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Is social attachment an addictive disorder?

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Abstract

There is a considerable literature on the neurobiology of reward, based largely on studies of addiction or substance abuse. This review considers the possibility that the neural circuits that mediate reward evolved for ethologically relevant cues, such as social attachment. Specifically, mesocorticolimbic dopamine appears important for maternal behavior in rats and pair bonding in monogamous voles. It is not yet clear that dopamine in this pathway mediates the hedonic properties of social bond formation or whether dopamine's role is more relevant to developing associative networks or assigning salience to social stimuli. The neuropeptides oxytocin (OT) and vasopressin (AVP) appear to be critical for linking social signals to the mesocorticolimbic circuit.
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1. Introduction

In his classic work on brain-behavior evolution, Paul MacLean [1] described three forms of behavior associated with the transition from reptiles to mammals: nursing, audiovocal communication for maintaining maternal–offspring contact, and play. He hypothesized that the emergence of a thalamocingulate limbic system in mammals was critical to these behavioral transitions. Nursing, vocalization, and play all share a common motivation for social interaction and under the appropriate circumstances may lead to social attachment. MacLean speculated that substance abuse and drug addiction were attempts to replace opiates or endogenous factors normally provided by social attachments [1] (see also Ref. [2]). And he wondered if mother–infant, infant–mother, and male–female attachment might share a common neurobiology [1].

In this review, we will explore MacLean's hypothesis by suggesting an approach to the neurobiology of attachment, one of our most complex and powerful if least understood emotions. This review will follow the following lines of inquiry. First, we will consider the role of mesocorticolimbic dopamine pathways in the mediation of natural rewards. Second, we will look at two experimental models of powerful social attachments, examining their relationship to mesocorticolimbic dopamine. Finally, we will explore a mechanism by which social stimuli become linked to this "reward" pathway, demonstrating with transgenic and viral vector techniques that peptide receptors may be able to provide this key link. Paul MacLean may never have accepted ownership of his famous dictum but he was fond of reminding all who worked in his laboratory that some of the best experiments are those that Nature has done for us. Accordingly, this review will use a comparative approach to understand brain–behavior relationships.

2. Dopamine and addiction

Addiction is a form of compulsive behavior with an increasing narrowing of the behavioral repertoire towards drug intake. The essence of addiction is a subjective sense of a loss of control. Addiction involves a poorly understood switch process in which an initially positive, rewarding response to a drug is replaced by preoccupation, compulsive intoxication, and withdrawal symptoms [3]. We know surprisingly little about how this switch occurs but several lines of evidence implicate mesocorticolimbic dopamine in the addiction process. The pathway of interest includes the ventral tegmental area (VTA) that projects directly and indirectly via the amygdala/bed nucleus of the stria termi-

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nalis to the nucleus accumbens, which, in turn, projects to the ventral pallidum and thalamus. Thalamic projections to the prefrontal and cingulate cortex are believed to activate cells that ultimately feedback to the VTA (Fig. 1) [4]. In general, drugs that lead to dopamine release in this system, such as psychostimulants, are addictive [5].

Based on results of psychostimulant administration, there has been a casual assumption that dopamine release in this circuit mediates the hedonic properties of psychostimulants or natural rewards. Experimental findings with relatively simple natural rewards, such as access to sweets, are only partially supportive of this notion. Studies of VTA firing patterns in monkeys suggest that activity predicts reward rather than signaling reward [6]. Indeed, firing decreases with reward delivery. Berridge and Robinson [7] have suggested that dopamine release in the nucleus accumbens signals the salience or motivational value of the stimulus, perhaps marking the transition from "liking" to "wanting." And others, noting that dopamine is released in this pathway in response to shock or withholding reward, have suggested that this pathway signals a behavioral switch or a change in effort or attention irrespective of the valence of the stimulus [8]. Although the evidence for mesocorticolimbic pathways mediating reward is relatively strong, the neurochemical basis of addiction and substance abuse is certainly more complicated than dopamine release. While the various players in this network still need to be elucidated, there is already evidence that excitatory amino acids, opiates, and several novel gene products such as CART peptides modulate activity in this circuit [9].

