurons: a physiological model of morphological neuronal and glial plasticity in the adult hypothalamus. Front Neuroendocrinol. 2002;23(1):101-135.

125. Tasker JGV, Volsin DL, Armstrong WE. The Cell Biology of Oxytocin and Vasopressin Cells. 3 edn. Academic Press; 2017:3.

126. Onaka T, Yagi K. Involvement of N-methyl-D-aspartic acid receptor activation in oxytocin and vasopressin release after osmotic stimuli in rats. J Neuroendocrinol. 2001;13(2):166-174.

127. Volk L, Chiu S-L, Sharma K, Huganir RL. Glutamate synapses in human cognitive disorders. Annu Rev Neurosci. 2015;38:127-149.

128. Soto D, Altafaj X, Sindreu C, Bayés À. Glutamate receptor mutations in psychiatric and neurodevelopmental disorders. Commun Integr Biol. 2014;7(1):e27887.

129. LoParo D, Waldman I. The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: a meta-analysis. Mol Psychiatry. 2015;20(5):640-646.

130. Guastella AJ, Hickie IB. Oxytocin treatment, circuitry, and autism: a critical review of the literature placing oxytocin into the autism context. Biol Psychiatry. 2016;79(3):234-242.

131. Di Giorgi-Gerevini V, Melchiorri D, Battaglia G, et al. Endogenous activation of metabotropic glutamate receptors supports the proliferation and survival of neural progenitor cells. Cell Death Differ. 2005;12(8):1124-1133.

132. Cappuccio I, Verani R, Spinsanti P, et al. Context-dependent regulation of embryonic stem cell differentiation by mGlur5 metabotropic glutamate receptors. Neuropharmacology. 2006;51(3):606-611.

133. Komuro H, Rakic P. Modulation of neuronal migration by NMDA receptors. Science. 1993;260(5104):95-97.

134. Manent J-B, Demarque M, Jorquera I, et al. A noncanonical release of GABA and glutamate modulates neuronal migration. J Neurosci. 2005;25(19):4755-4765.

135. Barnes JR, Mukherjee B, Rogers BC, Nafar F, Gosses M, Parsons MP. The relationship between glutamate dynamics and activity-dependent synaptic plasticity. J Neurosci. 2020;40(14):2793-2807.

136. Feldman D, Nicolli R, Malenka R. Synaptic plasticity at thalamocortical synapses in developing rat somatosensory cortex: LTP, LTD, and silent synapses. J Neurobiol. 1999;41(1):92-101.

137. Jansson LC, Åkerman KE. The role of glutamate and its receptors in the proliferation, migration, differentiation and survival of neural progenitor cells. J Neuro Transm. 2014;121(8):819-836.

138. Luján R, Shigemoto R, López-Bendito G. Glutamate and GABA receptor signalling in the developing brain. Neuroscience. 2005;130(3):567-580.

139. Tau GZ, Peterson BS. Normal development of brain circuits. Neuropsychopharmacology. 2010;35(1):147-168.

140. Bureshnev N, Szepetowski P. NMDA receptor subunit mutations in neurodevelopmental disorders. Curr Opin Pharmacol. 2015;20:73-82.

141. Moretto E, Murru L, Martano G, Sassone J, Passafaro M. Glutamatergic synapses in neurodevelopmental disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84:328-342.

142. Celli R, Santolini I, Van Luijtelaar G, Ngomba RT, Bruno V, Nicoletti F. Targeting metabotropic glutamate receptors in the treatment of epilepsy: rationale and current status. Expert Opin Ther Targets. 2019;23(4):341-351.

143. Hanada T. Ionotropic glutamate receptors in epilepsy: a review focusing on AMPA and NMDA receptors. Biomolecules. 2020;10(3):464.

144. Uno Y, Coyle JT. Glutamate hypothesis in schizophrenia. Psychiatry Clin Neurosci. 2019;73(5):204-215.

145. Coyle JT, Basu A, Benneyworth M, Balu D, Konopaske G. Glutamatergic synaptic dysregulation in schizophrenia: therapeutic implications. Nov Antischizophrenia Treat. 2012;213:267-295.

146. Rubenstein J, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav. 2003;2(5):255-267.

147. Nelson SB, Valakh V. Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. Neuron. 2015;87(4):684-698.
148. Uzunova G, Pallanti S, Hollander E. Excitatory/inhibitory imbalance in autism spectrum disorders: implications for interventions and therapeutics. *World J Biol Psychiatry*. 2016;17(3):174-186.

149. Südhof TC. Neurotrophins and neurotrophins link synaptic function to cognitive disease. *Nature*. 2008;455(7215):903-911.

150. De Rubeis S, He X, Goldberg AP, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*. 2014;515(7526):209-215.

151. Satterstrom FK, Kosmicki JA, Wang J, et al. Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell*. 2020;180(3):568-584.e523.

152. Mei Y, Monteiro P, Zhou Y, et al. Adult restoration of Shank3 expression rescues selective autistic-like phenotypes. *Nature*. 2016;530(7591):481-484.

153. Berg EL, Copping NA, Rivera JK, et al. Developmental social communication deficits in the Shank3 rat model of phelan-mcdermid syndrome and autism spectrum disorder. *Autism Res*. 2018;11(4):587-601.

154. Drapeau E, Riad M, Kajiwara Y, Buxbaum JD. Behavioral phenotyping of an improved mouse model of phelan-McDermid syndrome with a complete deletion of the Shank3 gene. *eNeuro*. 2018;5(3):ENEURO.0046-18.2018.

155. Rein B, Yan Z, Wang ZJ. Diminished social interaction incentive contributes to social deficits in mouse models of autism spectrum disorder. *Genes Brain Behav*. 2019;19(1):e12610.

