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Authors

Berendzen, Kristen M

Bales, Karen L

Manoli, Devanand S

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Attachment across the lifespan: examining the intersection of pair bonding neurobiology and healthy aging

Kristen M. Berendzen[a,b,c,d,*], **Karen L. Bales**[f,g], **Devanand S. Manoli**[a,b,c,d,e]

[a]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco; San Francisco, CA 95158, USA

[b]Center for Integrative Neuroscience, University of California, San Francisco; San Francisco, CA 95158, USA

[c]Weill Institute for Neurosciences, University of California, San Francisco; San Francisco, CA 95158, USA

[d]Kavli Institute for Fundamental Neuroscience, University of California, San Francisco; San Francisco, CA 95158, USA

[e]Neurosciences Graduate Program, University of California, San Francisco; San Francisco, CA 95158, USA

[f]Department of Psychology, University of California, Davis; Davis, CA 95616, USA

[g]Department of Neurobiology, Physiology, and Behavior, University of California, Davis; Davis, CA 95616, USA

Abstract

Increasing evidence suggests that intact social bonds are protective against age-related morbidity, while bond disruption and social isolation increase the risk for multiple age-related diseases. Social attachments, the enduring, selective bonds formed between individuals, are thus essential to human health. Socially monogamous species like the prairie vole (*M. ochrogaster*) form long-term pair bonds, allowing us to investigate the mechanisms underlying attachment and the poorly understood connection between social bonds and health. In this review, we explore several potential areas of focus emerging from data in humans and other species associating attachment and healthy aging, and evidence from prairie voles that may clarify this link. We examine gaps in our understanding of social cognition and pair bond behavior. Finally, we discuss physiologic pathways related to pair bonding that promote resilience to the processes of aging and age-related disease. Advances in the development of molecular genetic tools in monogamous species will allow us to bridge the mechanistic gaps presented and identify conserved research and therapeutic targets relevant to human health and aging.

Keywords

Pair bonding; aging; prairie voles; social attachment

[*]Corresponding author. Kristen.berendzen@ucsf.edu, University of California, San Francisco, Department of Psychiatry and Behavioral Sciences, Nancy Friend Pritzker Psychiatry Bldg., 675 18th St, Box 3130, San Francisco, CA 94107.

1. Introduction

The nature and patterns of social relationships evolve over the life course, with social attachments defining not only the early relationships between parents and offspring, but those developing later in life between mating partners and friends. The study of human bonding and relationships is often conducted from a developmental perspective, with early life attachments thought to impact those formed in adolescence and adulthood. Our conceptualization of the nature of attachment arose from early work by John Bowlby and Mary Ainsworth examining mothers and infants (Bowlby 1969; Ainsworth 1979). Despite a primary focus on the influence of early life relationships, Bowlby asserted that attachment representations were likely to exert influence 'from the cradle to the grave' (Bowlby 1979). Yet, relatively little attention has been paid to the importance of attachment in later life in comparison with other developmental stages (Michael Bradley and Cafferty 2001). As the population ages, the interest in extending lifespan, and in particular healthspan (years of healthy life), has increased. Studies motivated by this interest are uncovering an intriguing association between the maintenance of social bonds and health outcomes (Robles 2014; Holt-Lunstad, Smith, and Layton 2010; Rutter et al. 1999; Berkman and Syme 1979). The mechanisms underlying this connection remain elusive, thus there is great potential for the development of animal models that can address these questions.

Social attachment is defined by the selective, enduring bonds formed between members of a species; this definition includes bonds between offspring and a parent or caregiver, those between unrelated partners or peers in adolescence and adulthood, as well as mating partners that are typically unrelated (Ainsworth 1979; Bowlby and Bowlby 1982; Harlow and Harlow 1965). Early life attachments, particularly between caregivers and offspring have been studied extensively for their impact on psychological development as well as broader health outcomes and are thought to continue to impact patterns of attachment behavior into late age (Bales et al. 2021; Hazan and Shaver 1987; Ainsworth 1979; Bowlby and Bowlby 1982). While less is known about the role of same-sex affiliative bonds in late life, the strength and endurance of these bonds likely influences healthy aging in both similar and distinct ways compared to mating or romantic attachments (Holt-Lunstad, Smith, and Layton 2010). Attachments between mates are typically organized around the formation and maintenance of pair bonds (Hazan and Shaver 1987). Adult pair bonds are characterized by long-term, preferential mating between two individuals (partners) and the active rejection of novel potential mates. These bonds are also associated with physiological distress upon separation from the partner, and reduced anxiety with reunion (Brewster 1950; McNeal et al. 2014; Hazan and Shaver 1987). A wealth of data supports the health impacts of enduring pair bonds in adulthood in humans and other species (Kiecolt-Glaser and Wilson 2017; Verstaen et al. 2020; Grewen et al. 2003). Thus, pair bonds represent rich substrates by which to begin to dissect the mechanisms that mediate resiliency or vulnerability to age-related processes, and we focus our discussion primarily on these types of attachments.

