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REVIEW

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Prairie voles as a model for adaptive reward remodeling following loss of a bonded partner

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Abstract

Loss of a loved one is a painful event that substantially elevates the risk for physical and mental illness and impaired daily function. Socially monogamous prairie voles are laboratory-amenable rodents that form life-long pair bonds and exhibit distress upon partner separation, mirroring phenotypes seen in humans. These attributes make voles an excellent model for studying the biology of loss. In this review, we highlight parallels between humans and prairie voles, focusing on reward system engagement during pair bonding and loss. As yearning is a unique feature that differentiates loss from other negative mental states, we posit a model in which the homeostatic reward mechanisms that help to maintain bonds are disrupted upon loss, resulting in yearning and other negative impacts. Finally, we synthesize studies in humans and voles that delineate the remodeling of reward systems during loss adaptation. The stalling of these processes likely contributes to prolonged grief disorder, a diagnosis recently added to the Diagnostic and Statistical Manual for Psychiatry.

KEYWORDS
bereavement, loss, pair bond, prairie vole, prolonged grief disorder, reward systems

INTRODUCTION

Pair bonding is an innate, fundamental human experience that positively contributes to our health and well-being. Yet, the benefits of these relationships come with the potential costs associated with losing them. Losing a loved one and the corresponding grief is so emotionally painful and cognitively taxing that it is frequently reported as the most traumatic event of a person's life.[1,2] Accordingly, bereavement imposes a substantial personal burden and societal cost. Grieving individuals are at a substantially increased risk of developing a myriad of physical and mental illnesses, as well as enhanced suicidality.[1,3–9] Bereavement results in impaired daily function and time away from work, the costs of which is estimated at $37 billion annually in 2003.[3] These costs continue to escalate in the face of elevated rates of bereavement due to SARS-CoV-2 and an aging US population.[10,11]

Despite the universality of loss and the widespread negative impacts of bereavement, research on loss is far less developed than that of other mental and emotional states (Box 1). The paucity of information is due to the many challenges related to studying loss. It is difficult to recruit subjects to participate in studies during the sensitive period following the death of a loved one, and retention of these participants can be difficult either due to other post-loss stressors (e.g., financial difficulties) and/or the emotionally triggering nature of the stimuli or interviews.[12] Further, funding support to characterize the trajectories of bereavement is hampered because grief is not a disease but rather a natural reaction to loss and, therefore, does not have a definable cure or endpoint per se. Compounding the difficulties of human studies is the lack of appropriate animal models for understanding the processes underlying partner loss.[13–15] Complex grief-like behaviors have been observed in many wild and captive animals.[16–18] Whales and dolphins will attend to a dead member of the pod—most frequently, a mother to a dead calf.[19] This can involve dragging or carrying a dead corpse or more spontaneous and active behaviors, such as lifting a corpse up to the surface as if to help it breathe, and hauling, spinning, and diving with it. Chimpanzees have also been observed carrying deceased offspring for days to weeks,[20–22]

BOX 1

DEFINING LOSS

Defining loss is challenging. We have multiple meanings for the word, referring to loss both as an event (the loss of a loved one) and the negative behavioral state that follows (e.g., experiencing loss). Neurobehavioral research is far more concerned with loss as a negative emotional behavioral state, while much of public health and medicine focuses on preventing loss (the event) from occurring. In an effort to more explicitly state the goals of addressing loss from a neurobehavioral research perspective, the National Institutes of Mental Health added loss as a construct within the negative valence systems in Research Domain Criteria (RDoC), defining it as a state of deprivation from a motivationally significant conspecific, object, or situation.[24,25]

and elephants exhibit multiple responsive behaviors following loss, included postural changes, guarding/keeping vigil, touching, investigating the carcass, epimeletic behaviors, and vocalizations.[23] However, the most commonly used laboratory animals—flies, worms, mice, and rats—do not form the long-lasting adult social bonds that are a prerequisite for loss.[13–15] Together, these hurdles have resulted in a limited understanding of a fundamental human experience and its underlying neurobiology.

