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Female alternative mating tactics, reproductive success and nonapeptide receptor expression in the social decision-making network

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Abstract

The decision to mate may be one of the most important decisions that animals make. For monogamous species, this decision can carry the added weight of limiting future mating opportunities. The mechanisms that govern these decisions have presumably been shaped by evolution in ways that optimize decision-making processes. In particular, a so-called social decision-making network (SDM) has been proposed, which integrates brain structures comprising the ‘social behavior network’ with a neural system associated with reward. Here, we investigate the neural phenotypic differences in the SDM for oxytocin and vasopressin receptors (OTR, V1aR) of female socially monogamous prairie voles living in naturalistic conditions. We focus on these receptors because they are profoundly involved in mammalian social behavior. We found that V1aR in the bed nucleus of the stria terminalis, medial amygdala and ventral pallidum, and OTR in the nucleus accumbens and hippocampus significantly differed between pregnant and non-pregnant females. Most of these areas are more closely related to the reward component of the SDM. V1aR in the ventral pallidum was also greater in paired than in single females. Finally, reproductive success within mating tactics was related to receptor density in brain structures across the SDM, particularly those serving as the interface between the social behavior network and the reward system. Our data support the hypothesis that neural phenotype for neuromodulatory nonapeptide receptors within the SDM relates to natural behavior associated with reproductive decisions.

Keywords

oxytocin; vasopressin; *Microtus ochrogaster*; social behavior; mating tactics; cognitive ecology

1. Introduction

At some point in their lives, all animals must decide when (and usually with whom) to reproduce. Typically, females base mate choice decisions on their assessment of various male features, which presumably enhance the female’s ability to produce offspring, or the

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offsprings' probability of accruing their own reproductive success [2]. Such discrimination on the part of females tends to lead to species recognition and sexual selection, and accounts for a considerable selective pressure that shapes the process of evolution [50].

When animals form life-long pairs, mating decisions carry even greater importance. Monogamous mating systems, like all mating systems, represent a collection of several individual reproductive choices [7]. Mating systems and individual mating tactics emerge from individuals of a population - each assessing the ecological and social landscapes in which they find themselves [14, 52]. Most females, for example, must consider their access to resources, the energetic requirements necessary to maximize their reproductive success, and the types of benefits that they and presumably their offspring will enjoy based on the mating partners they choose. Based on their best estimate of the context and the status of their own somatic integrity, individuals will then act in a way concordant with the tactic that will most likely produce the greatest reproductive success [38]. As a result, the selective pressures generated by reproductive decisions can lead to phenotypes that promote reproductive success directly, and/or behavioral tactics that interact with the social world to enhance reproductive success.

Reproductive decisions are inherently cognitive processes [33, 47, 51]. Individuals must gather both internal and external information, evaluate this information, and then produce an action based on some set of decision rules [23, 49, 51]. These actions represent the observable outcomes of reproductive decisions. Information gathering - however sound or flawed - is used to assess the state of the world with respect to the individual and its position in it. Particularly important is the evaluation of the sensory input, on which the final decisions are based. Because reproductive decisions are inherently reactions to the social environment, the influence of the social world has the potential to significantly impact reproductive decisions and mating tactics.

The social brain hypothesis postulates that evolution has responded to the demand from complex social systems with neuroanatomical adaptation and modification [13]. Originally this hypothesis was used to explain the relatively large primate neocortex; however, more basal neural structures found primarily in the limbic forebrain function to respond to varied social contexts and behavioral responses of conspecifics [34]. This so-called social behavior network (SBN) may promote the neocortex function to process higher order tasks such as tactical deception and coalition formation. Unlike the advanced brain size seen in most primates, the SBN is highly conserved across vertebrates [8, 20, 35]. Specifically, the SBN represents a network of inter-connected brain structures, and inter-related mechanisms operating on those structures that evaluate social conditions and inform reactions to the social world by producing context-dependent, and often sex specific, patterns of activity across the network [34]. The SBN is comprised of the medial amygdala (MeA) and bed nucleus of the stria terminalis (BST), the lateral septum (LS), the preoptic area (POA), the anterior hypothalamus (AH), the ventromedial hypothalamus (VMH), and the midbrain (primarily the periaqueductal gray; PAG). Although these brain regions are not the only nuclei involved in social behavior, they are perhaps best viewed as the 'core' of the vertebrate social brain [34]. The accumulation of a large amount of evidence delineating functional pathways involved in a broad array of social behaviors, led Newman to propose these structures comprise an integrated social behavior circuit (c.f., [34, 35]). Indeed, each node of the SBN has been implicated in control of social behavior, including aggression, sexual behavior, communication, social recognition, affiliation, bonding, parental care and stress coping (see [8, 20, 35] and references therein).