Commonly used genetic animal models do not form adult pair bonds, limiting efforts to understand the underlying neurobiology of pair bonding and their relationship to healthy aging. Socially monogamous species allow us to investigate the genetic and

neurophysiological mechanisms mediating long-term attachments throughout the lifespan (Kleiman 1977; Lukas and Clutton-Brock 2013). Across such species, social attachments are defined by the patterns of behavior described above, which include parental behavior, peer affiliation, and mate (or pair) bonding (Bales et al. 2017; Reichard and Boesch 2003; Turner et al. 2010; Lee and Beery 2022; Ribble and Salvioni 1990). Numerous studies of pair bonding originate from mammalian and non-mammalian species, in particular bird species as ~90% of avian species form socially monogamous mated pairs (Jeffrey M. Black 1996; Reichard and Boesch 2003). In birds, reproductive success is associated with both age and long-term pair bonding, and several studies identify a relationship between mortality and aspects of mating strategy, including bond maintenance, in select species_(Holmes and Austad 1995; Macdonald 1977; Richdale and Warham 1973; R. Sun et al. 2022; J. M. Black 2001). The impacts of pair bonds on subsequent fitness and life expectancy may thus be conserved across diverse lineages. Of the 3-9% of mammals that form such sustained, selective affiliations (Lukas and Clutton-Brock 2013; Kleiman 1977; Kleiman and Malcolm 1981) prairie voles (*Microtus ochrogaster*) are widely studied in the field and in the lab to understand the mechanisms of pair bonding (Getz, Carter, and Gavish 1981a; C S Carter, DeVries, and Getz 1995; Insel and Young 2001; Young et al. 2011). Given their relatively short lifespan, more physiological similarity to humans and other mammals, and amenability to laboratory study, they provide a particularly useful model for exploring the links between pair bonding and aging (Williams, Catania, and Carter 1992; Carp et al. 2016; Hiura and Donaldson 2022; Walum and Young 2018; Getz et al. 1997).

In this review, we will focus primarily on adult pair bond behavior and its impact on healthy aging, although there are clearly mechanistic overlaps with other aspects of social aging. In humans and other socially monogamous species, the formation of long-term pair bonds is intimately related to other patterns of social behavior and experience that may differentially impact aging, including social integration, social status, or early life stress (Fletcher et al. 2015; Schacht and Kramer 2019; Pedersen 2006; Razzoli et al. 2018; for review see Snyder-Mackler et al. 2020). A wealth of data from wild populations of non-human primates have examined the links between social health and longevity and consistently find that greater social integration and strong social bonds are associated with increased fitness and longevity (Alberts 2019; Archie et al. 2014; Chiou et al. 2020; Silk et al. 2010).

Below, we begin by summarizing the existing research on pair bonding and aging biology in prairie voles. Importantly, while there has been much focus on the effects of social structure and environment on age-related health, the aging process itself may also lead to changes in social behavior. Thus, we first address potential age-dependent changes to neuroendocrine signaling and cognitive function implicated in pair bonding in mammalian species, primarily motivated by human research and supported by complementary data in prairie voles (Figure 1A). We then turn to the impacts of bonding behavior on age-related health, examining both the mechanisms underlying vulnerability with bond disruption and the beneficial effects of sustained pair bonds (Figure 1B). We propose that overlap in the cognitive processes and the physiological and molecular systems described present high yield entry points for understanding the neurobiology of attachment in late age (Figure 1). The mechanistic study of aging biology and pair bonding is an emerging field, thus the observations and hypotheses outlined here draw on data from humans, prairie voles, and other mammalian species in

order to provide an initial framework for understanding the complex interaction between bonding behavior and aging.

While outside of the scope of this review, the potential co-evolution of lifespan with social structures or the impacts of reproductive strategy on lifespan determination are intriguing and important aspects of aging and attachment. More comprehensive lifespan, molecular, and neural information in socially monogamous and closely related promiscuous species may allow for novel approaches to examine classic genetic and trade-off models of aging (Kirkwood 2005). Our discussion centers on identifying the potential proximate mechanisms that may link pair bonding to resilience and healthy aging and explain the age-related risk of bond disruption. This focus stems from a rich history examining the mechanisms underlying pair bonding in species like prairie voles, which may intersect with factors that impact known aging hallmarks (López-Otín et al. 2013; 2023) (Figure 1C). These hallmarks represent the cellular and systemic processes indicative of age-related changes and include genomic instability, epigenetic alterations, disrupted intercellular signaling, as well as inflammation and altered immune function, all of which have been implicated in social aging more broadly (Snyder-Mackler et al. 2016; 2019; Stevenson et al. 2019). Below, we present a cognitive and neurobiological perspective to explore the intersection of intra-individual pair bonding and aging biology while identifying directions for future study.

1.2 Prairie voles and pair bonding with age

Studies of prairie voles have been foundational for our understanding of the biology of attachment. In the wild, prairie voles live in burrows generally consisting of extended family units, and the same male-female pairs are consistently trapped together in the field (Getz, Carter, and Gavish 1981b). Comparisons of social behavior and neural substrates in prairie voles to those of closely related promiscuous species have provided a basis for understanding the neurobiology of social monogamy. Unlike promiscuous species, prairie voles display long-term social attachments between mates such that mating partners show an enduring pair bond characterized by preference for spending time in close contact with a partner (Insel and Young 2001; Young et al. 2011; Carp et al. 2016; Walum and Young 2018; Williams, Catania, and Carter 1992; Beery 2021). The formation of affiliative bonds with a partner is also accompanied by aggressive rejection of novel potential mates (C S Carter and Getz 1993; Resendez et al. 2016; Resendez and Aragona 2013). Both sexes display bonding behaviors and prairie voles show biparental care of offspring, a hallmark of many monogamous species (C S Carter and Getz 1993; A Courtney DeVries, Johnson, and Carter 1997; Ahern, Hammock, and Young 2011). Furthermore, separation of bonded mates results in increased anxiety- and depression-like behaviors and stress-related physiological changes, suggesting neural and physiologic mechanisms that facilitate the maintenance of such attachments between individuals (Grippo et al. 2011a; Grippo, Cushing, and Carter 2007; Martin II et al. 2006; Resendez et al. 2016; Resendez and Aragona 2013; Sadino et al. 2023).