PRAIRIE VOLES AS AN EMERGING MODEL FOR STUDYING LOSS

Socially monogamous prairie voles (*Microtus ochrogaster*) are an emerging animal model for studying the loss of a pair-bonded partner. Whether in the laboratory or in the wild, these small rodents form lifelong pair bonds with their mating partner.[26,27] Pair bonding results in striking sociobehavioral changes, including selective partner-directed affiliative behaviors, aggression toward novel individuals of either sex, and robust and organized biparental care.[13,28–31] Further, compared to other rodents—and even other closely related species of voles—prairie voles form socially exclusive bonds with a partner.[32,33] When a vole has pair bonded, despite the potential for extrapair copulations, they will not form a bond with a second mate.[34,35] Rather, bonded pairs will raise even mixed-parentage litters together and the majority will share the same burrow throughout their adult lifetime.[36,37] Notably, like humans, prairie voles can form more than one sequential pair bond throughout their lifetime.[25,38]

Social monogamy is observed in only 3%–5% of mammals and represents a rare sociosexual phenotype among mammals.[32,33] We have learned much by studying similarly rare or extreme physiologies, including sound localization mechanisms in barn owls, parthenogenesis in lizards, and cardiac hypertrophy in the Burmese python.[39–41] Research spanning nearly five decades has delineated major neural regulators and circuitry underpinning pair bonds in this species.[30,42–45] Notably, much of what we know about human pair bonding has parallels in prairie voles. In both instances, a pair will share a dwelling, and upon reproducing, both parents will care for the offspring.[29] These behavioral traits also share physiological bases; humans, voles, and other taxa-spanning species from fish to apes, engage mesolimbic reward circuitry and nonapeptide systems when forming a pair bond.[46–48]

We can draw on extensive prior research about pair bonding in prairie voles to inform our understanding of loss. Loss is operationalized in prairie voles by physically separating partners.[25,49,50] Partner separation is ethologically relevant as it mirrors what happens in the wild where many voles lose their partners to predation.[27] A primary advantage to using prairie voles to study loss is the powerful and sustained nature of a pair bond which, when disrupted, results in robust and persistent phenotypes that can be measured in the laboratory. Prior studies have detailed how partner separation activates the hypothalamic–pituitary–adrenal axis, increases anxiety-like behaviors, alters stress-responsivity, decreases pain tolerance thresholds, and alters autonomic function.[50–57] Many of these metrics have also been measured after separation from a same-sex peer.[50,52,56,58–60] Prairie voles will show an affiliative preference for a same-sex peer,[49,61] so by comparing peer and partner relationships and the responses to their disruption, we can home in on the unique facets of pair bond loss. Broadly, but not universally, pair bond disruption results in more pronounced loss-induced phenotypes than does separation from a same-sex peer.[50,52,54,62] These studies have been extensively reviewed elsewhere.[63,64]

Prior studies provide essential face and construct validity for using partner separation in prairie voles to study loss. Specifically, separation-induced behavioral and physiological changes mirror those observed in grieving humans,[8,9,63,65–69] and these changes are initiated by a similar disruption of a specific social bond (Figure 1). These phenotypes also reflect the multifaceted nature of loss, which affects systems as diverse as cognition, stress coping, anxiety, pain, sleep, and immune function.[70,71] However, these deleterious effects are not unique to loss. Other forms of trauma, and even chronic stress, can induce many of the same cognitive, behavioral, and physiological changes.[2,72–77] Thus, an important question for the field is whether and how loss is different from other adverse events or negative mental states.

YEARNING AS A CORE FEATURE OF GRIEF

Yearning is a core feature of grief that differentiates loss from other negative emotional states.[2,78–79] Yearning is emotionally painful, encompassing not only rumination on the past but also a frustrated appetitive desire for the lost individual.[78] For instance, a bereaved individual may want their deceased spouse to return home at night, but this desire will ultimately go unfulfilled, resulting in yearning. Yearning is not a feature of other negative mental states or disorders such as depression.