Is the neural pathway of substance abuse also involved in ethologically relevant aspects of reward? It seems unlikely that this pathway evolved for drug abuse, so one might hypothesize that cocaine or heroin actually hijacks a neural system that was selected for incentive behaviors associated with reproduction [10]. If this hypothesis were valid, one would expect (a) that motivated states, such as maternal care and pair bonding, would activate the same pathways as drugs of abuse and (b) that cocaine or opiates might reduce these motivated behaviors. Below we will examine the evidence for maternal behavior and pair bonding. The relationship of mesolimbic dopamine to sexual motivation has been reviewed recently elsewhere for both male [11,12] and female rats [13,14] and therefore will not be described here.

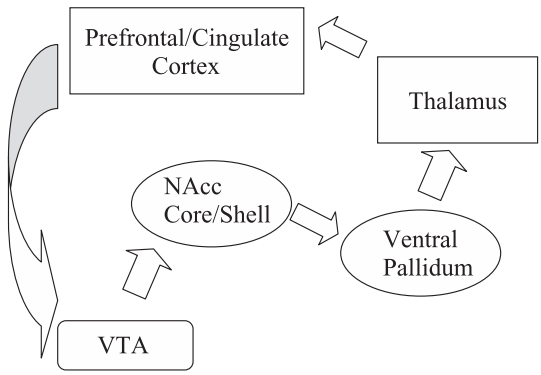

Fig. 1. Putative reward circuit. Cartoon shows basic pathway from midbrain dopamine cell bodies in the VTA to nucleus accumbens (NAcc) that projects via ventral pallidum to thalamus. There is a broad thalamic projection to prefrontal and cingulate cortex. The cortex completes this loop by projecting to VTA. The VTA projects directly to cortex and amygdala in addition to the NAcc (not shown).

3. Dopamine and social behavior

3.1. Maternal care

Maternal care is an excellent behavior for the study of social motivation because, in rats, it is tied to parturition. Virgin female rats or even pregnant rats will either avoid or attack pups. Just prior to parturition, there is a profound change in the female's behavior with the onset of nest building, intense interest in pups (measured by approach and grooming), and a general decrease in fearfulness [15]. It seems likely that the transition from avoidance to approach involves not only overcoming a fear of pups but also a selective motivation to interact with pups.

Several groups have tested the hypothesis that mesocorticolimbic pathways mediate mother–infant interactions in rats. The evidence can be summarized as follows: (a) dopamine is released [16] and fos is activated in the nucleus accumbens [17,18] following pup exposure in maternal females, (b) either VTA or nucleus accumbens lesions disrupt maternal behavior [19–23], specifically reducing the females approach and interaction with pups, and (c) either cocaine or the nonspecific dopamine agonist c-flupenthixol injected directly into the nucleus accumbens decreases pup retrieval [24,25]. If dopamine is released with pup exposure and dopamine injected into the same region decreases pup retrieval, it seems possible that dopamine in this region signals reward or satiety. However, the available data are also consistent with a role for dopamine release in prediction, salience, or other aspects of pup-directed behavior.

Three recent studies have begun to investigate the relationship of pup care to reward in a more operational sense. Mattson et al. [26] have used a place preference paradigm to compare the mother's interest in pups vs. cocaine. In this study, postpartum females were trained to go to one cage for access to pups and a different cage for access to cocaine. Assuming that cocaine represents a paradigmatic reward signal, this experiment essentially titrates the reward or hedonic value of pups at various times postpartum. Indeed, Mattson et al. [26] report that at Day 8 postpartum females prefer pups to cocaine, whereas at Day 16 cocaine appears more attractive than pups. Although it is possible that the reinforcing properties of cocaine change across lactation, these results are consistent with the notion that access to pups is even more reinforcing than one of the most potently rewarding psychostimulants. Of

course, these data do not demonstrate the involvement of any specific dopaminergic pathway.

Using a different approach to measuring the incentive value of pups, Wilsoncroft [27] adapted an earlier method allowing females to bar press for access to pups. Females can be trained to bar press for access to pups [28]. As females become maternal, their rate of bar pressing increases roughly fourfold as a measure of their motivation to access pups [28]. This approach, which borrows the operant techniques familiar for studying the incentive properties of psychostimulants, permits a careful quantification of the reward properties of pups. Lee et al. [28] report that lesions of the nucleus accumbens decrease pup retrieval but, surprisingly, do not decrease bar pressing for pups. By contrast, lesions of the medial preoptic area (MPOA) decrease both pup retrieval and bar pressing [28].