Recent work more directly examines the relationship between aging and pair bond behavior in prairie voles. Kenkel et al. examined the propensity for bonded males to form new bonds with unknown females following the dissolution of their established bonds. While

aged (1.4-2.8 years old) males go on to form new pair bonds, showing preference for a new partner after dissolution of a prior bond, they spend less time in social contact with unfamiliar females (Kenkel et al. 2019b). Repairing may be sex-specific as earlier studies showed that females do not re-pair after loss of a mate, while the effect of age on repairing is unknown (Thomas and Wolff 2004). The trend towards age-associated decreased social behavior outside of the pair bond is consistent with studies from other species. For example, humans tend to show higher levels of social selectivity in older age, and older individuals of diverse species including primates and rodents interact with fewer social partners and spend less time in affiliative behavior (Rosati et al. 2020; Almeling et al. 2016; Shoji et al. 2016; Boyer et al. 2019; Salchner, Lubec, and Singewald 2004).

Importantly, a recent study in prairie voles examining neophobia found increased avoidance of a novel object by young adults compared with one year old animals, but no effect of age on social approach towards familiar animals (Powell et al. 2022). The authors conclude that with age, prairie voles are less able to adjust behavior to social context, as aged animals exhibited aggression towards intruders even in the absence of pair bond formation (Powell et al. 2022). In compliment to examination of the impacts of age on social behavior, additional work has examined the ability of pair bonding to buffer the effects of social stress with age (Akinbo et al. 2022). The authors found that pair bonding is protective to the behavioral and neuroendocrine effects of acute restraint stress in aged animals when compared to those that had been socially isolated (Akinbo et al. 2022).

The studies above have largely examined long-standing breeder pairs within established laboratory colonies. A more extensive representation of late-age prairie voles and formal lifespan analysis is therefore required for comprehensive, systematic assessment of bonding with age. With validated and conserved markers of the aging process as well as the application of Clustered regularly interspaced short palindromic repeats (CRISPR) and other molecular genetic approaches, the use of a broader range of species, including voles (Horie et al. 2019; Berendzen et al. 2023; Rajamani and Harony-Nicolas 2023), is now feasible and likely to yield relevant insights into the impacts of social aging on health. Initial targets for mechanistic study are the neuromodulatory systems and the cognitive processes highly implicated in attachment behavior, which may be differentially regulated with age. As much of the work related to these systems has been done in humans and other species, we present these studies as well as motivation for future approaches in prairie voles.

2. Neuroendocrine mechanisms integrating bonding behavior and aging

A major motivation for utilizing the prairie vole model for aging research is to explore neuroendocrine mechanisms that link social bonds to aging. Changes to intercellular signaling, including neuroendocrine systems, are hallmarks of age-related change and may play an important role in mediating the changes to social behavior with age (López-Otín et al. 2013; 2023). Examination of the neuroendocrine mechanisms for social behavior, in particular pair bonding, has focused primarily on oxytocin (OXT) and arginine vasopressin (AVP) (C S Carter 2017; Loth and Donaldson 2021; Lieberwirth and Wang 2016; Bosch and Young 2017; Walum and Young 2018; Rigney et al. 2022), often with a heavy emphasis on OXT. OXT and AVP are both nine-amino acid peptides synthesized primarily, but not

exclusively, in two nuclei of the hypothalamus, the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) (P. Wang et al. 2022; Zingg 2002; Althammer and Grinevich 2017). Studies in voles identified OXT and AVP as critical mediators of pair bonding: interspecies variation in the patterns of expression of the oxytocin receptor (OXTR) and vasopressin 1a (V1aR) receptors correlates with the potential for pair-bonding between closely related vole species (C S Carter, DeVries, and Getz 1995; Winslow, Shapiro, et al. 1993; Miranda M Lim and Young 2006). Consistently, pharmacologic inhibition of OXT and AVP signaling via their respective cognate receptors disrupts pair bonding, while exogenous administration of these hormones promotes pair bond formation without mating (Z. Wang et al. 1998; Winslow, Shapiro, et al. 1993; Winslow, Hastings, et al. 1993; Insel et al. 1998; C Sue Carter et al. 2008; M M Lim, Hammock, and Young 2004; Y. Liu, Curtis, and Wang 2001; Cho et al. 1999; Insel et al. 1995; 1998; Winslow, Shapiro, et al. 1993; Winslow, Hastings, et al. 1993; C Sue Carter et al. 2008). Rigorous mechanistic studies of neuronal and circuit function often necessitate animal models. However, the expense of maintaining laboratory animals until aging timepoints has contributed to relatively few studies of OXT and AVP in aged animals or in the context of aging. The effects of aging on OXT and AVP systems have been studied primarily in humans and rats, and we therefore initially focus on studies from these species in this section (Stewart and Finger 2021; Wierda et al. 1991; Arsenijevic et al. 1995).

In humans, OXT and AVP cell numbers in the PVN are relatively stable throughout aging (Wierda et al. 1991; Stewart and Finger 2021). However, the sex difference in AVP cells in SON, initially greater in males than in females, is lost with age; as postmenopausal women actually show an increase in AVP cells in the SON (Ishunina et al. 1999). Further examination of such sex- and age-dependent changes in OXT and AVP have largely been limited to measuring peripheral levels of these peptides due to the limited capability for invasive research in human studies of aging. Peripheral levels reveal valuable information despite imperfectly reflecting central activity (Tabak et al. 2023). Does aging have an effect on peripheral OXT and AVP levels in humans? One study examining effects of age on plasma levels of these peptides found that young women have the highest plasma levels of OXT, and older men the lowest, with no significant effect of age (Plasencia et al. 2019). In contrast, plasma AVP rises with age in both sexes, which do not differ from each other (Plasencia et al. 2019). Age-related increase in AVP were also found in urine samples from older adults at risk of dehydration (Reyes et al. 2014). These patterns contrast somewhat with the hypothalamic patterns described above in the lack of a sex difference in young people, but are consistent in finding a rise in AVP in older women (Ishunina et al. 1999).