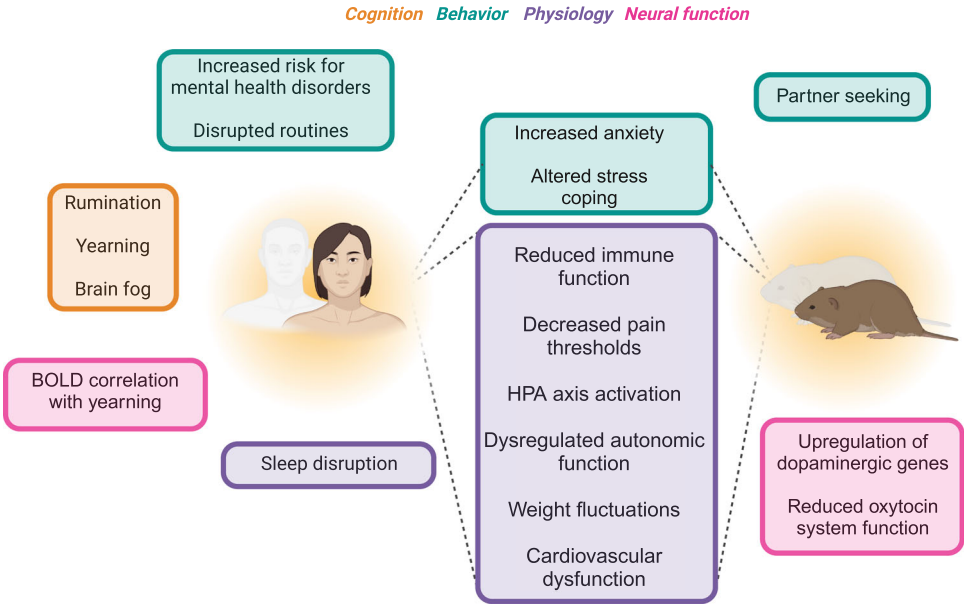

FIGURE 1 Loss-induced phenotypes in humans and voles. Loss is multifaceted, resulting in diverse effects on cognition (orange), behavior (teal), physiology (purple), and neural function (pink). Dotted lines indicate phenotypes that have been studied across both species. Other phenotypes either have not yet been studied or cannot be easily studied in one of the species, such as rumination in voles or neural transcription in humans. Abbreviations: BOLD, blood-oxygenation-level-dependent; HPA, hypothalamic–pituitary–adrenal.

Yearning reflects social motivation and reward processes that help to reinforce and cement bonds over time. Yearning likely engages brain reward systems in order to drive an individual to seek out a partner in much the same way that hunger or thirst results in a drive to seek food or water (putative circuit mechanisms reviewed in Ref. 80). When bonds are intact, the proximity-seeking and drive for connection induced upon partner separation is important for maintaining bonds. When the bond is lost, there is no way to satisfy this motivation for reunion, which leads to intense yearning for that specific individual. Thus, yearning represents an outcome of a natural homeostatic process, differentiating it from craving and withdrawal as observed following substance abuse.[80]

All homeostatic mechanisms engage reward and motivational systems to drive an organism to return to a specific state. In the context of pair bonds, social interaction with a partner is highly rewarding. This is evidenced in prairie voles by their selective preference to huddle and interact with the partner and by forming a conditioned place preference for locations previously paired with a partner.[28,81] Of note, these sources of reward are specific to a particular individual. This is in contrast to laboratory mice and rats, which are innately driven to seek social interactions but do not develop selectively rewarding relationships with a single adult conspecific.[13–15]

ENGAGEMENT OF REWARD SYSTEMS DURING BONDING AND LOSS

The mechanisms underlying the selectively rewarding nature of pair bonds have been examined in humans and in prairie voles. Much of this work has focused on the nucleus accumbens (NAc), a critical hub for regulating reward and aversion processing, motivation, and action selection—all behaviors key for forming and maintaining a pair bond, although other brain regions are also important.[44,82] In voles, oxytocin and dopamine signaling in the NAc are required to form a bond. Specifically, signaling at dopamine D2 class (DRD2) receptors facilitates partner preference, while dopamine D1 class (DRD1) receptor activation impairs partner preference formation.[83–85] Blockade of oxytocin receptors (OXTR) in the NAc similarly impairs pair bonding, OXTR and DRD2 signaling interact to facilitate bonds; blockade of either receptor cannot be overcome by activation of the other.[86–90] This suggests opposing regulation by different classes of dopamine receptors and a concomitant input from the oxytocin system is required when forming a bond.

