PRIZE ESSAY

NEUROBIOLOGY

Circuits for care

A small population of hypothalamic neurons orchestrates parenting behaviors

By **Johannes Kohl**

Raising a child to independence requires an estimated 13 million calories (*1*), near-constant attention, and the ability to survive on little sleep. Because parents perform this monumental task without any immediate benefit, it has been suspected that parental behavior relies on evolutionarily sculpted neural circuits. What do we know about the neural basis of parenting?

Classical lesion experiments in rodents have implicated many brain areas in this fascinating behavior (*2*–*4*). One region consistently identified as essential is the medial preoptic area (MPOA), nestled deep within an evolutionarily conserved part of the brain, the hypothalamus (*5, 6*). The identity of MPOA parenting neurons was elusive until a few years ago, when my mentor, Catherine Dulac, and her group found that MPOA neurons expressing the neuropeptide Galanin ($MPOA^{Gal}$ neurons) are crucial for parental behavior in both sexes (*7*).

This was a breakthrough, but a key question remained: How can a small population of neurons—10,000 out of a total of 100 million in the mouse brain—control such a complex behavior? Mouse parenting consists of stereotyped motor routines such as grooming pups, retrieving them to the nest and, in females, nursing. But parental animals also have an increased motivation to seek out infant stimuli, have distinct hormonal states, and engage less in nonparental behaviors such as mating (*3*).

We hypothesized that $MPOA^{Gal}$ neurons orchestrate these diverse behavioral components by assuming a "hub" position in a brain-wide, dedicated parenting circuit. My goal in the past 4 years has been to test this hypothesis.

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A POTENTIAL PARENTING CIRCUIT EMERGES

I started my project by tracing the connections that $MPOA^{Gal}$ neurons form with the rest of the brain. An impressive palette of viruses has been developed for this purpose in recent years. Some have the ability to jump backwards through neural circuits, thereby visualizing a neuron's direct inputs. Others label the fine axonal arborizations and synaptic terminals of infected neurons. These tracing experiments revealed a staggering complexity: $MPOA^{Gal}$ neurons receive inputs from about 20 brain areas and send out a similar number of projections (*8*). However, on closer inspection, a simple organizational principle emerged: $MPOA^{Gal}$ neurons are organized in distinct pools, or subpopulations, each projecting to a different brain area. Intriguingly, each pool has access to incoming information from all 20 brain areas (see the figure).

DISCRETE NEURONAL CLUSTERS ARE ACTIVE DURING SPECIFIC PARENTING BEHAVIORS

We next asked which of these neuronal pools are crucial for parental behavior. In fact, most of the areas targeted by $MPOA^{Gal}$ neurons have been found to play a role in parenting (*2*–*4*). We therefore sought to determine which pools were most highly activated during pup interactions. Three candidate pools were identified for further investigation: those projecting to the periaqueductal gray (PAG), the ventral tegmental area (VTA) and the medial amygdala (MeA) (*8*).

Are these different pools active during specific aspects of parenting? Using fiber photometry, an imaging approach that can record population activity from genetically specified neurons in behaving animals (*9*), we found the entire $MPOA^{Gal}$ population to be activated during all components of parenting. Surprisingly, however, individual pools were tuned to discrete parenting episodes (*8*), suggesting that they might indeed represent functionally distinct modules. We tested this hypothesis by optogenetically manipulating each of the three candidate pools.

MANIPULATING SPECIFIC CLUSTERS INDUCES DISCRETE PARENTING BEHAVIORS

First, we turned to the PAG. Sexually inexperienced male mice typically attack pups, only becoming parental in the weeks following mating (*10*). Strikingly, activation of PAG-projecting $MPOA^{Gal}$ neurons suppressed

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Johannes Kohl received his undergraduate degree from the University of Magdeburg in Germany and his Ph.D. from the University of Cambridge. Dr. Kohl is currently a postdoctoral fellow at Harvard University and the Sainsbury Wellcome Centre for Neural Circuits and Behaviour in London where he has been exploring the neural circuits underlying parenting. In early 2019, Dr. Kohl will start his own group at the Francis Crick Institute in London.