In parallel, work has also sought to determine if plasma OXT and AVP are associated with social and non-social cognition and affective processes in aging populations. Higher AVP levels have been linked to higher attachment anxiety, assessed by standardized scales measuring the experience in close relationships (Plasencia et al. 2019). Plasma OXT in humans of 65-90 years of age was positively associated with experience of adverse events, but diminished stress, in securely attached participants (Emeny et al. 2015). In healthy older men (55-95 years of age), higher plasma OXT was associated with lower ability to identify emotion, with this relationship mediated by non-social cognitive abilities, while plasma AVP was not related to emotion identification (Polk et al. 2022). Both plasma OXT and AVP

were negatively correlated with “crystallized cognition”, i.e. semantic knowledge from past experiences (Polk et al. 2022). In contrast, in older Japanese women (on average, 76.2 ± 6.91 years), serum OXT was positively correlated with performance on a logical memory task. Seven years later, the serum OXT from the first timepoint was still positively correlated with logical memory at the second timepoint, although the overall levels of OXT were significantly lower (Kunitake et al. 2023).

While interesting and suggestive, the above studies do not inform causal mechanisms relating OXT, aging, and cognition. Such a causal role has been interrogated through intranasal administration of OXT in human subjects. Many of these trials contain a younger adult comparison group, as well as placebo controls for OXT (P. Liu et al. 2022; Lin et al. 2022; Frazier et al. 2021). These studies often examine the areas of the brain regarded as the “salience network”, a functional connectivity network described primarily in humans and other primates, consisting of nodes in the anterior insula, anterior cingulate cortex, striatum, hypothalamus, PAG, and amygdala (Seeley et al. 2007). Intrinsic functional connectivity is a measure of BOLD signal that is taken when an individual is in a resting-state, and which reflects a functional relationship between brain regions (Greicius et al. 2003). This network of brain regions coactivates in response to social contexts and stimuli, among other experimental tasks and conditions (Seeley et al. 2007). The subocortical regions above heavily overlap with brain areas implicated in the social behavior network, a collection of brain regions identified across diverse species that is tied to various social decision-making and behavioral outputs (Tremblay, Sharika, and Platt 2017; Prounis and Ophir 2020; Newman 1999). All areas comprising the salience and social behavior network are expected to be affected by OXT and/or AVP (P. Liu et al. 2022; Frazier et al. 2021). Intranasal OXT reduced connectivity between the ventral salience network and the left amygdala, but only in older adults (71.12 ± 5.25 years) (P. Liu et al. 2022). However, OXT did not affect amygdala activity, or ratings of face trustworthiness, in older adults (Lin et al. 2022). In response to a breach of trust, OXT treatment modulated activity in the left superior temporal gyrus (Frazier et al. 2021).

Consistent with an important influence of age or context in mediating the effects of OXT, older men in an OXT treatment group showed improved emotion recognition (Campbell et al. 2014). It is notable that OXT also improved the ability of older men in a theory of mind task (testing the ability to perceive others’ mental states and intentions), when given minimal information, but not in women and not in men when given additional context (Grainger et al. 2018). These results suggest that OXT may be most effective in sensitized situations. Thus, the effects of OXT treatment on the social salience network and related psychological constructs such as trust, remain unclear in relationship to age and require further study.

While little is known about OXT and AVP during aging, even less is known about the effects of aging on OXTR and V1aR in humans and other species, although both are widespread throughout the mammalian brain (Loup et al. 1991). Aged male Sprague-Dawley rats show lower OXTR binding in the head of the caudate-putamen, the olfactory tubercle, and the ventromedial nucleus of the hypothalamus (Arsenijevic et al. 1995). A recent study in prairie voles also examined regional differences in OXTR signaling with age and showed age-related increases in ligand binding in the caudate-putamen in aging males, in contrast to

the findings in rats (Kenkel et al. 2019a). Such species differences in age-dependent receptor expression may provide insight into mechanisms underlying changes in attachment-specific behavior with age.

The relationship between aging and OXTR and V1aR expression and function thus represents an important gap in the literature. One predominant theory suggests that social bonds promote healthy aging through buffering of the physiological response to social stressors, like isolation (Holt-Lunstad, Smith, and Layton 2010). Given both its role in social bonding, as well as its function in suppressing hypothalamic-pituitary-adrenal (HPA) axis activity (Peen, Duque-Wilckens, and Trainor 2021), OXT may play a critical role in the mechanism linking social bonds to healthy aging. Complementary genetic, molecular, and pharmacological manipulations in prairie voles that impact neuromodulator systems throughout pre- and post-natal development and into adulthood will provide essential mechanistic insight into the human data presented that suggests an ongoing and evolving role for neuroendocrine systems with age.