The coordinated activity of dopamine and oxytocin systems in the NAc during pair bond formation likely triggers long-term changes that help to encode and cement a pair bond. In humans, participants who thought they were holding hands with a romantic partner exhibited enhanced blood-oxygen-level-dependent (BOLD) signal in the NAc relative to when they held hands with someone they did not know.[91] Supporting this shift in accumbal activation by a bonded partner, long-term, bond-induced changes have been examined at multiple biological levels in prairie voles. Mature pair bonds are characterized by persistent and consistent shifts in NAc gene expression.[49,92] Partner-associated alterations in neuromodulation and neural activity in the NAc have also been observed following bonding. These include the identification of enhanced partner-associated dopamine release and larger partner-associated neuronal ensembles, the size of which correlate with the strength of partner preference for an individual vole.[93,94]

Long-term bond-induced changes within the brain's reward circuitry contribute to implicit and explicit expectations that a pair-bonded partner will be there to provide a reliable and enduring source of reward and support. In humans, attachment theory refers to this as a secure base from which to explore the world.[95-99] As a result, being away from a partner for long enough engages motivational systems that drive proximity-seeking and reunion.[99] In voles, such proximity-seeking can be measured using tasks in which a vole exerts effort to gain transient access to their pair-bonded partner by lever pressing or climbing a barrier.[94,100-102]

Recent studies examining the neuromodulatory basis of active partner-seeking suggest an important role for dopamine in the NAc. Once a bond is formed, dopamine signaling is no longer required for the display of partner-directed huddling and interaction.[84,94] Instead, dopamine signaling in bonded voles plays an important role in stranger-directed aggression and in active partner-seeking. Blockade of DRD1 impairs both selective aggression and partner-seeking behaviors.[85,94] In addition, seeking and interacting with a pair-bonded partner results in greater NAc dopamine release than the same behaviors directed toward a stranger vole. In concert with enhanced DRD1 expression post-bonding, these data suggest that dopamine signaling at DRD1 drives partner-seeking.[85,94] These findings align well with other work on the role of dopamine in maintaining homeostasis: dopamine is particularly important for behavioral activation and reward-seeking but is dispensable for reward consumption (e.g., partner interaction).[103]

Working from a framework in which bonding informs our understanding of loss, we can synthesize the above experimental findings to gain insight into the biology underlying yearning. Specifically, being separated from a highly rewarding partner activates motivational systems that drive partner-seeking. These systems rely on dopamine signaling, and in the context of loss, this motivation cannot be satisfied. This frustrative nonreward may sensitize key neuromodulatory systems within days of loss. Separation from a pair-bonded partner results in upregulation of dopamine-associated genes and downregulation of *Oxtr* in the NAc.[49,52] There is also upregulation of dopamine receptor genes (*Drd1* and *Drd2*) in cortical regions (anterior cingulate cortex and insular cortex) after the loss of a high-quality partner and reduced oxytocin mRNA in the hypothalamus.[52,62]

Yearning occurs when partner-seeking does not result in a reunion. In other contexts, when access to an expected reward fails to occur, it results in an error signal within the brain.[104] A similar error signal may underlie yearning, transitioning a healthy mechanism that maintains bonds through partner-seeking to one that contributes to the emotional distress and burden of loss. Although the nature of this potential error signal has not yet been elucidated in the context of pair bond loss, work on maternal–offspring interactions has delineated dopaminergic error signals that shape maternal care of offspring.[105] A similar error signal has also been observed in a social operant task in mice.[106] Thus, it is intriguing to imagine that a similarly conserved system may function in adult attachment relationships. Prairie voles provide an ideal animal model for further exploring this hypothesis.

PROLONGED GRIEF DISORDER AND STALLED LOSS ADAPTATION

Yearning and other painful features of grief resolve as the individual integrates the loss, with most people indicating significant improvement in daily function within around 6 months of the loss.[107] However, for a subset of ~7%–10% of bereaved people, stalling of normal adaptive processes leads to prolonged grief disorder (PGD)—an understudied mental health disorder recently added to the DSM5[108,109] (Figure 2A). The World Health Organization approved a new diagnosis of PGD for inclusion in its International Classification of Disease in 2018[110,111] (Figure 2B).

PGD is defined as a persistent and pervasive grief response characterized by longing for and preoccupation with the deceased. Symptoms may include identity confusion, intense emotional pain, and difficulty engaging in ongoing life, among others. There is often a conflation of grief/PGD and depression, but the core symptoms of grief and PGD—especially those focused on yearning for the lost person—are not present in mood or anxiety disorders.[78,79,114] Further, while advances in cognitive behavioral therapies tailored for PGD have shown promise, traditional pharmacological treatments for depression and other psychiatric disorders do not ameliorate the core symptoms or augment the effects of PGD therapy.[115] Together, these lines of evidence indicate that PGD has distinct biological underpinnings and will require novel treatment options.

