COMMENTARY

# The transient joys of others–neural ensembles encode social approach in bonded voles

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Social bonds are an essential part of the human experience. We bond with our parents, our children, our romantic partners, and our friends; these bonds not only shape our emotional well-being but have profound consequences for our health and longevity (1). Perhaps because these bonds are so profoundly important, we often imagine them to be uniquely human. They are not. Indeed, much of what we know about human bonding has its origins in animal behavior. In the first volume of *Attachment and Loss*, John Bowlby (2) drew on the ethological work of Konrad Lorenz to formulate attachment theory, a conceptual framework that continues to inform social psychology some 50 y later (3). In subsequent decades, work on the pair-bonding prairie vole has revealed the role of the brain's reward circuits in bonding (4). A study by Scribner et al. (5) explores how these bonds are manifest in the changing patterns of neural activity within the brain's reward system, work that promises broad insights into the mechanisms of attachment.

Prairie voles are small rodents that live in the greater Midwest, ranging from Saskatchewan to Oklahoma, and from Colorado to West Virginia. In the 1970s, researchers noticed that they often caught specific males and females together in the same traps and suspected that such pairs were bonded mates (6). We now know that the repeated mating of a pair over the course of a day leads to a bond; males and females share a nest, a territory, as well as the care of their young, but this familial commitment does not always translate into sexual fidelity—a pattern of behavior known as "social monogamy" (7–9).

Some of our first insights into the neurobiology of attachment came from the realization that the socially monogamous prairie vole differs from its promiscuous, nonbonding relatives in the neural distribution of neuropeptide receptors (4). Receptors for the hormones oxytocin and vasopressin are found in several brain areas that are essential for reward, including the nucleus accumbens, ventral pallidum, and prefrontal cortex (4) (Fig. 1*A*). Manipulating oxytocin or vasopressin function in any of these areas can alter the ability to form bonds (4). Parallel work revealed roles for an array of other modulators, including peptides, monoamines, and steroids (4, 10–13). Dopamine in particular seems essential, with projections from the midbrain's ventral tegmental area to this broader circuit shaping not only the deep attachments between mates but also the more subtle social rewards exhibited in laboratory mice and primates (13–15). Imaging studies on humans have found that photographs of a loved one elicited activity in the nucleus accumbens and ventral tegmental area (16, 17). Holding the hand of a romantic partner, or more specifically believing that you were, also prompted activity in the accumbens (18). Although studies of bonding have consistently implicated reward circuits, we lack a detailed understanding of how pair-bonds emerge.

The article by Scribner et al. (5) explores the neural dynamics of bond formation in the nucleus accumbens of both male and female prairie voles. To visualize the activity of neurons, the researchers first injected the nucleus accumbens with a gene therapy vector that drives neuronal expression of a protein known as GCaMP6f (19). Neuronal firing drives bursts of intracellular calcium release, and imaging calcium levels has become a popular proxy for monitoring neural activity. GCaMP6f was made by fusing green fluorescent protein (GFP) with a natural calcium-sensitive protein, calmodulin (CaM), and identifying mutants that rapidly translate calcium transients into fluorescent flashes (19). One common method for assessing a pair-bond is to allow a subject to choose between a novel animal and his or her mate (8). In this "partner preference test," bonded voles show preferences for their mates over strangers. The work couples GCaMP6f imaging with a 20-min partner preference test to examine how neural dynamics within the nucleus accumbens map onto the second-by-second behavior of subjects. By imaging the accumbens activity repeatedly, first before bonds have formed, then 3 d after pairing, and finally after 2 wk of cohabitation, the researchers examine how neural activity and behavioral patterns are shaped by social bonding (Fig. 1 *C* and *D*).