Why would bar pressing remain high in females with lesions of the nucleus accumbens even in the presence of impaired maternal care? One obvious possibility is that the nucleus accumbens is essential for aspects of pup care other than maternal motivation. Thus, the Fos activation in the nucleus accumbens could be secondary to the sensory processing of pup odors or the activation of motor responses. Another possibility is that the neural basis of motivation for pups is more widely distributed, such that the MPOA is required but that other regions may support maternal motivation in the absence of the nucleus accumbens. Indeed, there are some intriguing data from Numan's laboratory consistent with this possibility. First, the MPOA projects to the nucleus accumbens shell and, more specifically, cells within the MPOA activated during maternal behavior (as measured by Fos induction with pup exposure) project to the VTA, which, in turn, projects to the nucleus accumbens [29]. Second, unilateral knife cuts of the MPOA combined with contralateral lesions of the VTA impair maternal behavior, similar to the effects of bilateral lesions of the MPOA [20]. This suggests that the efferent pathway from the MPOA to the VTA is critical for maternal care. And finally, unilateral lesions of the MPOA reduce Fos staining in the nucleus accumbens shell in response to pups [18]. Taken together, these results suggest that the nucleus accumbens shell (as opposed to the nucleus accumbens core) may be part of a circuit with the VTA and MPOA that supports maternal behavior. Whereas lesions of the nucleus accumbens core did not reduce bar pressing for pups, there is still the possibility that lesions of either the nucleus accumbens shell or the VTA would reduce maternal motivation, as seen with MPOA lesions.

3.2. Pair bonding

Pair bonding is the development of a selective, enduring relationship with another individual. As with the onset of maternal behavior in rats, pair bonding requires overcoming avoidance and a motivated attraction to a specific individual, sometimes measured as a partner preference. Unlike maternal behavior, which is ubiquitous in mammals, pair bonding is restricted to less than 5% of the mammalian species recognized as monogamous. Much of what we know about the neurobiology of monogamy in general and pair bonding specifically has been generated from studies of voles, burrowing rodents that are common in many parts of the United States [30]. Voles have proven particularly useful for comparative studies of social bonds. Prairie and pine voles form partner preferences and pair bonds after mating; montane and meadow voles generally do not form a selective attachment after mating. Prairie and pine voles

