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Title

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Permalink

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Journal

Neuron, 110(12)

ISSN

0896-6273

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Publication Date

2022-06-01

DOI

10.1016/j.neuron.2022.05.023

Peer reviewed

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Author manuscript

Neuron. Author manuscript; available in PMC 2023 July 06.

Published in final edited form as:

Neuron. 2022 June 15; 110(12): 1889–1890. doi:10.1016/j.neuron.2022.05.023.

Fatherhood is life changing: Uncovering structural and functional changes in the dad brain

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Abstract

What are the cellular-level structural and functional changes underlying newly adaptive behaviors in the mammalian brain? In this issue of **Neuron**, Inada et al. (2022) identify the brain-wide connectivity and synaptic plasticity changes of hypothalamic oxytocin+ neurons in male mice contributing to their parental behaviors.

Why does the sound of babies crying upset almost everyone and yet their parents appear immune? For many non-parents, just the thought of a crying baby in a restaurant is enough to elicit a strong negative reaction. However, the parental response to a crying infant triggers newly adaptive behaviors to promote caregiving. In addition, sex differences have also been spotted in brain activity of human parents' response to a baby's cry (Piallini et al., 2015). In light of these changes, how is neural connectivity being rewired during parenthood, and how is that restructuring related to behavioral changes? This is a simultaneously fundamental and difficult question to address, especially at a cellular or synaptic resolution.

In the emerging field studying the neural basis of innate parental behaviors, researchers have extensively investigated the brain and maternal behaviors of female rodents (Yoshihara et al., 2017). One of the changes in female rodent brains during the transition from virginity to maternity is increased sensitivity of ventromedial hypothalamic neurons to social cues (Liu et al., 2022). However, male rodent parental behavior, specifically the transition from infanticidal to caregiving behavior, is less well understood. In this study in this issue of *Neuron*, Inada et al. (2022) investigated circuit changes in oxytocin (OT) neurons across the behavioral transition to parenthood in male mice, leveraging advanced viral-genetic tools.

OT has long been recognized to mediate the positive effects of social interaction including parental behaviors (Uvnas-Moberg, 1998). It facilitates the onset of parental behavior in both sexes and is important for the maintenance of maternal behavior under stressful conditions (Yoshihara et al., 2017). Recent studies have also highlighted the roles of OT in synaptic plasticity (Grinevich and Stoop, 2018). For example, it increases the

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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firing of inhibitory interneurons in the hippocampal CA1 region, making the inhibitory neurotransmitter (GABA) less available for evoked release, and thus increases the signal-to-noise ratio and sensitivity to external stimuli (Owen et al., 2013). In the mammalian brain, the paraventricular hypothalamus (PVH) is one of three main areas that produce OT, and PVH OT neurons project to numerous cortical and subcortical regions (Knobloch et al., 2012). A recent study suggests that PVH OT neurons play crucial roles in social touch-based behavioral changes (Yu et al., 2022). It also shows that inputs to the PVH from the periaqueductal gray modulate PVH neuron firing and lead to increased social interactions in mice. However, no changes in these neuronal inputs or connectivity were measured before or after the social touching intervention. In contrast, the approach taken by Inada et al. (2022) makes full use of genetic and viral tools to measure anatomical and functional changes in the PVH OT circuitry before and after fatherhood. Especially, in the use of rabies virus monosynaptic tracing to determine PVH OT input connectivity changes before and after this critical behavioral transition.