3. Cognitive processes underlying bonding are impacted by aging

The oxytocinergic and vasopressinergic systems described here act across diverse neural circuits to regulate various cognitive and affective processes important of social behavior. The studies in prairie voles described above suggest that aging affects aspects of social behavior and thus may impact underlying cognitive processes important for the demonstration of pair bonding. The cognitive systems that support pair bonding may show particular vulnerability to the process of aging, thus providing a sensitive read-out of age-related change. However, there are currently substantial gaps in our understanding of how the cognitive systems supporting pair bonding evolve with age in voles. We aim to highlight potential avenues towards filling these gaps and the relevance of specific cognitive systems to age-related social behavior. While multiple sensory, affective, and cognitive processes are thought to be required for pair bonding, we focus the discussion on those related to memory, reward, and valence processing as the underlying circuitry has been implicated in both healthy and pathological age across species (Walum and Young 2018; Samson and Barnes 2013)

3.1 Memory systems supporting pair bonding

Memory function and the underlying medial temporal circuitry are perhaps the most extensively studied systems with regards to age-related impacts on cognition, primarily because of their relevance to Alzheimer’s disease, the most prevalent age-related cognitive disorder (Buckner 2004). With healthy aging in humans, there is variability in the degree of memory dysfunction with age and changes are mild in the absence of pathological processes (Wilson et al. 2020). Episodic memory refers to an individual’s recollection of a particular event in place and time and particularly impacts spatial memory and navigation (Leal and Yassa 2015). Across species advanced age leads to deficits in episodic and working memory, with particular impairments in spatial memory (Gracian et al. 2013; Kubo-Kawai and Kawai 2007; Samson and Barnes 2013; Leal and Yassa 2015). Such deficits may implicate changes in the underlying circuitry, including medial temporal circuits, the hippocampus and

projections from entorhinal, parahippocampal, and perirhinal cortices with age (Leal and Yassa 2015). Loss of plasticity in hippocampal circuits as well as selective vulnerability of these regions is associated with Alzheimer's disease (reviewed in Samson and Barnes 2013).

Age-related impacts on memory systems are also linked to the strength of social bonds in humans (Zahodne et al. 2019; Holwerda et al. 2014; Kuiper et al. 2015; H. Liu et al. 2020). Both structure and quality (based on contact, perceived support, and strain) of social relations are correlated with baseline memory performance in older adults (Zahodne et al. 2019). In contrast, only social structure (being married or having frequent contact with friends) is independently associated with subsequent slower memory decline with age (Zahodne et al. 2019). Social isolation or the loss of social bonds are independent, significant risk factors for dementia (Holwerda et al. 2014; Kuiper et al. 2015; H. Liu et al. 2020). Functional networks comprised of cortical and limbic nodes that support processing of social stimuli and learning, such as the default mode (DMN) and salience networks, are especially vulnerable to cognitive aging and particularly impacted by the neuropathology of Alzheimer's and other neurodegenerative diseases (Spreng et al. 2020; Buckner 2004). Though the underlying circuitry for memory function is conserved in mammals, including prairie voles, a mechanistic understanding of these effects is lacking.

The development of a partner-specific memory during pair bond formation is thought to be critical for bonding behaviors (Ophir 2017; Ophir et al. 2012; Walum and Young 2018). Much of the data from prairie voles examining behavior related to memory function focuses on spatial navigation and its relationship to mating strategy (Ophir 2017). Studies have consistently found that male prairie voles rely heavily on memory systems for sexual decision-making, as males must not only recognize and remember their partner consistently, but must recognize non-partner females and intruder males in order to defend their territory and guard their mate (Ophir 2017). Male fidelity is therefore thought to depend on the need to balance the demands of mate guarding with the reproductive value of multiple mates (Emlen and Oring 1977). Lower levels of V1aR in regions of a spatial memory circuit that includes retrosplenial cortex and laterodorsal thalamus in males correlate with reduced fidelity, greater rates of intrusions into other male territories, and poorer mate guarding (Ophir, Wolff, and Phelps 2008; Okhovat et al. 2015). Retrosplenial cortex, as part of larger functional networks like the DMN, is a region of the brain that, in rats as well as in humans, has been linked to variability in spatial memory function with age (Ash et al. 2016; Andrews-Hanna et al. 2007). In addition to such observations implicating region-specific V1aR expression in fidelity, expression patterns of OXTR within the hippocampus also predict the use of monogamous or non-monogamous strategies in a sex-dependent manner (Ophir et al. 2012; Rice et al. 2017; Ophir 2017).

Though no studies to date have examined age-related changes in memory function in voles, a recent study found altered dendritic morphology in the hippocampal dentate gyrus in one year old male prairie voles compared to young adults independent of environmental enrichment (Akinbo et al. 2022). While this study is suggestive, the impacts of altered anatomy or changes to receptor expression in hippocampal or other circuits on memory-based cognition with age in the context of pair bonding has yet to be determined.

3.2 Valence processing and reward in pair bond formation

The development of rewarding associations towards a partner is thought to be critical to the formation of a pair bond following mating, driving partner-selective motivated behaviors (Lieberwirth and Wang 2016; Vahaba et al. 2022). As a partner-reward association forms, so do negatively valenced associations towards novel potential mates, resulting in rejection of non-partners. Human studies of loneliness find reduced reward signaling in mesolimbic systems with social cues (D'Agostino, Kattan, and Canli 2019; Inagaki et al. 2016) and animal studies have consistently identified differences in subcortical reward systems associated with social isolation (Cacioppo and Hawkley 2009).