The biological mechanisms contributing to manifestations of loss, including the pathological symptoms of PGD, remain unknown. The extended symptoms of PGD, which can last for months to years, mirror the symptoms that are prominent during acute phases of grief, and the predominant model suggests that PGD results from stalled adaptive processes.[113,116-118] Thus, one extremely promising avenue for new treatment options is to identify the molecular and neural processes that facilitate healthy loss adaptation, with the ultimate goal of stimulating these processes in patients with PGD.

What neural changes underpin successful loss adaptation? In a human neuroimaging study of women who had lost a mother or sister to breast cancer within the previous 5 years, PGD is associated with an enhanced signal in the NAc when viewing images of the lost loved one, while normal resolution of grief corresponds with a decrease in NAc activity elicited by reminders of the loss (Figure 2C). A similar study has not yet been performed following partner bereavement. In the same study, self-reported levels of yearning also correlated with NAc BOLD levels[112] (Figure 2D). A recent review also highlights the involvement of reward regions in grief and PGD, including a study that found that cortico–basal–ganglia interactions measured via functional magnetic resonance imaging (fMRI) have further been suggested to mediate avoidant grieving, a grief style aimed at preventing thoughts of loss, which is associated with poorer grieving outcomes.[24,119] While far from exhaustive, these preliminary studies suggest that changes in NAc activity, mediated by underlying changes in gene expression and/or neuromodulation, may contribute to the successful processing of loss. Prairie voles provide a unique opportunity to further

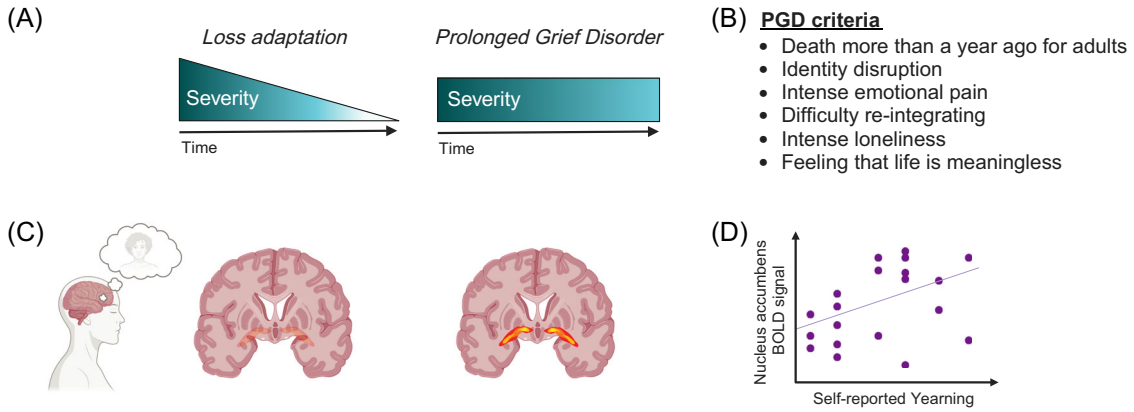

FIGURE 2 Stalling of adaptive processes in prolonged grief disorder. (A) For most people, the intensity of grief subsides within approximately 6 months, but this does not occur in PGD. (B) Diagnostic Statistical Manual criteria for diagnosing PGD. (C) Individuals who have adapted to their loss—as indicated by less severe loss phenotypes—have reduced fMRI BOLD signal in the nucleus accumbens (NAc) when viewing pictures of their deceased loved one. In contrast, individuals with PGD exhibit greater NAc BOLD signal upon reminders of their lost loved one. (D) BOLD signal in the NAc correlated with self-reported yearning levels (adapted from Ref. 112). Abbreviations: BOLD, blood-oxygenation-level-dependent; PGD, prolonged grief disorder.

examine the neuromolecular mechanisms that contribute to healthy loss adaptation and potentially identify systems contributing to PGD.

MODELING LOSS ADAPTATION IN VOLES

Studying loss and adaptation is inherently challenging, but one major approach to delineating loss adaptation in voles has been to focus on characterizing the lost bond. Prairie vole pair bonds are exclusive; when an animal is bonded, they cannot form a bond with a second mate.[34] Thus, the ability to form a new pair bond provides insight into the transition in the behavioral state between bonded and not bonded as a key feature of loss adaptation. However, it remains unclear how changes in bond state relate to the other negative aspects of loss, including heightened stress and anxiety systems, and so on.