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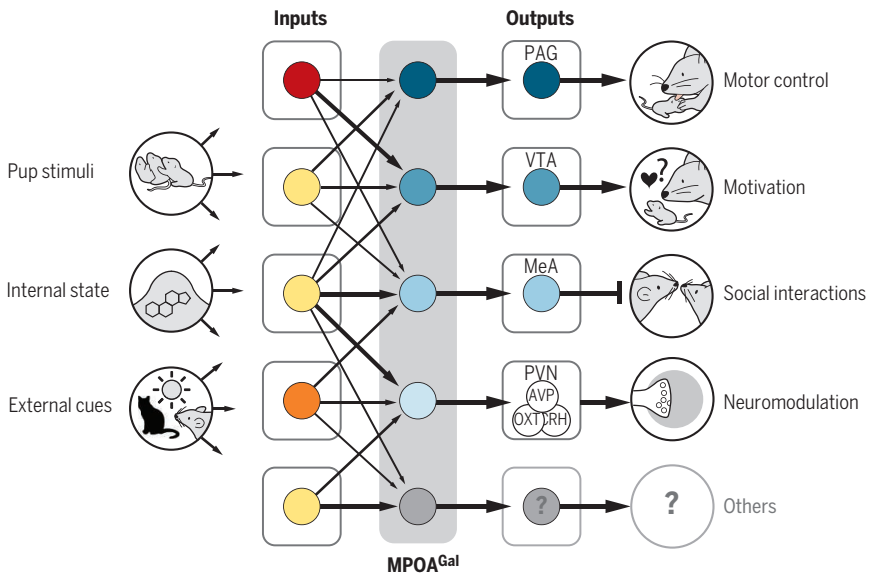
PHOTOS: (LEFT TO RIGHT) MCB GRAPHICS, HARVARD UNIVERSITY; SUSAN MERRELL/UCSF; NORTHWESTERN UNIVERSITY

Parental circuitry

A proposed model for how galanin-expressing neurons in the medial preoptic area (MPOA^{Gal}) orchestrate components of parental behavior. PAG, periaqueductal gray; VTA, ventral tegmental area; MeA, medial amygdala; PVN, paraventricular nucleus of the hypothalamus; AVP, vasopressin; OXT, oxytocin; CRH, corticotropin-releasing hormone.



pup-directed aggression in such males and increased pup grooming in both sexes, suggesting that this pool controls an important motor component of parenting. By contrast, activating the VTA-projecting neuronal pool did not directly affect pup interactions. The VTA has a well-established role in motivation and reward processing (*11*, *12*).

Because an increased motivation to interact with infants is a hallmark of parental animals (*13*), we inserted a climbable barrier between the test animal and pups. In this simple assay, activation of the VTA-projecting pool drastically increased the frequency with which animals crossed over to the pup compartment, suggesting that this circuit branch indeed controls the motivation to interact with infants.

Finally, activating those MPOA^{Gal} neurons projecting to the MeA affected neither pup interactions nor the motivation to interact with pups. However, we unexpectedly found that this manipulation suppressed interactions with adult mice in both males and females. This pool might therefore indirectly promote parenting by suppressing nonparental social behaviors.

CONCLUSIONS AND NEXT STEPS

Our work suggests a circuit motif in which projection-defined MPOA^{Gal} neuron pools each control specific aspects of parenting. This provides a novel model for how a small population of genetically defined neurons can orchestrate a complex behavior. But it also raises several intriguing questions. Do these pools interact with each other? If yes, how is their activity coordinated? If not, might moment-to-moment variations in sensory input determine which circuit element is active? And which pools control other motor aspects of parenting, such as pup retrieval or nest building?

We and others have made notable progress in uncovering how parenting and other social behaviors are wired into the brain (*8*, *14*, *15*). Such knowledge is crucial from both basic research and clinical perspectives. In humans, parental care is affected by stress and mental illnesses such as postpartum depression and anxiety, which together affect almost 20% of mothers in the United States (*16*). Addressing how physiological states and environmental factors interact with these circuits might therefore open new avenues for treatment of common mental illnesses. ■

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