In order to modulate behavioral reactions to social stimuli and context, some form of emotional valence must be assigned to the information processed by the SBN. To address

this problem, O'Connell and Hofmann [35–37] proposed that behavioral decisions require that salience of external stimuli be evaluated in conjunction with the SBN-mediated processing of social information. To this end, they argue that the mesolimbic reward system (MLR) enables animals to evaluate the relative importance of social stimuli, thus providing the valence needed to produce behavioral decisions. Whereas the MLR system relies heavily on dopaminergic innervation of the nucleus accumbens (NAcc) from the ventral tegmental area (VTA) [55], it also includes its own interconnected network of nuclei, including the basolateral amygdala (BLA), the ventral pallidum (VPall), the striatum (caudate-putamen; CPu), the hippocampus (Hi), the LS, and the BST. Interestingly, the BST and LS are shared between, and lie at the interface of, the two networks. O'Connell & Hofmann [35–37] argue that together the two systems comprise a larger network, which they call the 'social decision-making network' (SDM). The deep phylogenetic conservation of the SDM is largely supported by neural homologies based on topography, neurochemistry, hodology, and developmental gene markers. The putative SDM represents a theoretical framework with potential to inform how the brain produces context-appropriate behavioral patterns.

Oxytocin and vasopressin are nonapeptide hormones with a long and colorful history [67], which act centrally as neuromodulators and neurotransmitters in a diverse array of mammalian social behaviors [6]. Not surprisingly, many of the neural structures comprising the SBN express these peptides or their receptors. For example, the V1a receptor subtype for vasopressin is closely associated with social behavior and is broadly expressed throughout the SBN ([1], but see [56] for V1bR). Specifically, V1aR is found in every component of the SBN [3, 25, 63], though expression patterns vary across species. Oxytocin receptor (OTR) also expresses throughout the SBN, and is known to express in the POA, LS, BST, MeA, and VMH in various species [3, 25]. Because of the prominence placed on dopamine's involvement in the MLR system, the expression of OTR and V1aR in these structures is relatively less appreciated. Nevertheless, in addition to the LS and BST, these receptors have been described in the CPu, NAcc, BLA, Hi (for OTR), and in the VPall (for V1aR) [3, 25–27, 62]. The hypothesis that receptor expression patterns often represent the products of selective pressures [29] reinforces the view that particular emphasis should be placed on the receptors when searching for mechanisms that promote adaptive behavioral responses (e.g., [42]).

Here we investigate the receptor expression patterns of OTR and V1aR throughout the forebrain of female prairie voles (*Microtus ochrogaster*) living in semi-natural outdoor enclosures. Prairie voles are particularly interesting because, like males, females are generally socially monogamous, but some females remain single [16–18, 31, 32, 41, 46]. Individuals adopting a paired mating tactic generally have smaller home ranges than single 'wanderers', and paired prairie voles produce more offspring than single voles [41, 42, 46, 54]. In particular, we focus on females because presumably females heavily weigh the costs and benefits of mate selection and must carefully consider the decision to pair with respect to the current social environment.

Specifically, we ask if nonapeptide receptor expression in the SDM relates to female prairie vole behavior observed in natural conditions. We give special attention to OTR and V1aR expression in the mesolimbic reward system and social behavior network, and contrast receptor density between behavioral variation in mating tactic (paired or single) and reproductive success (pregnant or non-pregnant). We predict that, if the action of neuromodulators such as vasopressin or oxytocin in the SDM shapes reproductive decisions (for instance the decision to mate or the decision to pair), then the patterns of receptor expression in the various nodes of each system should concord with the reproductive choices females make.

2. Methods

2.1 Animals

We used a total of 48 female and 48 male prairie voles to explore individual differences in brain phenotype and how they related to mating tactic (defined as socially monogamous pairs or non-monogamous singles) and reproductive success (defined as pregnant or non-pregnant) in female prairie voles living freely under semi-natural field conditions. All test animals (F1–F3) originated from wild caught individuals from either Shelby County, Tennessee or Champaign County, Illinois. Elsewhere we have demonstrated that animals from these locations show no differences in brain or behavior in the lab or field [39] and we therefore treated animals as a single population. We bred the animals at the University of Memphis and weaned offspring at 21 days. Post-weaning, animals were grouped in same sex litters in polycarbonate cages (29 × 18 × 13 cm) under a 14:10 light: dark cycle. We provided rodent chow (Harland Teklad, Madison, WI, U.S.A) and water *ad libitum*. Temperature was maintained at 21 ± 2°C. Two days before introduction into field enclosures (see below), all test animals were ear-tagged, weighted, tail clipped, and outfitted with a 1.9g transmitter (BD-2C, Holohil Systems Ltd., Carp Ontario) and collar. All animals were of similar age and weight. Our procedures were in accordance with the guidelines set and approved by the Institutional Animal Care and Use Committee of the University of Memphis.

2.2 Study design

We distributed the animals into eight groups, each consisting of six nulliparous females and six mature males. Each group was placed in one of four outdoor semi-natural enclosures. Each enclosure measured 20 × 30m and was populated by natural grasses and dicots endemic to the study site (Shelby County, TN). We tracked animals using a LA12 Ratio Telemetry Receiver (AVM Instruments Co, Ltd., Livermore, California). We ran four trial blocks, each consisting of two trials, over the breeding season.

During a trial, we took telemetry readings twice a day for 12 days, varying time of day and enclosure order. We began trapping animals from enclosures three days before females would have given birth had they been impregnated on the first day in the enclosures (~ 18 d) [41].