156. Teng BL, Nikolova VD, Riddick NV, et al. Reversal of social deficits by subchronic oxytocin in two autism mouse models. *Neuropharmacology*. 2016;105:61-71.

157. Lee E, Lee J, Kim E. Excitation/inhibition imbalance in animal models of autism spectrum disorders. *Biol Psychiatri*. 2017;81(10):838-847.

158. Wang X, Bey AL, Katz BM, et al. Altered mGlu5-Homer scaffolds and corticostriatal connectivity in a Shank3 complete knockout model of autism. *Nat Commun*. 2016;7:11459.

159. Vicidomini C, Ponzoni L, Lim D, et al. Pharmacological enhancement of mGlu5 receptors rescues behavioral deficits in SHANK3 knock-out mice. *Mol Psychiatry*. 2017;22(5):689-702.

160. Peca J, Feliciano C, Ting JT, et al. Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. *Nature*. 2011;472(7344):437-442.

161. Blundell J, Blaas CA, Etherton MR, et al. Neuroloj-in-1 deletion results in impaired spatial memory and increased repetitive behavior. *J Neurosci*. 2010;30(6):2115-2129.

162. Bozdagi O, Sakurai T, Papapetrou D, et al. Halpoininsufficiency of the autism-associated Shank3 gene leads to deficits in synaptic function, social interaction, and social communication. *Mol Autism*. 2010;1(1):15.

163. Wang X, McCoy PA, Rodriguiz RM, et al. Synaptic dysfunction and abnormal behaviors in mice lacking major isoforms of Shank3. *Hum Mol Genet*. 2011;20(15):3093-3108.

164. Yang M, Bozdagi O, Scattoni ML, et al. Reduced excitatory neurotransmission and mild autism-relevant phenotypes in adolescent Shank3 null mutant mice. *J Neurosci*. 2012;32(19):6525-6541.

165. Penagarikano O, Lazaro MT, Lu XH, et al. Exogenous and evoked oxytocin restores social behavior in the Cntnap2 mouse model of autism. *Sci Transl Med*. 2015;7(271):271ra8.

166. Resendez SL, Namboodiri VMK, Otis JM, et al. Social stimuli induce activation of oxytocin neurons within the paraventricular nucleus of the hypothalamus to promote social behavior in male mice. *J Neurosci*. 2020;40(11):2282-2295.

167. Ring RH, Schechter LE, Leonard SK, et al. Receptor and behavioral pharmacology of WAY-267464, a non-peptide oxytocin receptor agonist. *Neuropsychopharmacology*. 2010;58(1):69-77.

168. Harony-Nicolás H, Kay M, du Hoffmann J, et al. Oxytocin improves behavioral and electrophysiological deficits in a novel Shank3-deficient rat. *Elife*. 2017;6:e18904.

169. Rajamani KT, Wagner S, Grinevich V, Harony-Nicolás H. Oxytocin as a modulator of synaptic plasticity: implications for neurodevelopmental disorders. *Front Synaptic Neurosci*. 2018;10:17.

170. Lung L, Neuner S, Polepalli J, et al. Gating of social reward by oxytocin in the ventral tegmental area. *Science*. 2017;357(6358):1406-1411.

171. Aharoni D, Khakh BS, Silva AJ, Golshani P. All the light that we can see: a new era in miniaturized microscopy. *Nat Methods*. 2019;16(1):11-13.

172. Modahl C, Fein D, Waterhouse L, Newton N. Does oxytocin deficiency mediate social deficits in autism? *J Autism Dev Disord*. 1992;22(3):449-451.

173. Green JJ, Hollander E. Autism and oxytocin: new developments in translational approaches to therapeutics. *Neurotherapeutics*. 2010;7(3):250-257.

174. Hammock EA, Young LJ. Oxytocin, vasopressin and pair bonding: implications for autism. *Philos Trans R Soc Lond B Biol Sci*. 2006;361(1476):2187-2198.

175. Insel TR, O’Brien DJ, Leckman JF. Oxytocin, vasopressin, and autism: is there a connection? *Biol Psychiatry*. 1999;45(2):145-157.

176. Lee SY, Lee AR, Hwangbo R, Han J, Hong M, Bahn GH. Is oxytocin application for autism spectrum disorder evidence-based? *Exp Neurol*. 2015;244(4):312.

177. Lukas M, Neumann ID. Oxytocin and vasopressin in rodent behaviors related to social dysfunctions in autism spectrum disorders. *Behav Brain Res*. 2013;251:85-94.

178. Wagner S, Harony-Nicolás H. Oxytocin and animal models for autism spectrum disorder. In: Hurlemann R, Grinevich V, eds. *Behavioral Pharmacology of Neuropeptides: Oxytocin*. Springer International Publishing. 2017:213-237.

179. Preti A, Melis M, Siddi S, Vellante M, Doneddu G, Fadda R. Oxytocin and autism: a systematic review of randomized controlled trials. *J Child Adolesc Psychopharmacol*. 2014;24(2):54-68.

180. Guastella AJ, Hickie IB. Oxytocin treatment, circuitry, and autism: a critical review of the literature placing oxytocin into the autism context. *Biol Psychiatry*. 2016;79(3):234-242.

181. Huang Y, Huang X, Ebstein RP, Yu R. Intranasal oxytocin in the treatment of autism spectrum disorders: a multilevel meta-analysis. *Neurosci Biobehav Rev*. 2021;122:18-27.

182. Chiocchetti AG, Bour HS, Freitag CM. Glutamatergic candidate genes in autism spectrum disorder: an overview. *J Neural Transm* (Vienna). 2014;121(9):1081-1106.