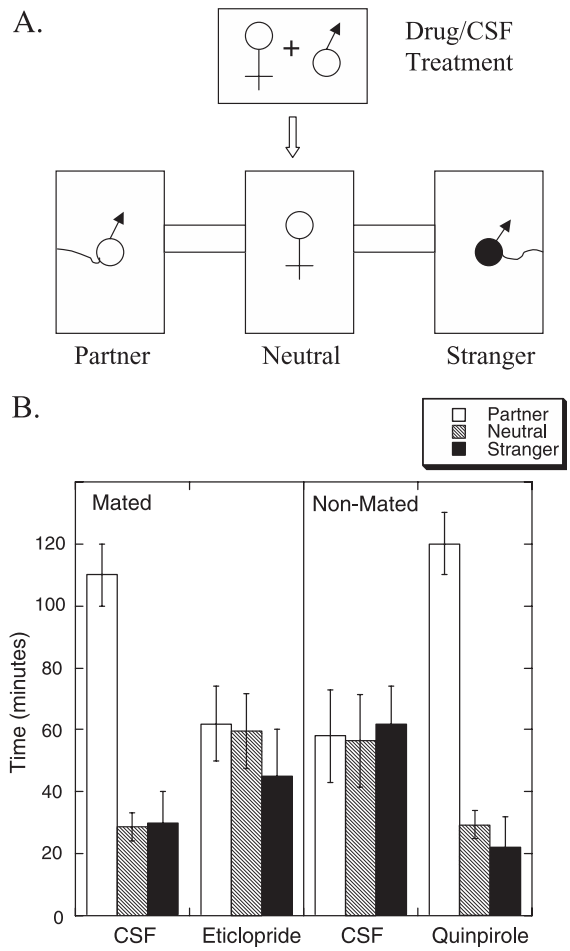

Fig. 2. Dopamine influences partner preference formation. (A) A female prairie vole is injected with CSF, eticlopride (dopamine D2 receptor antagonist), or quinpirole (dopamine D2 receptor agonist) into the nucleus accumbens while housed with a male. After this exposure, the female is tested for preference in a choice apparatus with the partner tethered on one side and a novel male tethered on the other. (B) Following mating (24 h), female voles treated with CSF show a clear preference for the partner relative to time spent in the neutral or stranger's cage. Females treated with eticlopride (100.0 ng/side × 2) show no preference for the partner relative to the stranger. In the absence of mating (6 h), females show no preference for the partner. However, if treated with quinpirole (1.0 ng/side), females develop a significant partner preference even in the absence of mating. These results, adapted from Ref. [31], demonstrate that activation of the D2 receptors in the nucleus accumbens is necessary and sufficient for partner preference formation.

are also more social and, like most monogamous mammals, exhibit paternal as well as maternal behavior.

As mating is an important aspect of pair bonding, one might ask whether mating activates mesocorticolimbic pathways in monogamous voles. Using in vivo microdialysis, Gingrich et al. [31] were able to demonstrate dopamine release in the nucleus accumbens with mating in prairie voles. However, this can hardly be considered strong evidence for dopamine involvement in pair bonding, as dopamine is released in the nucleus accumbens or VTA in nonmonogamous rats and hamsters with sexual stimulation [32,33]. More suggestive evidence has come from pharmacological studies (Fig. 2). Dopamine (D2 receptor but not D1 receptor) agonists induce partner preferences even in the absence of mating [34]. Moreover, D2 (but not D1) receptor antagonists prevent the development of a partner preference in mated pairs of prairie voles without influencing the mating per se [34]. Although these effects could be due to dopamine actions in many brain regions, Gingrich et al. [31], in a subsequent study, showed that a partner preference could be facilitated with a D2 agonist (quinpirole 1–10 ng/side) infused directly into the nucleus accumbens. Conversely, a D2 antagonist (eticlopride 100 ng/side) infused directly into the nucleus accumbens (but not the prelimbic area) blocked development of a partner preference in the presence of mating [31]. These studies support the notion that mesolimbic dopamine activation of D2 receptors is necessary and sufficient for the development of a partner preference in prairie voles.

4. Specificity—a role for neuropeptides

If mesolimbic dopamine is critical for maternal behavior and pair bonding, why are attachments formed to pups or to mates rather than to other stimuli in the environment? In other words, how do social stimuli become linked to the mesolimbic pathway? One possibility is that peptides or specifically peptide receptors mediate this link in much the way that they modulate other monoaminergic circuits. In this section, I review the evidence that oxytocin (OT) or vasopressin (AVP) may be particularly important for linking social signals to reinforcement pathways.

OT and AVP are found exclusively in mammals [35]. OT mediates the prototypically mammalian function of milk ejection during lactation by binding to receptors in the cells lining the lactation ducts, causing these ducts to contract and expel milk. AVP, originally called antidiuretic hormone, has a classic role in the kidney where it promotes reabsorption of water. Both hormones are made in the hypothalamus, stored in the posterior pituitary, and released into the circulation following suckling (OT) or osmotic challenge (AVP). In most mammals that have been studied, both OT and AVP are released during labor to increase contractions via receptors in the uterus. Vaginocervical stimulation is a potent releaser of both peptides, either during labor or copulation [35]. And receptors for both peptides are found in the brain. Considerable evidence suggests that OT is necessary and sufficient for the onset of rat maternal behavior. Whereas infusions of OT facilitate the onset of maternal behavior, decreasing OT neurotransmission by lesioning OT cells, reducing OT synthesis, or injecting antagonists of OT binding inhibits the onset of maternal behavior [36]. None of these treatments was effective in females with established maternal behavior. That is, OT is necessary for the onset not the maintenance of maternal behavior.