2.3 Determination of mating tactic and breeding success

We have reported the analysis for mating tactic and sexual fidelity elsewhere [46]. We used shared nest sites and home range overlap to determine which animals were considered paired and which were single (see [40–42] for more discussion). We determined that females were pregnant by extracting and counting embryos. We defined females as successful breeders if they were pregnant at the time of capture and unsuccessful breeders if they were not. Because female prairie voles experience induced ovulation [11, 48], we assume the estrus states of non-breeders were equivalent.

2.4 Tissue extraction and autoradiography

Trapped animals were returned to the lab and euthanized with CO₂ gas. We extracted brains, placed them on powdered dry ice, and stored them in –70°C. Later, we coronally cryosectioned brains at 20µm and mounted sections at 100µm intervals on Superfrost slides (Fisher Scientific). Each of four sets was then stored at –80°C until they were used to visualize receptor density using autoradiography. On two of the four sets we used ¹²⁵I radioligands to visualize either oxytocin receptor (ornithine vasotocin analog, ([¹²⁵I]-OVTA); NEX 254, PerkinElmer; Waltham, MA) or vasopressin 1a receptor (vasopressin (Linear), V-1A Antagonist (Phenylacetyl1, 0-Me-D-Tyr2, [¹²⁵I-Arg6]-); NEX 310,

PerkinElmer; Waltham, MA). To process tissues, we lightly fixed sections in 0.1% paraformaldehyde (4°C) for 2 min, washed them twice in 1X Tris-HCL (pH 7.4, 4°C) for 10 min, incubated them either with 40pM [¹²⁵I]-OVTA or with 50pM ¹²⁵I-labeled vasopressin (Linear), V-1A antagonist for 90 min at RT. Next, we washed slides at RT in a series of 5 min baths of 1X Tris-HCL (pH 7.4) with MgCl₂ followed by a final wash in 1X Tris with MgCl₂ for 30 min (50 mM Tris, 100 mM MgCl₂), and then rapidly air-dried them.

We exposed radiolabeled tissue to film (GE Healthcare, Buckinghamshire, UK) for three (OTR) or four (V1aR) days; different exposure lengths compensated for differing degrees of ligand radioactive decay at the time of use. We used ¹²⁵I labeled radiographic standards (American Radiolabeled Chemicals; St Louis, MO) to allow for conversion of optical density to receptor density. We digitized films on a Microtek ArtixScan M1 (Microtek, Santa Fe Springs, CA) and measured optical densities using NIH ImageJ Software. Optical density measurements serve as a proxy for receptor density. We calculated receptor density by first converting optical density to disintegrations per minute, adjusted for neural tissue equivalence in rat, by using a log function to fit curves generated by radiographic standards.

We measured OTR in the nucleus accumbens, lateral septum, striatum (caudate-putamen), basolateral amygdala, and hippocampus (figure 1). We measured V1aR in the ventral pallidum, lateral septum, medial, lateral and ventral portions of the bed nucleus of the stria terminalis (BSTm, BSTl, BSTv, respectively), medial amygdala, anterior hypothalamus, and the ventral medial hypothalamus (figure 1). We did not section brains to the midbrain and therefore were unable to describe the PAG or VTA. Neither the VTA nor the POA express V1aR or OTR in female prairie voles [26, 27, 62]. It should be noted that V1aR and OTR expression is not limited to the SDM or MLR in prairie voles and therefore the assessment of nonapeptide receptor profiles in these circuits is not tantamount to assessing their distribution across the entire brain. However we limit our evaluation of receptor density to these structures to specifically address the questions outlined above. Specific binding was calculated by subtracting nonspecific binding from total binding for each area. Nonspecific binding was estimated from background levels of cortex that do not express either receptor on the same sections.

2.5 Analysis

We used two-factor analysis of variance (ANOVA) to investigate differences in female V1aR and OTR expression. Our factors were mating tactic (paired or single) and reproductive success (pregnant or non-pregnant). Where interactions were significant, we used Tukey-Kramer post hoc tests.

In order to test their natural mating decisions, females must be allowed to choose their own mating tactic and decide when and with whom to mate. Furthermore, the most common reproductive tactic for female prairie voles is to form pairs [41], and females that form pairs usually become pregnant. Although we view this as an important and valuable approach to ask if natural variation in neural phenotype relates to behavioral phenotype, the unfortunate consequence was that we were unable to assign females to groups *a priori* and sample sizes were unequal. Furthermore, some animals were lost due to either unsuccessful survival in the field, or lost radio-transmitters [41]. Moreover, we omitted one individual from the non-pregnant paired group for VMH (V1aR), two individuals from the pregnant paired group for NAcc, LS, CPu, and BLA (OTR), and one individual from the pregnant paired group for Hi (OTR) due to poor tissue quality while processing brains.

Not surprisingly, the unbalanced design violated the assumption of orthogonality and our ability to obtain an additive partition of the sum of squares necessary to run a parametric test. Fortunately, the methods of van Belle et al. [58] can correct for disparity in sample

sizes, satisfy these statistical assumptions, and enable the use of the 2-factor ANOVA. Our statistics package (Aabel 2.4.4, Gigawiz Ltd.; Tulsa, OK) used these methods to adjust for these important statistical issues.

