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Neurobiological mechanisms of social attachment and pair bonding

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Abstract

Species have evolved diverse social behavior and mating strategies in response to selective forces in their environments. While promiscuity is the predominant mating strategy across most vertebrate taxa, convergent evolution of monogamous mating systems has occurred multiple times across distant lineages. Monogamous behavior is thought to be facilitated by a neurobiological capacity to form and maintain selective social attachments, or pair bonds, with a mating partner. The neural mechanisms of pair bonding behavior have been investigated most rigorously in *Microtine* rodents, which exhibit diverse social organizations. These studies have highlighted mesolimbic dopamine pathways, social neuropeptides (oxytocin and vasopressin), and other neural systems as integral factors in the formation, maintenance, and expression of pair bonds.

Introduction

The relationships we form with family, friends, and romantic partners are integral to the organization and function of human society. Though complex, these bonds comprise component processes that can be investigated across species. One excellent opportunity for investigating the neurobiological basis of social attachments is the independent evolution of pair bonding behavior across taxa. While sexual promiscuity is the dominant mating strategy in animals (exhibited by 95–97% of mammals), socially monogamous mating strategies have evolved in diverse lineages, including invertebrates, fishes, amphibians, reptiles, birds, and mammals. These systems are characterized by enduring, often lifelong, selective social attachments between mating partners, although not always sexual exclusivity. The underlying neurobiology of these pair bonds is the subject of this review.

Investigating pair bonding

The most powerful opportunities for investigating the biology of behavior are rooted in: firstly, phylogenetically distant species exhibiting convergent behavior, secondly, closely related species exhibiting strikingly divergent behavior, and thirdly, individual species exhibiting high levels of intraspecific variation in behavior. Within these contexts,

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comparative approaches can accelerate the identification of neurobiological, genetic, developmental, and evolutionary factors underlying the behavior in question [1]. Much of our understanding of the neurobiology of pair bonding has come from comparative approaches in all three contexts, particularly through investigations of the prairie vole, *Microtus ochrogaster*. The neurobiology of pair bonding in prairie voles will be a primary, but not exclusive, focus of this review.

The genus *Microtus* comprises many species with diverse social organizations. Prairie voles exhibit socially monogamous behavior as well as bi-parental care of offspring, selective aggression toward opposite-sex strangers, and depressive-like behavior following partner loss [2•,3]. Prairie voles also exhibit a high degree of intraspecific variation in these behaviors; for example, both males and females can exhibit promiscuous 'wandering' phenotypes.

Interrogation of pair bonding in the laboratory was initiated through a series of experiments using the partner preference test, in which a subject can freely spend its time with its familiar mating partner, a novel sexually receptive individual, or in isolation in a 'neutral' zone [4]. These experiments demonstrated that after just 24 hours of co-habitation with a mate, prairie voles — unlike promiscuous montane or meadow voles — preferentially affiliate with their partner. These 'partner preferences' became a laboratory metric for pair bond formation, and neurobiological manipulations within this paradigm have identified unique molecular features of the prairie vole brain mediating selective social attachment.

Social neuropeptides in pair bonding

The social neuropeptides oxytocin (OT) and vasopressin (AVP) have deeply conserved roles in regulating sociosexual behavior across invertebrate and vertebrate taxa, including humans [5]. In mammals, the neuroanatomical organization of OT-producing and AVP-producing neurons and their axonal projections throughout the brain are largely conserved, while the distributions of their target receptors — oxytocin receptor (OTR) and arginine-vasopressin receptor 1a (AVPR1a) — vary greatly both within and across species [6,7]. Evolutionary plasticity in these systems is thought to have contributed to the diverse sociality observed in nature [7–9].

OTR and AVPR1a distribution in the prairie vole brain differs substantially from closely-related promiscuous species, with differences concentrated in specific mesolimbic reward areas including the prefrontal cortex (PFC), nucleus accumbens (NAcc), ventral pallidum (VP), and lateral septum (LS) [10]. In prairie voles, blockade of OTR or AVPR1a in these areas during co-habitation — specifically OTR blockade in the NAcc or PFC or AVPR1a blockade in the LS or VP — prevents pair bonding [10].

Comparative analyses of four *Microtine* species found that monogamous prairie and pine voles exhibit higher AVPR1a expression in the VP compared to promiscuous montane and meadow voles, suggesting that increased AVPR1a expression in the VP may be a mechanism contributing to the evolution of pair bonding across *Microtines* [10]. In support of this hypothesis, overexpression of AVPR1a in the VP of promiscuous meadow voles induces pair bonding, and RNA knockdown of AVPR1a in the VP of prairie voles inhibits

pair bonding[11•]. However, both monogamous and non-monogamous deer mice have high AVPR1a expression in the VP[12], suggesting that multiple mechanisms contribute to the evolution of monogamous mating strategies across rodents; yet the possibility that high AVPR1a expression in the VP is a necessary feature for the evolution of monogamy requires further comparative investigation.