Prior work indicates that up to 4 weeks of partner separation is required before a male vole can form a pair bond with a new partner.[25] Male voles were cohoused with a female for 2 weeks (partner 1) and then separated for either 48 hours, 2 weeks, or 4 weeks before the males were re-paired for another 2 weeks (partner 2).[25] After re-pairing, only males that had been separated for 4 weeks showed a consistent preference for the second partner. Males in this group also chose the second partner over the first, indicating that the second bond successfully supplanted the first bond. This time course also matches what is known to occur in the wild; male voles will remain at their pair-bond burrow for an average of 17 days after partner loss.[36] These results are critical as they indicate that, as in humans, loss adaptation in voles takes time, and they provide a time course for examining the associated neural changes that likely contribute to adaptation.

A number of studies have now examined the social behavioral changes that occur multiple weeks after partner separation, when male voles are capable of forming a new pair bond. Results of partner preference maintenance are mixed and potentially depend on experimental variables such as length of pairing, reproductive status, age, and potential reminders of the absent vole. Males and females who were paired for 2 or more weeks prior to separation retained their partner preference for at least 4 weeks of separation.[49,120] For shorter pairing periods, pair bonds were not always retained.[54,121] In tests that enable short, repeated rounds of partner or novel interaction after 4 weeks of separation, female voles with long-term bonds exhibited dramatically reduced partner-directed huddling. They also showed increased direct investigation of both stimulus voles, but with more investigation of their partner.[94] Together, these behavioral changes are consistent with partial behavioral erosion of the pair bond without forgetting the partner. This parallels the human condition and further supports the use of this model to understand loss adaptation.

The partial erosion of bond-related behaviors and the ability to form a new bond after 4 weeks of partner separation is accompanied by erosion of bond-induced transcriptional and neuromodulatory phenotypes (Figure 3). Bonded voles exhibit enhanced partner-associated dopamine release, but this enhancement erodes following 4 weeks of separation.[94] As a result, following prolonged separation, dopamine release no longer distinguishes the partner and novel voles, consistent with the devaluation of the previous partner.[94] These shifts in dopamine dynamics may also contribute to changes in NAc transcriptional signatures. Bonding results in persistent shifts in NAc gene expression, and this transcriptional signature erodes after 4 weeks of separation, potentially reflecting the shift in bond status.[49] Bonding also results in changes in oxytocin systems that revert upon long-term separation.[54,120] In both male and female voles, partner separation increases the number of oxytocin immunoreactive cells in the periventricular nucleus to the level of sexually naïve same-sex sibling pairs.[120] This remodeling of social reward systems may ultimately be key indicators of loss adaptation.

The model that has emerged from the above studies, along with work in humans, suggests that reward remodeling underlies

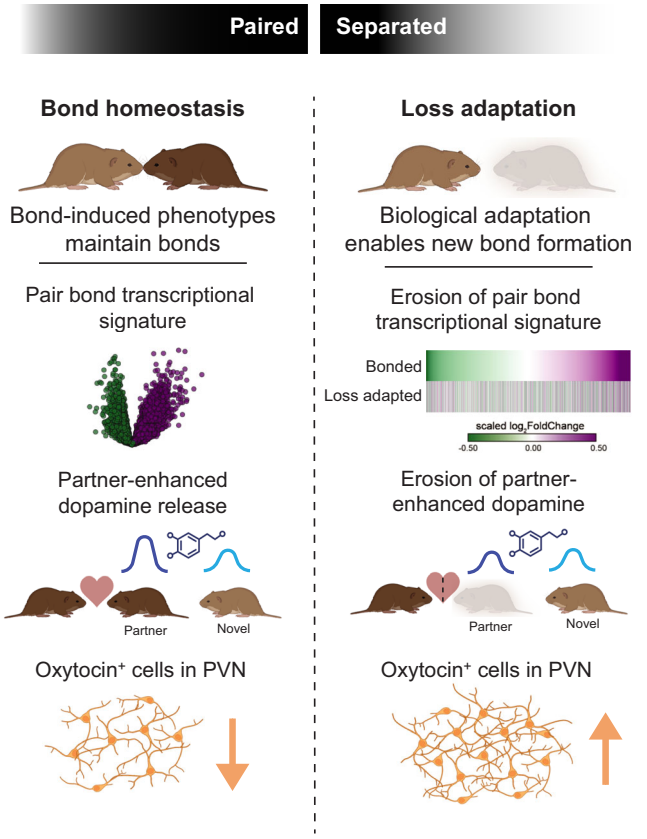

FIGURE 3 Proposed model for social reward mechanisms that maintain bonds and their remodeling during loss adaptation. Pair bonding results in changes in gene expression, dopamine release, and oxytocin immunoreactivity, all of which likely contribute to the homeostatic mechanisms that help to maintain bonds. Loss adaptation is accompanied by erosion of these bond-induced transcriptional and neuromodulatory phenotypes.