Both OT and AVP have been shown to influence social memory [37,38]. The paradigm involves introducing a novel intruder into the cage of the test animal for 5 or 10 min. The test animal will investigate the novel intruder for several minutes. If the intruder is removed and then returned 30 or 60 min later, the test animal shows a clear reduction in investigation, presumably reflecting recognition of the intruder. A novel animal introduced at this point is investigated as much as the test animal in the original exposure. When this simple test has been used to measure social recognition in OT-knockout mice, they appear conspicuously socially amnestic [38]. Mice lacking OT spend as much time as wild-type mice investigating the stimulus mouse initially but show no reduction in subsequent tests, even when these tests are only 5 min apart. This deficit in social recognition is particularly intriguing for its specificity. OT-knockout mice perform normally on tests of spatial memory, olfactory memory, and habituation [38]. Indeed, they are able to recognize the stimulus mouse if this mouse is painted with lemon or almond, a nonsocial scent (author's unpublished data). Curiously, there is less evidence that OT is essential for social memory in rats. Instead, it is AVP that appears critical for rats to consolidate social memories [37].

Given the evidence implicating OT in maternal behavior and OT as well as AVP in social memory, these neuropeptides are obvious candidates for the study of attachment in voles. OT (but not AVP) given centrally to females facilitates the development of a partner preference in the absence of mating [39,40]. A selective OT antagonist given before mating blocks formation of the partner preference without interfering with mating [40]. This effect appears specific: Neither CSF nor an AVP antagonist given in an identical fashion blocks partner preference formation. Presumably, the OT antagonist prevents the binding of OT to its receptor and thereby blocks the behavioral consequences of mating. These results suggest that OT released with mating is both necessary and sufficient for the formation of a pair bond in the female prairie vole. Essentially, female prairie voles given the OT antagonist resemble montane voles—they mate normally but show no lasting interest in their mate.

In males, it is not OT but AVP that is critical for partner preference formation. An AVP antagonist administered centrally to male prairie voles before mating blocks the development of a partner preference and precludes the associated increase in aggression towards an intruder [41].

As with females, the antagonist does not interfere with mating, rather it appears to block the consequences of mating. An OT antagonist has no effect, suggesting that the AVP effects are specific. AVP may also be sufficient for male pair bonding. When males are not permitted to mate, but are exposed to ovariectomized females, they fail to form a partner preference. However, when AVP is given centrally, in the absence of mating, males form a partner preference for the unreceptive female and will exhibit increased aggression towards an intruder [41]. OT given in the same fashion has no effect on these measures.

Most important, OT and AVP fail to induce pair bonding in montane voles, which, in contrast to prairie voles, are promiscuous and fail to form pair bonds after mating. Indeed, OT and AVP, even at high doses, have little effect on social behavior in montane voles [42,43]. The species difference in behavioral response may be explained by profound species differences in the brain distribution of receptors. Indeed, the maps of both OT and AVP V1a receptors are nearly complementary in prairie (or pine) voles and montane (or meadow) voles [44,45]. Recent studies have demonstrated that the species differences in receptor binding maps can be replicated by maps of receptor mRNA expression [43,46]. In fact, there are virtually identical cDNAs in both species for the OT and V1a receptor—demonstrating that these species share the same receptors but differ in the regional expression of both receptors.

Where are the most salient receptor differences? In the prairie vole, OT receptors are found in brain regions associated with reward (nucleus accumbens and prelimbic cortex), suggesting that OT might have reinforcing properties selectively in this species [45]. Recent evidence supports this mechanism, as an OT antagonist injected directly into these regions is sufficient to block formation of a partner preference following mating [47]. Moreover, the number of OT receptors in the nucleus accumbens appears to predict the increase in preproenkephalin following a local OT infusion [47]. In the montane vole, which lacks receptors in this reward circuit, OT may be released with mating but it would not be expected to release opiate peptides and would not confer reinforcing properties.

Similarly, in the prairie vole but not the montane vole, the V1a receptor is found in the ventral pallidum, a major projection field for the nucleus accumbens and a critical part of the reward circuit [48]. AVP release would therefore be expected to have markedly different cognitive effects in these two closely related species. Two observations suggest that the differences in V1a receptor distribution may be related to the species differences in social behavior. First, a transgenic mouse created with the prairie vole V1a receptor gene shows patterns of receptor distribution similar to the prairie vole and responds to AVP with an increase in social affiliation [49]. Mice without this transgene lack the prairie vole pattern of receptors and do not respond to AVP with an increase in social behavior. In a second study, the V1a receptor was increased in the ventral pallidum specifically by local injection of an adeno-associated virus engineered to deliver the V1a receptor gene [50]. Voles with increased V1a receptor binding in the ventral pallidum exhibited increased affiliative behavior and more rapid partner preference formation relative to voles receiving the virus with lac-Z into the ventral pallidum. As a second control, the virus with the V1a receptor gene was injected into another brain region (caudate putamen). These voles showed no change in their social behaviors. Injecting an AVP V1a antagonist directly into the ventral pallidum appears to reduce partner preference formation in preliminary studies [51]. The effect may not be specific to the ventral pallidum as injection of the same antagonist into the lateral septum also prevents partner preference formation [52]. Infusion of AVP into the lateral septum facilitates partner preference formation in the absence of mating, an effect that surprisingly is blocked by either a selective AVP V1a or an OT antagonist [52].