Like prairie voles, monogamous marmosets have elevated OTR density in the NAcc, while monogamous coppery titi monkeys have elevated AVPR1a in this area [13,14••]. Analyses of human tissue have used ligands promiscuous for both OTR and AVPR1a [15], but have reported high densities in the VP [16]. It will be important to re-analyze human tissue using more sensitive and selective techniques; however, to the best of our knowledge, every socially monogamous species examined to date has exhibited high OTR and/or AVPR1a expression in the NAcc-VP circuit; these data encourage further research on neuropeptidergic regulation of this circuit in the evolution of social bonding.

OT and AVP modulate bonding behavior in diverse lineages [17]. Blockade of OTR and AVPR1a homologs in monogamous cichlid fishes reduces affiliative behavior during bond formation [18], and exogenous OT delivery promotes affiliative behavior toward conspecific and human partners in dogs [19]. The OTR homolog mediates pair bonding behavior in monogamous zebra finches[20,21•,22]. OT and AVP regulate pair bonding behavior in marmosets and coppery titi monkeys, respectively[23–25]. Humans display a range of pair bonding behavior, and *OXTR* and *AVPR1A* gene variants are associated with relationship status [26,27]; plasma OT levels predict future success rates in romantic relationships [28]; and in romantically attached men, intranasal OT increases NAcc activity while viewing a partner's face and increases preferred interpersonal distance from unfamiliar females[29••, 30].

Mesolimbic dopamine system in pair bond formation

All nervous systems face the challenge of filtering, converting, and updating a continuous barrage of multimodal sensory information into learned associations that guide adaptive behavior [8]. In vertebrates, the mesolimbic reward system — comprising in part connections between the ventral tegmental area (VTA), PFC, NAcc, VP, and LS — is an evolutionarily conserved neural system that facilitates this process by generating motivation to seek reward and avoid aversion, and by assigning salience to cues associated with these outcomes. The action of dopamine (DA) within this system is critical for these functions [31].

The mesolimbic DA system is essential for pair bonding. Partner preference formation is facilitated by mating, which increases DA release and turnover in the NAcc[10]. DA action at one of its target receptors, D2R, in the NAcc is necessary for bond formation [10]. After bonding, a second DA receptor, D1R, is upregulated in the NAcc and is critical for bond maintenance by mediating aggression toward opposite-sex strangers [32].

Increased D1R:D2R signaling ratio in the ventral striatum has also been implicated in drug addiction and abuse[33]. In mice, repeated administration of cocaine increases the ratio of D1R:D2R expression in the NAcc, and this reorganization mediates subsequent behavioral

plasticity. As mentioned, in prairie voles, pair bonding increases the ratio of D1R:D2R expression in the NAcc, and this reorganization mediates subsequent behavioral plasticity [32]. These data have contributed to the hypothesis that pair bonds represent social addictions between mating partners, mediated in part by organization and plasticity of mesolimbic DA pathways [33]. Studies in the zebra finch and coppery titi monkey have also reported reorganization in mesolimbic reward areas following bond formation, suggesting that neural plasticity in these pathways may be an evolutionarily conserved feature of pair bonding across species [34,35].

Component processes and other systems in pair bond formation

Numerous component processes contribute to pair bonding. Initial social interaction depends on tolerance of social proximity, social approach, and inhibition of avoidance/rejection behavior. As partners interact, affiliative behavior, social recognition, and reward systems contribute to formation of the bond. After bonding, social buffering, mate guarding, negative affect during separation, and sociospatial memory facilitate bond maintenance.

Microtine species vary in social tolerance and affiliation, perhaps in part due to differences in mesolimbic D1R organization. In prairie voles, which have low baseline levels of NAcc D1R, bond-induced upregulation of NAcc D1R mediates a drastic shift in behavior toward opposite-sex strangers (from affiliation to avoidance/rejection), and selective NAcc D1R *activation* during co-habitation inhibits bonding [10]. In meadow voles, which have higher baseline NAcc D1R densities and are less affiliative, selective NAcc D1R *blockade* increases affiliative behavior[10]. In zebra finches, activation of mesolimbic DA systems correlates with approach, avoidance, and affiliative behavior during male–female social interaction [36], suggesting that mesolimbic DA pathways may modulate social tolerance and affiliation across species.