We note that analyses for two structures (OTR: Hi, NAcc) have been reported elsewhere [46], however these analyses did not account for the unbalanced design. Here, we provide a more exhaustive set of analyses of these, and other unreported data, and use the statistical models discussed above to account for the unbalanced design. Therefore, the data reported here are entirely novel.

3. Results

The natural distribution of V1aR across the social decision-making network of female prairie voles indicates that vasopressin is broadly active throughout the SDM but may be more heavily involved in modulation of the social behavior network. Within the SBN, V1aR expression was detected in the AH, VMH, LS, BST, and MeA. In other words, every component of the social behavior network we investigated expressed V1aR except the preoptic area (figure 1). V1aR was also found in the VPall, which is a core component of the mesolimbic reward system. On the other hand, oxytocin receptor expression was restricted exclusively to nodes within the mesolimbic reward system, including the LS CPu, NAcc, Hi, and BLA. However, we note that the LS is also a node of the SBN (figure 1).

We performed 2-factor ANOVA (corrected for unequal sample sizes) to ask if the neural expression patterns of OTR or V1aR related to whether females were paired (N=31) or single (N=5), or if females were pregnant (N=29) or not pregnant (N=7). Overall, we found that OTR density in most brain areas did not differ with respect to these factors (table 1). Two important exceptions to this were the nucleus accumbens and the hippocampus, which differed between pregnant and non-pregnant females (see below). On the other hand, we found several areas of the brain expressing V1aR in which receptor density showed a main effect of mating tactic (VPall), reproductive success (BST, MeA, and VPall), or showed significant interactions between mating tactic and reproductive success (table 1). Below we discuss these results in more detail in terms of the mesolimbic reward system, the social behavior network, and the structures at the interface between the two systems.

3.1 Mesolimbic Reward System

Below we discuss the LS and BST as areas that are part of both the mesolimbic reward system and the social behavior network. We do not consider the VTA here because we did not section to the midbrain, however prairie voles do not express OTR or V1aR in this structure [26, 27, 62].

OTR is expressed in the striatum and basolateral amygdala, however no main effects of mating tactic (paired v single: $F'_{s(1,30)} = 0.019$; $p's > 0.50$) or reproductive success (pregnant v non-pregnant: $F'_{s(1,30)} = 1.57$; $p's = 0.22$) were found for OTR density in these structures. Similarly, no interaction effect in these structures was found ($F'_{s(1,30)} = 0.04$; $p's > 0.50$, table 1).

Paired females expressed more V1aR in the VPall than single females ($F_{(1,32)} = 5.28$; $p = 0.028$; figure 2). This was the only case in which we found a main effect for mating tactic in any structure we investigated, however, V1aR density in the BSTv showed a non-significant trend in the same direction (see below).

Nonapeptide neural expression differed by reproductive success in several MLR structures. Specifically, pregnant females expressed less V1aR than non-pregnant females in the VPall

($F_{(1,32)} = 4.93$; $p = 0.03$). Similarly, pregnant females expressed less OTR than non-pregnant females in the NAcc ($F_{(1,30)} = 8.12$; $p = 0.008$). The reverse was true for OTR in the Hi; pregnant females expressed more OTR in the Hi than non-pregnant females ($F_{(1,31)} = 8.88$; $p = 0.006$).

Neither the VPall (V1aR) nor the NAcc (OTR) showed interaction effects between mating tactic or breeding success (VPall: $F_{(1,32)} = 0.45$; $p > 0.50$; NAcc: $F_{(1,30)} = 1.06$; $p = 0.31$). The interaction between mating tactic and breeding success, however, was significant for OTR in the Hi ($F_{(1,31)} = 9.55$; $p = 0.004$, figure 3a). OTR density in the Hi was significantly lower in non-pregnant paired females than in non-pregnant single females (Tukey-Kramer HSD, $p = 0.003$), but significantly higher in pregnant paired females than pregnant single females (Tukey-Kramer HSD, $p < 0.001$).

3.2 Social Behavior Network

The POA does not express either V1aR or OTR in female prairie voles (figure 1). Although female prairie voles do express V1aR in the PAG, we did not section brains past the forebrain and were unable to measure receptors in the midbrain.

V1aR density for paired and single females did not differ in the MeA (ANOVA; $F_{(1,32)} = 0.12$; $p > 0.50$), the VMH ($F_{(1,31)} = 1.38$; $p = 0.25$) or in the AH ($F_{(1,32)} = 0.61$; $p = 0.44$). Although pregnant and non-pregnant females did not differ in V1aR density in either of these hypothalamic structures (VMH: $F_{(1,31)} = 0.19$; $p > 0.50$; AH: $F_{(1,32)} = 3.39$; $p = 0.08$), pregnant females expressed more V1aR in the medial amygdala and tended to express more in the anterior hypothalamus than non-pregnant females. The interaction between mating tactic and breeding success was significant for V1aR in the AH ($F_{(1,32)} = 4.72$; $p = 0.04$; figure 3d). V1aR density in the AH was significantly higher in pregnant paired females than in non-pregnant paired females (Tukey-Kramer HSD, $p < 0.05$), and significantly higher in pregnant paired females than pregnant single females (Tukey-Kramer HSD, $p = 0.02$). The interaction was not significant for V1aR in the MeA or VMH (see table 1).