Across species, the ventromedial prefrontal cortex and striatal nucleus accumbens are thought to mediate social reward behaviors (Lebreton 2009). Age-related changes in prefrontal cortex (PFC) have mostly been studied in the realm of attention and reduced processing speed. With age, declines in the volume and function of regions of PFC affect not only executive functions like attention, but valence systems regulating reward learning and aversion (Samson and Barnes 2013). While the PFC may undergo the largest age-related volumetric changes in adulthood relative to other brain regions (Raz et al. 2004), striatal volumes decline by about 3% per decade (Raz et al. 2003). Further, frontal white matter tracts decline in density and accumulate lesions with age, which may also affect memory, executive, and attentional cognitive processes involving frontostriatal networks (Hedden and Gabrieli 2004). Beyond volume loss, changes to neurotransmitter levels in the striatum occur with age. Across species, substantia nigra and ventral tegmental area (VTA) dopaminergic neurons degenerate with age, resulting in a decline in dopamine (DA) (Bäckman et al. 2006). fMRI studies have shown that changes to phasic dopaminergic signals within the striatum and decreased BOLD activity in ventromedial PFC may underlie deficits in reward prediction learning in older adults (B. Eppinger et al. 2013). These studies find that while learning from aversive outcomes and subsequent avoidance is intact in older adults, they perform worse when learning to approach reward (Ben Eppinger and Kray 2011; B. Eppinger et al. 2013).

In prairie voles, the process of reward learning towards the partner is initiated with mating and appears to be dependent on frontostriatal function. Mating stimulates ventrotegmental area (VTA) neurons to release DA in the ventral striatum, specifically nucleus accumbens (NAc), resulting in a 51% increase in extracellular DA in the NAc of females (Gingrich et al. 2000). DA is also released with mating in the medial prefrontal cortex (mPFC) (Ross et al. 2009) and mating may increase dopamine turnover in males (Aragona et al. 2003; Valera-Marín et al. 2021). Functional connectivity between the mPFC and the NAc is altered post-mating and dynamic activity across these frontostriatal circuits enhances partner preference formation in response to mating in female prairie voles (Amadei et al. 2017; López-Gutiérrez et al. 2021). Increased DA signaling through administration of a dopamine agonist in the NAc facilitates partner preference formation in the absence of mating (Aragona et al. 2003; Williams, Catania, and Carter 1992). The interaction between OXT and DA is also important for pair bond formation. Blocking either OXTR or dopamine receptor D2 (DRD2) in the NAc prevents mating-induced bond formation (Y. Liu and Wang 2003). OXT and its interaction with dopaminergic signaling in the striatum may

thus be important for facilitating the reward to social contact. However, it is unknown how dopaminergic signaling in the NAc as well as functional connectivity between the NAc and other cortical and limbic regions may change with age. Given the role for dopaminergic and other neuromodulatory systems in the NAc and other regions for pair bonding, age related changes to baseline function of these neuromodulator systems may impact the dynamics of bonding in late age.

While caution is warranted when translating age-related behavioral changes from rodents to humans, we present evidence for common cognitive systems impacted by age across species as a guide for initial investigations. Cognition specifically relevant to social behavior may deteriorate due to deficits in distinct component processes, such as sensory processing, memory, valence processing, or motivated behavior. Alternatively, age-related insults may occur in cortical and subcortical regions that integrate multiple inputs important for the orientation towards social information, the enhanced salience of social cues, or generating context-appropriate social behavior. Future experiments examining changes to behavior in other non-social paradigms such as food or other reward- or fear-motivated learning will be helpful to determine whether the cognitive domains of memory and valence processing, including approach and aversion, as well as other cognitive processes are altered regardless of their involvement in social attachment behavior. Should these capacities show changes with age, but conservation in the context of intact pair bonds, this may reveal mechanisms for compensation leading to possible cognitive and systemic resilience to aging. Such plasticity has been implicated in the circuit dependent mechanisms required for the formation of the bond (Walum and Young 2018; Hiura and Donaldson 2022), making the pair bond a sensitive and potentially flexible read-out of age-related vulnerability.

4. Vulnerability and resilience: regulation of physiology in times of stress

Certain individuals succumb to the effects of age-related disease and environmental stressors, while others appear to be protected from these effects. Identifying the factors that contribute to vulnerability or resilience to pathological aging represents a key motivation in understanding the neurobiology of aging. There is a clear detriment to human health with loss of close relationships, social isolation and loneliness, while positive marital relationships and social interactions influence health in both men and women, including providing benefits for immune functioning, cardiovascular variables, stress reactivity, mood, and longevity (Grewen et al. 2003; Kiecolt-Glaser and Newton 2001; Lewis et al. 2017; Robles et al. 2014). A rich literature has focused on the potential of the loss or maintenance of social attachments to moderate the impact of aging in humans. We now turn to deficits associated with pair disruption and mechanisms that are implicated in pair-bond related resilience.

4.1 Consequence of bond disruption and isolation

The insults to attachment systems that commonly occur with aging include grief or bereavement states following the disruption or loss of a bond, social isolation, and loneliness (Brewster 1950; Shear and Shair 2005; Ong, Uchino, and Wethington 2016). Across species, isolation from social cohorts is often experienced as stressful (Cacioppo and Hawkley 2009;

Grippo et al. 2007; Zelikowsky et al. 2018; Mumtaz et al. 2018). In humans, grief, and especially grief due to the loss of a bonded partner, is a risk factor for poor health in aging adults (Sullivan and Fenelon 2014). Data across numerous studies reveal a clear effect of disrupted attachment relationships on all-cause mortality, cardiovascular health, metabolic function, and dementia in humans (Ong, Uchino, and Wethington 2016; Valtorta et al. 2016; Tomaka, Thompson, and Palacios 2006; Troxel 2005; H. Liu et al. 2020; Roberson et al. 2018). The disruption of a marital relationship, low social interaction, and increased loneliness are independently and significantly associated with incident dementia, with relative risks comparable to other established risk factors, such as low education, inactivity, and late-life depression (H. Liu et al. 2020; Kuiper et al. 2015).