successful loss adaptation. In short, pair bonding induces a myriad of changes within limbic and social reward circuitry, and these are eroded as a function of prolonged partner separation. Erosion of gene expression profiles, neuromodulatory signals, hormone production, and behavior contributes to a behavioral state that is permissive for new bond formation. Conceptually, this may uncouple partner-associated reward in a way that mirrors the human experience of memories transitioning from painful to bittersweet. This is highly adaptive, as it balances the need to maintain bonds over time while maximizing reproductive opportunities. It reduces the likelihood of mate rejection only after the vole has either reared an existing litter or is beyond the time when they would give birth (e.g., 3 weeks gestation).

The above framework also suggests a path forward for using prairie voles to gain insight into PGD. As PGD is conceptualized as a stalling of normal adaptive processes, manipulations that impair reward remodeling are a reasonable model for studying aspects of PGD. This could be achieved via manipulation of transcription—for instance, to stall the erosion of the pair bond transcriptional signature—or manipulations of neural activity designed with the same goal in mind. Alternatively, we may be able to harness individual variability of loss in voles by studying the individuals who exhibit behavioral extremes as a model for delayed or stalled loss adaptation. This latter approach has the advantage of studying natural differences that contribute to normal and slowed adaptative processes rather than imposing an *a priori* framework for how stalled reward remodeling contributes to adaptation.

THE EMERGING FIELD OF PRECLINICAL GRIEF RESEARCH

While the unusual biology of prairie voles, married with their experimental tractability, makes them an excellent emerging animal model for studying loss, other pair-bonding animal models are also starting to be examined.[122] Monogamous species such as titi monkeys (*Plecturocebus cupreus*) and California mice (*Peromyscus californicus*) are also providing insights into how the brain is restructured during pair bonding and following loss. Pair bonding in titi monkeys is associated with higher glucose uptake across the brain, yet this uptake is gradually lessened the longer the pairs are separated, suggesting an erosion of the pair-bonded state.[123] However, in contrast to prairie voles, long-term separation in titi monkeys results in a reversal of the heightened cortisol levels seen after acute separation and increased plasma oxytocin concentration.[124] In California mice, males separated from their partner for 20 days show anxiety-like behaviors in the forced swim test, mirroring what is seen in prairie voles.[125] A phenotype that California mice are uniquely suited for investigating (i.e., rapid wound healing) is impaired after partner separation, revealing a distinctive response that mirrors reduced immune function in humans following loss.[126,127] Developing parallel models is important, as it provides an opportunity to identify universal features of loss and increases the likelihood that potential therapeutic opportunities will translate to humans.

There is an ongoing need for dialogue between preclinical researchers who study loss in humans and animal researchers. Research in humans has demonstrated a level of nuance that we have not yet achieved in animals. Each loss is different, and the context of the loss—whether expected or unexpected, occurring at different life stages, and the intersectional identity of the bereaved—can all influence the loss experience and may contribute to the likelihood of developing PGD. These facets of loss remain underexplored in animals, where there are opportunities to better understand how these differences manifest at a mechanistic level. In addition, animal research can be used to help refine human research. For instance, extensive work on oxytocin and bonding has inspired recent studies examining the role of intranasal oxytocin on approach/avoidance behaviors in grieving individuals.[128] In addition, there are as yet untapped opportunities to examine how social support or even the formation of a new pair bond contributes to loss adaptation.

Finally, while we have focused here on reward systems and re-bonding as a metric of loss adaptation, there is a need for deeper characterization across broad modalities. What learning-related and/or extinction mechanisms contribute to loss? Do reward systems act in a hierarchical fashion to modulate stress and other effects of loss? Is there a feasible way to model conscious or unconscious rumination

following loss? Thus, there is substantial room for growth in preclinical loss research, and prairie voles are optimally positioned to lead the charge.

AUTHOR CONTRIBUTIONS

J.M.S. and Z.R.D. equally contributed to the conceptualization, writing, and editing of the manuscript.

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COMPETING INTERESTS

The authors declare no competing financial interests.

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