3.3 Social Behavior Network and Mesolimbic Reward System Interface

The lateral septum, and the bed nucleus of the stria terminalis each express V1aR, and the lateral septum also expresses OTR (figure 1). Nonapeptide receptor density between paired and single females did not differ in these 'interface' structures. Although there was a tendency toward greater V1aR density in the BSTv in paired females ($F_{(1,32)} = 3.27$; $p = 0.08$), receptor density for all other structures (LS, BSTm, BSTl) was similar regardless of mating tactic (all $F_{(1,32)} \leq 0.54$; $p \geq 0.47$; table 1). Furthermore, OTR in the lateral septum did not differ between paired and single females ($F_{(1,30)} = 2.43$; $p = 0.13$).

V1aR density of pregnant females was greater in the BSTm and BSTl than non-pregnant females ($F_{(1,32)} = 10.06$; $p = 0.01$; see table 1), whereas it was lower for pregnant females in the BSTv ($F_{(1,32)} = 5.91$; $p = 0.02$). No interaction effect between mating tactic or reproductive success for V1aR expression was found for the BSTv ($F_{(1,32)} = 0.13$; $p > 0.50$), however both the BSTm and BSTl showed significant interactions ($F_{(1,32)} = 6.49$; $p = 0.02$; see table 1). Specifically, V1aR density in the BSTm and BSTl was significantly higher in pregnant paired females than in non-pregnant paired females (Tukey-Kramer HSD, BSTm and BSTl: p 's < 0.001 , figure 3b–c), and higher in pregnant paired females than pregnant single females (BSTm: $p < 0.05$, BSTl: $p = 0.06$, figure 3b–c); the difference in the BSTl was not significant. Neither V1aR nor OTR in the LS differed between pregnant and non-pregnant females (V1aR: $F_{(1,32)} = 0.44$; $p > 0.50$; OTR: $F_{(1,30)} = 0.96$; $p = 0.33$), and no interaction effects were observed (V1aR: $F_{(1,32)} = 2.16$; $p = 0.15$; OTR: $F_{(1,30)} = 0.49$; $p = 0.49$).

4. Discussion

Both vasopressin and oxytocin and their receptors are of great interest due to their ability to modulate social behavior [21]. However, a broad conceptual framework for how these systems affect behavior has remained elusive given the complexity of their many specific behavioral effects [19–21]. One explanation for this complexity is that the profound taxonomic differences in receptor distribution and abundance reflect the varied ecological niches of individual species, driving species-specific effects on behavior [22], but see [37]. The individual variation exhibited among prairie voles, and the influence of nonapeptides on their mating decisions, reflects this complexity. Below we discuss how using the theoretical framework provided by the social decision-making network enables a cogent explanation for the particular patterns of OTR and V1aR seen throughout the forebrain.

4.1 Nonapeptide Receptor Expression and The Social Decision-Making Network

O’Connell and Hofmann [35–37] proposed a putative vertebrate social decision-making network which represents a synthesis of the social behavior network and the mesolimbic reward system. Their hypothesis is based on extensive comparative evidence, suggesting that the neural structures involved in processing reward and social behavior form two systems that are each ancient, highly conserved, and functionally interconnected. This synthesis, of what has occasionally been treated as separate circuits, provides a theoretical foundation on which a deeper understanding of the evolution of the neural basis for social behavior can be built. Furthermore, the nonapeptides oxytocin and vasopressin and their receptors OTR and V1aR (or their non-mammalian homologues) have become inextricably linked to discussions of social behavior [67]. Like the components of the SDM, these nonapeptides have deep evolutionary roots and are vastly incorporated into the modulation of social behavior across taxa [19–21].

Although our study cannot speak to the functional roles that vasopressin and oxytocin have in the social decision-making network of female prairie voles, the distribution across this network is informative and provides insight into their possible function within this system. For example, OTR expression is relatively restricted to structures that are either exclusively in the MLR (CPu, BLA, NAcc, and Hi) or shared between the MLR and SBN (the LS). On the other hand, V1aR was broadly expressed throughout the SBN (MeA, VMH, and AH), the MLR (VPall), or in areas that contribute to both sub-networks (BST and LS) (figure 1). It is therefore tempting to speculate that OTR may be more involved in rewarding aspects of social decisions, whereas V1aR may have broader functions in assessing social contexts (SBN), providing emotional valence to the context (MLR), and synthesizing this information (shared structures of the MLR and SBN).

4.2 Reproductive Success, Reward, and the Social Decision-Making Network

Several studies have implicated the mesolimbic reward system and its components in evaluating the salience of stimuli [10, 59]. This neural network is thought to provide the reinforcement necessary to promote adaptive behavior – for instance to promote reproductive success. Mating behavior represents the single best example of this, the immediate adaptive consequence of which is pregnancy.