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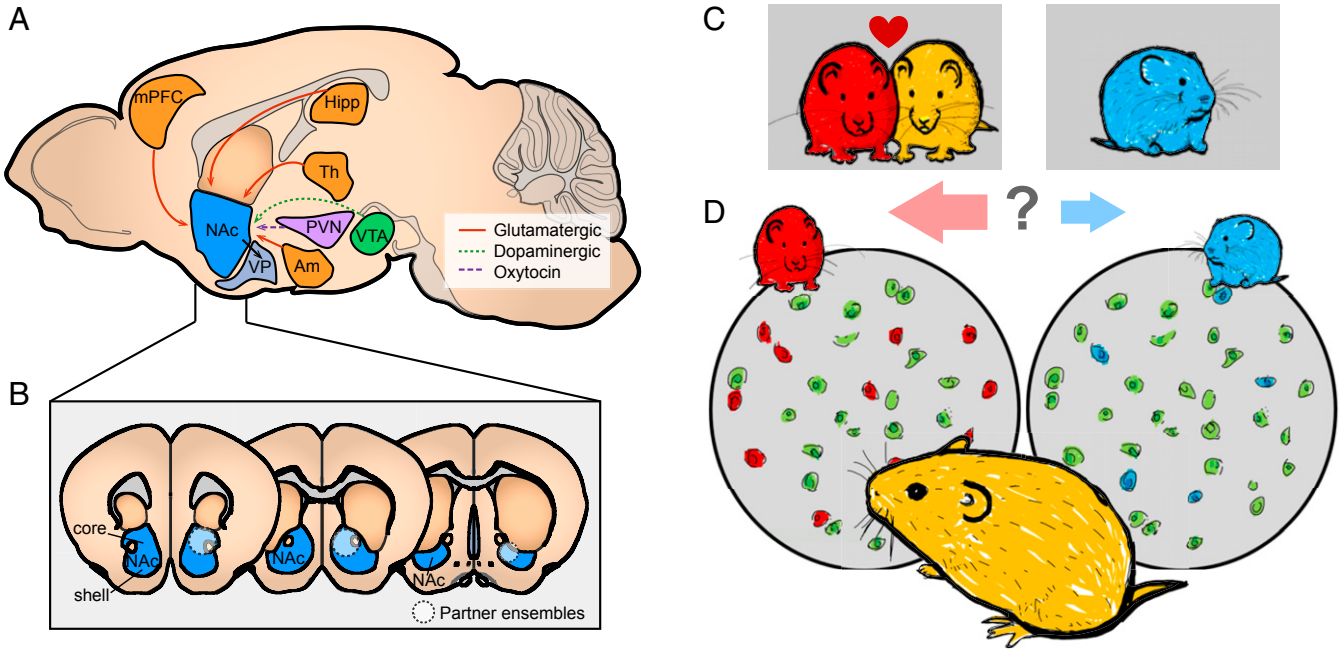


**Fig. 1.** (*A*) Schematic of nucleus accumbens (NAc) input and output projections in the rodent brain. Glutamatergic input projections come from medial prefrontal cortex (mPFC), hippocampus (Hipp), thalamus (Th), and amygdala (Am). Dopaminergic input comes from ventral tegmental area (VTA), and oxytocin neurons project to NAc from the paraventricular nucleus of the hypothalamus (PVN). One of the main targets of NAc is ventral pallidum (VP). (*B*) Schematic of locations of partner ensembles in prairie vole accumbens, represented in three coronal views. (*C*) Schematic depicting bonding and cohabitation of male–female pairs, followed by (*D*) Illustration of $Ca^{2+}$ transients in the nucleus accumbens of an animal choosing between a partner (red) and stranger (blue). (*A* and *B*) Modified from the interactive Allen Mouse Brain Atlas. © 2004 Allen Institute for Brain Science. Allen Mouse Brain Atlas. Available from: http://mouse.brain-map.org/.

During the partner preference test, animals approach both their mate and the novel stimulus animal, spending seconds or minutes at a time with a given animal. Scribner et al. (5) find that as the bond deepens with time, subjects visit their partners more often and their visits lasts longer. Surprisingly, approaching either the partner or a stranger is accompanied by comparable bursts of calcium release. Some neurons fired preferentially in response to approaching a partner, whereas others fired in response to approaching a stranger. The social-approach neurons did not reliably predict either direction or speed of movement but seemed tuned to approaching a specific individual. Remarkably, the firing of partner or stranger neurons usually preceded an approach. The data suggest that social interaction is generally rewarding but that activity patterns in the nucleus accumbens may prompt animals to approach partners more often than strangers.