In summary, highly affiliative, monogamous voles show distinct patterns of OT and AVP receptor distribution in brain. Both peptides appear to be important for pair bond formation. OT receptors in the nucleus accumbens and V1a receptors in the ventral pallidum appear critical for the development of selective social bonds, as measured with a partner preference. How do these systems interact with dopamine or D2 receptors? We do not have all the answers for this question yet. In rats, cocaine given acutely reduces OT content in the basal forebrain but increases the concentration in hippocampus and hypothalamus [53]. Peripheral administration of OT reduces cocaine-induced hyperlocomotion and stereotyped grooming, effects that can be blocked by central administration of an OT antagonist [53]. Injection of OT (10–50 ng) directly into the nucleus accumbens reduces cocaine-induced sniffing, so the available data suggest that OT in mesolimbic pathways of the rat brain may inhibit rather than facilitate cocaine's effects [54]. These observations are further supported by OT reversal of behavioral tolerance following chronic administration of cocaine [55].

These results in rats are actually contrary to what would be expected from the data in voles in which the peptides appear to facilitate dopamine effects. A working hypothesis from the vole research is that mating releases OT or AVP that amplifies the dopamine signal in the nucleus accumbens shell. The next step will be to infuse peptide antagonists and dopamine agonists (or peptide and dopamine receptor antagonists) to determine the hierarchy of neurochemical action. These studies have just begun in the laboratory of Zuoxin Wang. His early results suggest that in female prairie voles, the D2 agonist quinpirole's induction of a partner preference can be blocked by either the D2 antagonist eticlopride or the OT antagonist given intracerebroventricularly [56]. Conversely, OT's facilitation of partner preference formation can be prevented by coadministration of either an OT antagonist (given intracerebroventricularly) or the D2 antagonist eticlopride [56]. Thus, it appears that increases in both OT and dopamine receptor activation are

necessary for partner preference formation rather than one acting upstream of the other. The contrast in effects between voles and rats may reflect either differences in receptor localization (such as nucleus accumbens shell vs. core) or species difference in other factors that modulate dopamine neurotransmission. It may be particularly informative to investigate the effects of both dopaminergic D2 receptor agents and the neuropeptides in montane voles, which are much more closely related to prairie voles but fail to form partner preferences.

5. Conclusion

The literature on the hedonic properties of drugs of abuse has been our major source of information about the neurobiology of reward. Drugs such as cocaine are an easily manipulated stimulus and thus have permitted rigorous dissection of the pathways and the candidate genes involved in reward. It seems likely that these pathways and genes evolved not for drug abuse but for mediating the motivational aspects of social interaction, including pair bonding, maternal attachment to infants, and presumably infant attachment to mother. This review has presented the evidence that mesocorticolimbic dopamine, an important candidate in addiction, is also critical for maternal behavior in rats and pair bonding in voles. The results are far from conclusive but a circuit linking the anterior hypothalamus (MPOA) to the VTA and the nucleus accumbens shell may be especially important for mediating the rewarding properties of social interaction. The neuropeptides OT and AVP are released by sociosexual experience and may serve an important link by which parturition, copulation, and lactation can activate this reward circuit.

This review began by noting that Paul Maclean suggested that opiate use serves as a substitute for social attachments and that a common neurobiology underlies the major forms of attachment. Although we still lack the proof, MacLean's intuitions about attachment, as so many of his ideas about neuroscience, continue to spawn interesting studies that address an important yet previously neglected aspect of behavior.

Note added in proof

Aragona et al. [57] have demonstrated that dopamine agonist facilitate and dopamine antagonist inhibit partner preference in male prairie votes when injected directly into the nucleus accumbens.

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