Though loneliness and social isolation are correlated and often co-exist, loneliness is the psychological state related to the perceived lack of attachments and isolation, regardless of objective social contact (Vitale and Smith 2022). Loneliness is especially relevant to understanding the impacts of attachment on health as it differentiates the quality of social connections from the number of such contacts or degree of social connectivity, all of which have independently been linked to age-related processes and adverse health outcomes (Holwerda et al. 2014). It is unclear whether loneliness differentially engages mechanisms related to cognitive and physiological aging compared to social isolation, and thus results in distinct risk patterns of age-related disease. In studies assessing structural brain changes, loneliness has been associated with smaller gray matter volumes of the amygdala, hippocampus, and entorhinal cortex, and reduced white matter density in cortical regions related to social cognition (Düzel et al. 2019; Nakagawa et al. 2015). Loneliness has also been associated with altered connectivity across functional networks like the DMN (Spreng et al. 2020). However, the mechanism by which these social contexts differentially influence neural circuits and their vulnerability to age related processes is unclear. Voles and other species that form social bonds provide critical models to examine the neurobiology of grief and loneliness as the capacity for attachment informs the experience of such states (Vitale and Smith 2022).

In the prairie vole, loss of a bonded mate leads to anxiety- or depression-like behaviors, recapitulating components of the grief response in humans (Bales and Rogers 2022; Grippo et al. 2021a; Bosch et al. 2009; R. Sun et al. 2022). Bond disruption in adult male prairie voles following four weeks of separation elicits reduced time in the open arms of an elevated plus maze and increased immobility in a forced swim test (P. Sun et al. 2014). The response to acute stressor conditions, such as restraint stress or forced swim assays, has also been examined in voles following bond disruption. Pair bonded male and female prairie voles separated from their partner display increased passive coping behavior following acute stressors compared to intact pairs (Bosch et al. 2009; 2016b; Grippo, Cushing, and Carter 2007; McNeal et al. 2014). These behavioral changes have been linked to signaling through the oxytocinergic system. Separation from a bonded mate leads to reduced OXT expression in the PVN and reduced OXTR binding in the NAc shell. OXT infusion in the NAc, in contrast, reduces the stress response to separation (Bosch et al. 2016a). Studies of bond disruption in voles have relevance for our understanding of grief and pathological affective states, like depression and complicated bereavement, that are associated with late-life loss of attachments.

Studies in voles have also examined the effects of social isolation, unrelated to bond disruption, on behavioral and physiological outcomes in adult animals (Grippo et al. 2007; McNeal et al. 2014; Grippo, Cushing, and Carter 2007). Isolation from same-sex siblings in adult voles results in anhedonia, indicated by reduced sucrose intake and preference, and elevated activity in PVN and plasma OXT relative to cohoused animals (Grippo, Cushing, and Carter 2007; Grippo et al. 2007). Interestingly, chronic isolation in adult male voles has also been associated with increased reproductive behavior related to polygyny, a male having more than one mate, and physiological changes in gonadal hormones that may reflect adaptive changes to isolation stress (Perry, Carter, and Cushing 2016; Mabry et al. 2011). Such changes suggest an inherent plasticity in pair bond circuitry to support multiple mating strategies in response to environmental conditions (Streatfeild et al. 2011). Whether such flexibility is maintained with age and how the underlying molecular and circuit mechanisms evolve with age may reveal important aspects of age-related resilience.

4.2 Protective aspects of sustained pair bonds

Studies examining the impacts of social relationships on healthy aging in humans consistently demonstrate the benefits of intact, close social relationships on diverse health outcomes (Robles 2014; Bowlby and Bowlby 1982; O'Connor and Rutter 2000; Rutter et al. 1999; Holt-Lunstad, Smith, and Layton 2010; House, Umberson, and Landis 1988). In humans, stronger social relationships, measured by relationship quality, confer a survivorship advantage up to 50% (Holt-Lunstad, Smith, and Layton 2010), similar in effect size to interventions related to diet and exercise (Robles 2014). Relationship quality and gender modulate the effect of marriage on health outcomes, which includes increased risk of cardiovascular disease, cancer and respiratory diseases, particularly in males (Dhindsa et al. 2020; Kiecolt-Glaser and Wilson 2017; Steptoe et al. 2004). Positive marital relationships and social bonds influence health in both men and women, providing benefits for immune function, stress reactivity, as well as mood (Grewen et al. 2003; Kiecolt-Glaser and Wilson 2017; Kiecolt-Glaser and Newton 2001; Robles 2014; Verstaen et al. 2020; Uchino 2006; Haase et al. 2016). Most of the literature on human bonds and their effect on health outcomes focuses on marital relationships, although friendships also independently contribute to healthy cognitive aging (Zahodne et al. 2019). Prairie voles provide a unique model by which to assess the specific protective effects of pair bonding on physiological aging relative to other measures of social health.

Pair bonding in prairie voles results in resilience to social and environmental stress (Grippo et al. 2021b; Grippo, Cushing, and Carter 2007; McNeal et al. 2017; Bosch et al. 2009). Prairie voles demonstrate reduced passive stress coping, reduced anxiety and depressive-like behaviors, and improved peripheral markers of stress when compared to animals that have been isolated (Grippo et al. 2021b; Grippo, Cushing, and Carter 2007; McNeal et al. 2017; Bosch et al. 2009). Examination of the protective effects of sustained pair bonds compared to isolation with age using long term pairs up to 54 months of age revealed that, as with younger animals, aged pair bonded animals are protected from short-term stress reactivity in response to an acute stressor compared to isolated animals (Grippo et al. 2021b). Aspects of the dyadic or reciprocal interactions in a bonded condition may also be important to understanding resilience with age as bonded voles engage in "social buffering" behaviors

(Lieberwirth and Wang 2016; Peen, Duque-Wilckens, and Trainor 2021). The presence of a bonded partner following an immobilization stress reduces anxiety-like behaviors when compared to animals that recover alone (Donovan, Liu, and Wang 2018). Peer social relationships may also provide some aspect of social buffering or resilience to the effects of environmental stress. Females that remain in social pairing with a same-sex conspecific show resilience to acute stress compared to isolated animals (Grippo, Cushing, and Carter 2007). Social pairing protects against the development of depressive and anxiety-like behaviors seen in response to isolation as well as to acute stressors such as a forced swim test and tail suspension test (Grippo, Cushing, and Carter 2007; McNeal et al. 2017). However, this effect has not been evaluated in comparison to pair bonding in the context of aging. Such study designs that include a social housing condition will be important in order to evaluate protective effects specific to the context of opposite sex pair bonds.