The authors first showed that OT release from PVH OT neurons is necessary for the expression of male caregiving behaviors. Abolishing OT expression either globally or selectively in the PVH before mating reduced after-birth caregiving behaviors. Interestingly, when PVH OT neurons in the fathers were chemogenetically inhibited after the birth of pups, only a minor defect in parenting behavior ensued. These results suggest that PVH OT neurons are important for the initiation of caregiving behavior but play a lesser role in its maintenance. Conversely, chemogenetic activation of PVH OT neurons in virgin males promoted their caregiving behaviors, as evidenced by reduced aggression toward pups and increased pup retrieval. Furthermore, the authors analyzed the mRNA expression pattern of the immediate-early gene c-Fos, a commonly used marker for recent neuronal activation, and found that chemogenetic excitation of PVH OT neurons increased neural activity in the medial preoptic nucleus (MPN), a center associated with parental caregiving behaviors, but suppressed activity in the perifornical area (PeFA), a known center for infanticide. Notably, chemogenetic activation of PVH OT neurons could suppress pup-directed aggression even in $OT^{-/-}$ virgin males, suggesting that this effect is independent of OT. The caregiving behavior, in contrast, was elicited more vigorously in $OT^{+/+}$ than in $OT^{-/-}$ mice. Thus, PVH OT neurons modulate parental behaviors via both OT-dependent and -independent signaling.

Are neural connections to PVH OT neurons changed as the mouse transitions to parenthood? To test this, the authors performed an unbiased brain-wide screening, using rabies virus-based tracing to compare monosynaptic inputs to PVH OT neurons in virgin and father mice. They found that, on average, PVH OT neurons in fathers received more presynaptic inputs per cell than those in virgin males. This increased number of neuronal inputs was most prominent in the lateral hypothalamus (LHA) and the medial part of MPN (MPNm). Interestingly, this connectivity change was transient and reversible; if the father was housed without contacting the pups for 5 weeks, the number of inputs returned to the level of virgin males. Furthermore, it was found that the ratio between excitatory and inhibitory inputs from the MPNm and LHA also increased. To validate these observations, the authors performed channelrhodopsin 2-assisted circuit mapping (CRACM) in brain slices. Optogenetic stimulation of LHA (and, to a lesser extent, MPNm) resulted in larger excitatory postsynaptic currents in PVH OT neurons in fathers compared with virgin males.

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Together, the authors showed that excitatory inputs from LHA to PVH OT neurons increased in fathers both anatomically and functionally.

The anatomical and functional changes in LHA inputs to OT neurons prompted the authors to investigate how they lead to changes in parenting behaviors. Chemogenetic inhibition of excitatory LHA neurons in virgins moderately increased their aggressive behavior toward pups, but chemogenetic activation of such neurons significantly decreased the aggression, with a stronger effect in $OT^{+/+}$ than in $OT^{-/-}$ mice. These results suggest that the excitatory LHA to PVH OT neuron pathway relies on OT signaling to suppress pup-directed aggression.

Overall, Inada et al. (2022) provide important insights into the brain-wide and cell-type-specific anatomical and functional circuit adaptation underlying male parental behavior. In combination with genetic, electrophysiological, and behavioral methods, the authors creatively use rabies virus-based circuit tracing to identify key connectivity changes underlying the crucial transition from infanticidal to caregiving behaviors in male mice. The results demonstrate a surprising amount of neuronal plasticity in the hypothalamus, a brain region assumed to be hardwired. This exciting study indicates that rabies virus-based screening can serve as a useful platform to identify brain-wide synaptic connectivity changes associated with other experiences or life-stage-dependent behavioral changes.

While this study has shown the singular importance of OT and OT-expressing neurons in the PVH in caregiving behavior, many interesting questions await future studies. For example, what are the behavioral episodes (e.g., mating, social touch, co-housing with a female, or exposure to pups) that trigger the observed anatomical, functional, and behavioral changes? What molecular signaling mechanisms trigger the LHA to PVH OT neuron connectivity change? How do PVH OT neuron outputs change in paternal mice? What are the contributions of other neurotransmitters and neuromodulators expressed by PVH OT neurons and by their pre- or postsynaptic partners? Addressing these questions will help bridge the gap between the connectome and brain functions and yield a more comprehensive understanding of animal behavior.

ACKNOWLEDGMENTS

We acknowledge support from the UCSC start-up fund, the Whitehall Foundation, the Hellman Fellows Program (E.J.K.), and an NIH IRACDA Post-doctoral Training Grant (R.G.D.).

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