The expanded mesolimbic reward system can be quite complex. For instance there exists an elaborate and intricate set of afferent, efferent, and reciprocal neuronal connections throughout the brain (e.g., [24, 61]). Here, we discuss the more conventional and simplified network of neural structures for simplicity, which include the NAcc, VTA, VPall, LS, BST, CPu, BLA, and Hi [4, 35, 68]. It is particularly striking that all nodes of this system except the VTA express V1aR, OTR, or both (figure 1) in prairie voles. More interesting, is that the

density of these receptors across the majority of these structures predicted whether or not females were pregnant (table 1). Specifically, female pregnancy was predicted by OTR density in the NAcc and Hi, and by V1aR density in the BST and VPall. Only one structure outside of the MLR (the MeA) had receptor expression relating to reproductive success. Based on these results and given that oxytocin and vasopressin are neuromodulators, we speculate that oxytocin and vasopressin may modulate the decision to mate and that receptor density may act to enhance or reduce any such neuromodulatory functions.

An important question raised by our results is whether there is a causal relationship between nonapeptide receptor density in the mesolimbic reward system and successful breeding. Unfortunately the data from this study cannot address this question directly. However, elsewhere we have found that OTR and V1aR density in most structures is highly stable across the entire course of pregnancy among pairbonded primiparous females in the lab [45]. For instance, the difference in OTR density in the NAcc and Hi and V1aR density in the BST (and MeA) during pregnancy was stable. The chief exception is V1aR density in the ventral pallidum, which decreases as pregnancy progresses and suggests that being pregnant drives receptor expression in this structure. Notably, the current data are consistent with this result; pregnant females expressed less V1aR in the VPall than non-pregnant females. While we cannot rule out that reproductive status may have driven receptor expression in the VPall, it is highly unlikely that pregnancy caused the observed differences in receptor expression in most of the neural structures of the MLR. It is plausible, however, that successful reproduction could have been a consequence of neural phenotype in these structures. Whatever the case is, our data indicate that nonapeptide receptors, known for their significance in shaping social behavior, express broadly throughout the mesolimbic reward system and their expression appears to have a particularly important relationship with successful reproduction in females.

4.3 Mating Tactic and the Social Decision-Making Network

Most females are faced with the important decision of choosing mates. Unlike most mammals, however, female prairie voles are socially monogamous [41], and therefore are also faced with the complex decision of whether to form a pairbond or to remain single. While these decisions may seem to be one-in-the-same on a first pass, pairbonding and mating should not be equated, and represent different – albeit somewhat related – decisions. Indeed, the parsing of mating system and socialability may best be viewed as two independent axes [43].

Our results demonstrated that female V1aR density differed between paired and single females only in the ventral pallidum. Although this indicates that nonapeptide receptor expression in the SDM is not broadly related to the mating tactic that females ultimately adopted, the area that did show a significant relationship is particularly interesting. Indeed, much has been learned about the nature and the mechanisms of social bonding by studying vole species [5, 65, 66]. Comparative studies have shown that V1aR expression in the ventral pallidum and OTR expression in the nucleus accumbens are denser in monogamous species of voles than their non-monogamous counterparts [26, 27]. Further, central infusion of nonapeptide receptor antagonists targeting endogenous vasopressin or oxytocin [28, 60], and structure-specific studies suggest that these neuromodulators may have sex-specific effects on mammalian bonding. Specifically, V1aR antagonists delivered to the ventral pallidum inhibit the formation of partner preferences of males, but not females [30]. On the other hand, blockade of oxytocin receptor in the nucleus accumbens inhibits the formation of partner preferences of females, but not males [64]. This has led to a belief that (accumbal) oxytocin mediates female bonding, while (pallidal) vasopressin mediates male bonding, an assumption that has been extended to other mammals ranging from rats to humans [15, 57].

Strangely, due to the apparent sex-specific effects just discussed, the influence of pallidal vasopressin has largely been assumed to have no influence on female pairbonding, while the reverse is true for accumbal oxytocin for males. Our data that V1aR expression in the ventral pallidum differed between bonded or single females question this assumption. This idea is reinforced by a previously reported finding that parallels this in males; OTR in the NAcc is greater in bonded males than in single males [44]. These data fit well with the emerging idea that the actions of oxytocin and vasopressin in social bonding are not as sexually dimorphic as has been discussed. For example, oxytocin appears to have a more general purpose in governing affiliative behavior in males [12]. Similarly, the connectivity between the VPall, the NAcc, the prefrontal cortex, and other limbic structures has led to the hypothesis that, independent of gender, the VPall represents a ‘final common pathway’ for hedonic reward and may be involved in shaping higher order cognition [53]. Although our data do not tease apart whether the VPall is functionally important for the activation or maintenance of female pairbonds or the direction of the causal arrow between pairbonding and receptor expression, they do suggest that the vasopressinergic modulation of this reward-motivation mechanism may be important for female prairie vole pairbonding.