By monitoring the activity of many neurons over the course of a partner preference test, the researchers noticed that partner approaches tended to rely on a consistent set of neurons. Stranger neurons also tended to be consistent within a trial, and relatively few neurons were active during approach to both the partner and stranger. Brain regions often encode information in some topological way, with neighboring neurons responding to similar stimuli. That does not seem to be the case for social-approach neurons, however. Neurons that predicted partner approach were not closer to one another than predicted by chance. It seems as though a dispersed set of neurons encodes the identity of individuals appropriate to approach (Fig. 1*D*).

To understand the relationship between the nucleus accumbens and social approach, it is useful to consider its role in reward learning more generally. Inputs to the accumbens from the cortex and hippocampus provide complex sensory information needed to discriminate among suitable choices—choices that in nature presumably include the distinctions between one social partner and another (20–22). Activation of inputs arriving from the prefrontal cortex or other regions can also lead animals to approach the stimuli encoded by those neurons (20–22). Social rewards and their complex cues are less studied than food rewards, but representations of social partners within the prefrontal cortex of mice seem to lack a topographical organization (22), much like the representations reported in the current study. Moreover, a recent study of pair-bonding in voles showed that an increased coupling between the activity of the prefrontal cortex and the nucleus accumbens is critical to bond formation (23). Scribner et al. (5) posit that neural plasticity within the accumbens links the complex cues that identify individuals with the rewards of social proximity.

Finally, one of the most interesting findings in the study by Scribner et al. (5) is that the representation of the partner changes over the course of bond formation. Before pairing, some neurons fire with approach to the future partner and a roughly equal number fire with approach to the stranger. Over the course of mating and living together, however, an increasing number of neurons respond to the partner. The representation of the partner seems to grow, and this may underlie the increased time spent with a mate (Fig. 1*D*). Not only does the bond deepen over time, but it varies among pairs, with some couples relatively independent and others joined at the furry hip. Remarkably, the strength of the bond is associated with the number of partner neurons active in the nucleus accumbens.

The association between the number of active neurons and the strength of partner preference has interesting parallels in the

learning and memory literature. A recent focus of the field has been to use histological markers of neural activity to identify neurons that encode a remembered stimulus (24–26). By manipulating the activity of these neurons, researchers can manipulate memory itself, causing an animal to associate a shock with a location at which it has never been shocked, for example (25). The memory trace, or engram, is often a widely distributed pattern of activity (24). Among the field's many tools, researchers have used engineered G-protein–coupled receptors—a group of genes that includes receptors for a wide variety of neuromodulators—to manipulate the excitability of neurons within a region (24, 26). Nonselective excitation during training increases the number of neurons recruited into the memory trace and increases learned responses to the stimulus (24, 26). It is clear that receptors for the neuropeptide oxytocin and other modulators promote bond formation through their actions in nucleus accumbens (5). Although we do not know whether the activity of neurons within the accumbens constitute an engram, the current results suggest that one mechanism of bond formation may be for oxytocin or other modulators to increase the number of neurons representing a partner. Examining the emergence of social engrams and their modulation by the neuroendocrine system will undoubtedly be a significant focus of future work.

The work by Scribner et al. (5) is an exciting advance in our understanding of attachment and its mechanisms. As the field continues to deepen, however, it also harkens back to the seminal insights of Bowlby and others (2, 3, 27, 28). Before Bowlby, psychologists thought that fondness for a parent was an accidental by-product of rewards like food and warmth (2, 27). Bowlby drew on work with other species to recognize that social contact itself was a kind of reward—an "evolved system" that served to maintain social proximity. He developed his conceptual framework around the bonds between mothers and children, but eventually it was extended to romantic relationships as well (28). Bowlby envisioned an "attachment system" in the brain that transformed sensory information into social approach and reward (2, 27). In the intervening years, we have learned a great deal about the circuitry of reward, the representation of memories, and the ways in which these systems enable social interaction. As we enrich our understanding of how bonds form, we learn something meaningful about the natural world and perhaps also about the ways in which those we love bring us joy.

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