Pair bonding also depends on social recognition, a neural process that, in mice, is olfactory based and dependent on OT and AVP signaling. OTRs are distributed through olfactory processing nuclei in rodents, while in primates — in which audition and vision are more dominant sensory modalities — OTRs are expressed in areas critical for visual and auditory attention and processing, suggesting that OT signaling may modulate aspects of sensory processing across species, though the particular modalities may vary [13,14••,37]. Consistent with this hypothesis, human polymorphisms in *OXTR* predict ability to recognize faces, suggesting that OT's role in social recognition may be conserved between rodents and humans, across sensory modalities [38••].

Additional neural systems mediate additional components of bond formation and maintenance. Opioid signaling is important during reward learning and regulates formation and maintenance of pair bonds in prairie voles, perhaps by mediating positive hedonics during formation and negative hedonics during maintenance [39•,40]. The corticotrophin releasing factor (CRF) system mediates pair bond formation and depressive-like behavior following partner separation/loss [3,41]. Social buffering facilitates bond maintenance; in prairie voles, following a stressful experience, OT release in the presence of the partner reduces stress hormone levels and anxiety-like behavior [42•]. In nature, bond maintenance

depends on accurate recall of the partner's geographical territory. Recent field studies have shown that OTR and AVPR1a binding densities in spatial navigation/memory areas predict space use, mating strategy ('resident' or 'wanderer'), and reproductive success in prairie voles, possibly by facilitating integration of social information (e.g. territories of partner, reproductive competitors, and/or reproductive opportunities) into spatial maps [43,44,45•].

Other forms of selective social attachment (e.g. maternal bonds) require many of the same neural substrates and component processes — notably OT, DA, CRF, opioids and social recognition — as selective bonds between mates[17]. In fact, it is hypothesized that mammalian pair bonding may evolve by recruiting evolutionarily ancient maternal bonding systems during sociosexual interaction to produce a selective bond with the mating partner [46,47].

Experience and pair bonding

In prairie voles, like humans, early life social environment can impact adult pair bonding [48], a phenomenon that may be mediated by neuroplastic changes in systems critical for bonding. Consistent with this idea, early life stimulation of the melanocortin receptor (MCR) system, which interacts with neuropeptide and reward systems, facilitates pair bond formation in adulthood [49]. In contrast, selective D1R activation in neonates impairs adult bonding [50]. Intriguingly, chronic neonatal administration of intranasal OT at some doses was found to impair bonding in adult male prairie voles [51]; however, enhancing NAcc OTR expression in pre-pubertal females facilitates adult bonding [52], and early life paternal deprivation (a manipulation which likely reduces OT signaling) impairs bonding in adult prairie and mandarin voles [48,53]. These data encourage further research on the role of early-life experience and OT signaling in adult social function. Interestingly, blocking histone deacetylation during co-habitation increases NAcc OTR and AVPR1a expression and facilitates pair bonding in prairie voles, suggesting that epigenetic modification is one mechanism by which experience can shape the neural systems modulating bonding behavior [54].

As in humans, drugs of abuse impair the ability to form social attachments in prairie voles, presumably due to plastic changes in underlying neural circuits. In prairie voles, amphetamine-induced upregulation of D1R inhibits bonding; and after bonding, D1R is upregulated and mediates a decrease in the reward value of amphetamines (intriguingly, a phenomenon that is reversed by OT treatment) [55–57]. Interestingly, voluntary alcohol consumption inhibits bonding in male but not female prairie voles, and social facilitation and inhibition of alcohol consumption occurs in same-sex but not male-female pairs [58,59].

Conclusions and future directions: toward a network model of the pair bond

Common neural circuits, neuromodulators, receptors, and neuroplastic changes regulate selective social attachment across species. In prairie voles, it is hypothesized that unique organization of OTR, AVPR1a, and D1R/D2R in the forebrain facilitates unique encoding of partner-associated cues during sociosexual interaction. Our current model (as illustrated

in Figure 1) is that during mating, DA release modulates reward learning and salience of partner-associated cues, while OT and AVP release facilitate the transmission and neural encoding of the partner's sensory signature through olfactory processing circuits, into the amygdala, and ultimately into the NAcc-VP circuit where it is integrated with the reward of mating, mediated in part by D2R and μ-opioid receptor activation. These circuits are simultaneously modulated by higher order behavior-outcome and sensory cue-outcome circuits in the PFC and orbitofrontal cortex, respectively. After bond formation, upregulation of D1R in the NAcc biases these circuits toward encoding unfamiliar olfactory signatures as aversive and triggering avoidance/rejection behavior; OT release in the presence of the partner functions as a social buffer; and CRF-mediated negative affect during separation encourages reunion.