Conversely, it is strange that accumbal OTR did not differ between bonded and single females. This too is paralleled in male prairie voles; V1aR in the male VPall does not differ between paired and single males [42]. DeVries and colleagues have suggested that sex differences in the brain are sometimes responsible for eliminating sex differences in behavior, and serve a compensatory function in some species where evolution has led to divergent behavioral strategies in most others (c.f., [9]). It is possible that the natural differences and similarities between paired and single prairie voles for OTR and V1aR in regions that have been causally implicated in laboratory pairbonding reflect natural compensatory responses designed to balance (and facilitate) bonding in a species where reproductive success is closely tied to this behavior [41].

While there is general agreement that the action of vasopressin in the VPall and oxytocin in the NAcc are both important in monogamous pairbonding [65], what role oxytocin/OTR plays in male NAcc and vasopressin/V1aR plays in female VPall remains unclear. Our data suggest that although manipulations of nonapeptides in these targeted regions fail to eliminate or induce pairbonding in certain genders, males are open to oxytocinergic influences on pairbonding from the nucleus accumbens [44] while females are open to vasopressinergic influences on pairbonding from the ventral pallidum (figure 2). Together, the body of work to date suggests that the expression of both V1aR and OTR in the ventral pallidum and nucleus accumbens (respectively) appear to be important in the overall expression of natural pairbonding behavior for both genders.

4.4 Could Female Brains be Predisposed for Context-Dependent Decision-Making?

Finally, some structures that were spread across the social decision-making network differed in OTR or V1aR density as a function of whether females successfully reproduced within their given mating tactic. The anterior hypothalamus, medial and lateral portions of the BST, and the hippocampus all showed significant interaction effects between mating tactic and reproductive success (figure 3). For all of these structures, pregnant paired females expressed significantly more V1aR (AH, or BST) or OTR (Hi) than paired females that were not pregnant. Single females tended to show the opposite pattern; reproductively successful single females generally expressed less V1aR or OTR. If receptors are best viewed as a neural substrate for evidence of selection promoting adaptive behavior [29], then these results indicate that some nodes within the SDM are predisposed to potentially optimize particular behaviors necessary to succeed in either of the alternative reproductive tactics demonstrated by female prairie voles. In other words, once a reproductive tactic has been

adopted, the probability of producing offspring may be biased by the neural phenotype that females possess.

This interpretation should be tempered by at least two important considerations. First, it is important to note that these interaction effects should be viewed with caution. As we discussed earlier, we had no *a priori* control for how females would mate or the tactics they would adopt. Although we statistically controlled for this issue (see methods), dividing the animals into four groups (paired or single $\times$ pregnant or not pregnant) resulted in unbalanced groups, usually with very small sample sizes. Nevertheless, the patterns we report here are particularly interesting and strikingly similar to other patterns reported for males in which these groups were much more robust [42, 44]. For example, the identical pattern of hippocampal OTR in females (figure 3) has been observed in male prairie voles under the same conditions [44] suggesting that hippocampal oxytocin may be a particularly important influence on the reproductive success within alternative mating tactics for both males and females.

Secondly, it is not clear from our study whether the receptor densities we found are cause or consequence of the differences in behavior to which they related. However, it is unlikely that pregnancy alters the gene expression for OTR or V1aR [45], and we are unaware of any study that has demonstrated that pairbonding alters OTR or V1aR density, though this possibility cannot be ruled out. The lack of any main effects of mating tactic (with the exception of the ventral pallidum – discussed above) suggests that forming a pairbond is unlikely to alter OTR or V1aR density. Although the distribution of OTR and V1aR throughout the SDM is remarkably conserved across vertebrates qualitatively (present/absent), the ligands and the quantitative expression of nonapeptide receptors (i.e., density) are more labile, and potentially reflect differences associated with life history and ecology, or phylogenetic constraints unique to each species [37]. Therefore, if our results truly reflect differences in female neural phenotype, then they also indicate that recent evolutionary pressures have potentially biased females for differential reproductive success depending on the tactic they adopt. In other words, these interaction effects indicate that sensitivity (measured by the density of receptors available for binding) to vasopressin in the AH, BSTm and BSTl, and oxytocin in the Hi may shape the relative reproductive success of females prairie voles in a context-dependent way. Furthermore, because these neural structures span both the SBN and MLR, these effects could indicate that the influence of nonapeptides on reproductive decisions is more broadly important for integrating mating decisions with social information to which individual females have access.

5. Conclusion

We have considered nonapeptide receptor expression in light of the social decision-making network for free-living female prairie voles and the reproductive choices they make. Although the structures of the social behavior network and the mesolimbic reward system have been studied for over a decade [4, 8, 20, 24, 34, 55, 61, 68], considering these networks as parts of a larger unified system is a new approach [35–37] that may lead to a clearer understanding of behavior under natural contexts. Indeed, the expression profiles of mechanisms closely associated with social behavior (OTR and V1aR) across the female prairie vole SDM line up well with individual variation in their natural behavior, and with reproductive behavior in particular. Specifically we have shown that (1) nonapeptide receptors are differentially expressed across the social decision-making network in a way that may reflect the function of oxytocin and vasopressin in modulating social decision-making, (2) the influence of vasopressin in the ventral pallidum may be less sex-specific than has been previously thought, (3) oxytocin and vasopressin receptor density relates to whether females successfully reproduced, and (4) neural phenotype in some components of

the SDM might operate in a context dependent way to foster reproductive success within a chosen mating tactic. Viewing the expression profiles of nonapeptide receptors across the SDM broadens our understanding of the cognitive mechanisms that contribute to reproductive decisions. Examination of brain-behavior patterns in light of such a framework is sure to advance our ability to make sense of the neural substrates that contribute to social complexity in a dynamic and variable world.