With this basic framework in place, future studies should aim to identify the neuronal phenotypes mediating these component processes, their connectivity within social information processing networks, and precisely how various neurotransmitters modulate network function as a whole. Comparative genetic, neural, and behavioral analyses across species; optogenetic and electrophysiological interrogations of precise neural circuits in animal models; and functional brain imaging studies in humans will likely provide important insights into the neurobiological regulation of selective social attachment and bonding in the coming years.

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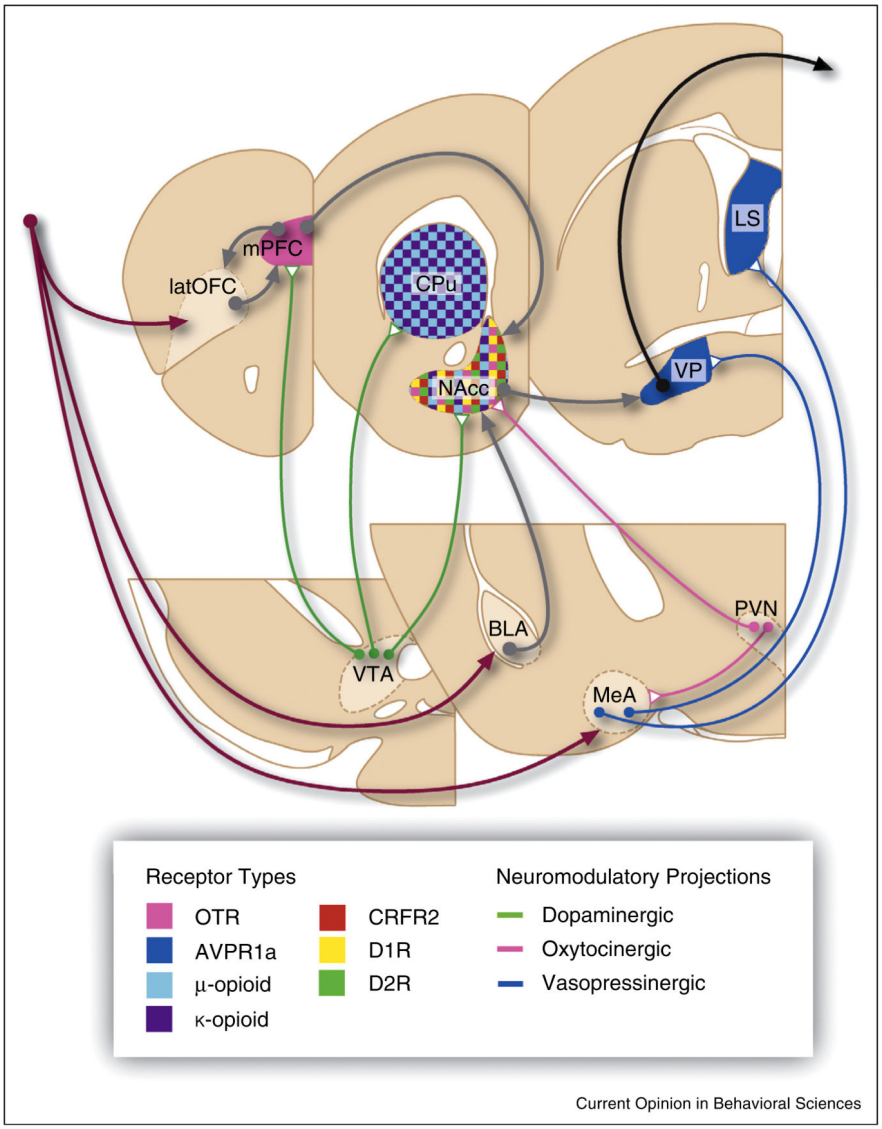

Figure 1.

Neurobiological systems mediating pair bonding behavior. This schematic illustrates a neural network model of pair bond formation and maintenance based on studies in prairie voles. The model highlights key axonal projections, neuromodulators, and receptor populations involved in pair bonding. Maroon arrows illustrate key points of entry for incoming sociosensory cues. Gray arrows represent axonal projections transmitting social information across brain areas during bonding. The black arrow represents axonal projections to downstream motor nuclei leading to behavior. As indicated in the figure legend, colored projections with closed white triangles indicate neuromodulatory projections (dopamine-green; oxytocin-pink; vasopressin-blue) that modulate transmission and encoding of social information during bonding. Receptor populations that have been implicated in either formation or maintenance of pair bonds in prairie voles are indicated by solid colors within brain areas. Important neural loci are indicated with abbreviated labels (BLA, basolateral amygdala; CPu, caudate putamen; latOFC, lateral orbitofrontal cortex; LS, lateral

septum; MeA, medial amygdala; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; PVN, paraventricular nucleus of the hypothalamus; VP, ventral pallidum; VTA, ventral tegmental area).