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Highlights

OTR expression in the SDM suggests oxytocin may modulate reward in social decisions

V1aR expression in the SDM suggests vasopressin broadly shapes social decisions

Monogamous females express more V1aR than single females in the ventral pallidum

OTR and V1aR density in much of the SDM relates to whether females reproduced

OTR/V1aR in parts of the SDM might facilitate context-dependant reproductive success

Figure 1.

Autoradiograms of high and low OTR (blue) and V1aR (red) expression in nodes of the social decision-making network. At the center-bottom is a schematic of the social decision-making network modified from [35] presenting the nodes of the mesolimbic reward circuit (MLR; white background), social behavior network (SBN; dark gray background), or nodes that are shared between both the MLR and SBN (light gray background). The autoradiograms follow this layout with MLR structures on the left and SBN structures on the right; the dotted line above the center represents shared structures. An inset of the BST is presented to show subdivisions (lateral, medial, and ventral). At the bottom right, we present two typical autoradiograms indicating no OTR or V1aR expression in the POA. The VTA and PAG are presented as outlines since we did not characterize nonapeptide receptors in midbrain structures. Scale bar for autoradiograms equals 5 mm. Abbreviations are defined in the text.

Figure 2.

V1aR expression in the ventral pallidum differs between paired and single females. Mean ($\pm$ SEM) V1aR expression measured as disintegrations per minute/mg of neural tissue in the VPall of paired and single females.

Figure 3.

OTR and V1aR expression predicts mating tactics and breeding success. Mean (±SEM) OTR or V1aR expression measured as disintegrations per minute/mg of neural tissue for females varying in mating tactic (paired or single) and pregnancy (successful [black] or unsuccessful [white]) in the hippocampus (Hi, panel *a*), the medial and lateral portions of the bed nucleus of the stria terminalis (BST, panels *b–c*), and the anterior hypothalamus (AH, panel *d*). Tukey-Kramer HSD post-hoc test results are reported within the panels. * $\equiv p < 0.05$; ** $\equiv p < 0.01$; *** $\equiv p < 0.005$.

Table 1
OTR and V1aR expression across the Social Decision-Making Network

ANOVA results for OTR (blue) and V1aR (red) expression (specific binding disintegrations per minute per milligram of neural tissue) in core brain regions for the mesolimbic reward system (left) and social behavior network (right) in female prairie voles. Areas that do not express OTR or V1aR are indicated in white.

	Mating Tactic			Reproductive Success			Interaction		
	F	p	n/a	F	p	n/a	F	p	n/a
VTA									
<i>VPall (V1aR)</i>	5.28	0.03	n/a	4.93	0.03	n/a	0.45	0.50	>0.50
<i>NAcc (OTR)</i>	0.32	>0.50		8.12	<0.01		1.06	0.31	
<i>Hi (OTR)</i>	2.15	0.15		8.88	0.01		9.55	<0.01	
CPu (OTR)	0.01	>0.50		0.06	>0.50		0.04	>0.50	
BLA (OTR)	0.19	>0.50		1.57	0.22		0.01	>0.50	
Mesolimbic Reward System									
LS (OTR)	2.43	0.13		0.96	0.33		0.49	0.49	LS (OTR)
LS (V1aR)	0.54	0.47		0.44	>0.50		2.16	0.15	LS (V1aR)
<i>BSTm (V1aR)</i>	0.12	>0.50		15.55	0.001		6.49	0.02	<i>BSTm (V1aR)</i>
<i>BSTl (V1aR)</i>	0.05	>0.50		10.06	0.003		6.74	0.01	<i>BSTl (V1aR)</i>
<i>BSTv (V1aR)</i>	3.27	0.08		5.91	0.02		0.13	>0.50	<i>BSTv (V1aR)</i>
Social Behavior Network									
	0.12	>0.50		5.98	0.02		3.10	0.09	<i>MeA (V1aR)</i>
	0.61	0.44		3.39	0.08		4.72	0.04	<i>AH (V1aR)</i>
	1.38	0.25		0.19	>0.50		<0.01	>0.50	VMH (V1aR)
	n/a			n/a			n/a		PAG* (V1aR)
	n/a			n/a			n/a		POA

Abbreviations are defined in text. Significant *p*-values are in bold and italics. Degrees of freedom were *F*(1, 30) for all OTR comparisons except the Hi, which were *F*(1, 31), and *F*(1, 32) for all V1aR comparisons except the VMH, which were *F*(1, 31).

* PAG expresses V1aR in prairie voles, but data were not available.