There is significant variability across species in individual susceptibility to age-related changes and pathology which may be accounted for by differences in inherent cognitive reserve (Stern 2012; Wilson et al. 2020). Beyond measures of reserve related to quantitative measures of brain volume, cognitive reserve refers to the functional coping of the brain to age-related insults (Stern 2012). Social bonding in prairie voles attenuates many of the stress responsive systems described above. These include responses that are potential indices of depression-like behaviors (such as reduced passive stress coping or learned helplessness in a forced swim task), altered production of neuromodulators, and, as described below, reduced HPA axis reactivity and autonomic system imbalance (Bosch et al. 2009; Grippo, Cushing, and Carter 2007; McNeal et al. 2014; P. Sun et al. 2014). Sustained social attachments may act as a buffer against negative consequences of stressful events by inducing mechanisms related to cognitive reserve and resilience.

4.3 Social stress and glucocorticoid and CRF system regulation

Activity across the HPA axis, specifically signaling through corticotropin releasing factor (CRF) and the glucocorticoid system, is frequently implicated in mediating the effects of social stressors, as well as adverse environmental agents (McEwen et al. 2015; Sapolsky et al. 1987a; Bosch et al. 2016b). The brain CRF system, through action on both CRF receptors type 1 (CRFR1) and type 2 (CRFR2), is a primary regulator of the HPA axis (Vale et al. 1981; Aguilera and Liu 2012). Studies across species identify the CRF and glucocorticoid systems as important regulators of the response to social stress at various developmental time points (Meaney 2001; Sapolsky et al. 1987a; Avitsur, Stark, and Sheridan 2001; Vitale and Smith 2022). Studies in humans and other species report increased hypothalamic CRF expression and compensatory CRFR1 downregulation during aging (Scaccianoce, Di Sciullo, and Angelucci 1990; Tizabi, Aguilera, and Gilad 1992; Ceccatelli, Calzá, and Giardino 1996; Aguilera 2011a). However, little is known about age-related CRF effects on circuits for pair bonding or their interaction with other neuromodulators.

In voles, the CRF system is intricately tied to attachment behavior as it regulates pair bond formation and mediates the response to partner loss. Central activation of CRF pathways or local infusion in the NAc facilitates pair bond formation in male prairie voles, even in the absence of mating (Bosch et al. 2009; DeVries 2002). Following acute stress in

the form of a forced swim test, infusion of CRFR2 antagonist into the NAc reduces the effects of partner loss on passive stress coping (Bosch et al. 2009). Further, enhanced CRF signaling leads to increased depressive-like behaviors in voles (Bosch et al. 2009). The OXT and CRF systems also interact as CRFR2 activation in the NAc suppresses OXT release from the PVN, whereas blocking CRFR2 stimulates OXT release (Bosch et al. 2016b). Beyond the interaction between CRF and OXT, other neuromodulators, including the Kappa opioid system, may modulate the response of OXT to specifically mediate the aversive state associated with bond disruption and chronic separation (Bales and Rogers 2022). The interactions between the OXT, CRF and opioid systems are dynamic (Bales and Rogers 2022), and both the function and levels of these various neuropeptides may be differentially impacted with age.

Downstream of CRF signaling in the brain, the HPA axis and implicated glucocorticoid signaling are among the most common mechanistic pathways implicated in chronic stress and adverse health outcomes associated with aging (McEwen et al. 2015; Sapolsky et al. 1987b). Female prairie voles immobilized for one hour show increased levels of anxiety-like behavior and plasma corticosterone (CORT) if they recover alone rather than with their male partner (Smith and Wang 2014). In male and female voles, pairing with an opposite sex partner leads to a decline in serum CORT directly following introduction. However, pairing with a same-sex novel animal does not affect serum CORT (DeVries et al. 1995; DeVries, Johnson, and Carter 1997). Further, male prairie voles separated from a female partner but not from a male sibling demonstrate increased plasma CORT and adrenal hypertrophy (Bosch et al. 2009). Interestingly, these findings suggest a differentiation in stress mechanisms buffered by social peers vs reproductive partners. Thus, as stated above, comparisons to social peer groups are informative for understanding benefits specific to pair bonding. Most studies in voles have relied on peripheral CORT or peptide measurements. However, tissue- and cell-type-specific gene expression downstream of glucocorticoid signaling as well as expression patterns that overlap with other conserved aging and senescence-related changes are important for ultimately understanding the physiological effects of chronic stress with age.

4.4 Pair bonding effects on autonomic physiology

Aging is characterized by a gradual decline in all physiological functions, a decrease in repair mechanisms, and tissue specific senescence (López-Otín et al. 2013). This decline is partially associated with changes in autonomic regulation, in particular, responsivity of the autonomic nervous system (ANS) to stress (Hotta and Uchida 2010; Seals and Esler 2000). These changes manifest in levels of neurotransmitter, specifically adrenergic, signaling in peripheral organs, as well as in processing of autonomic signals centrally (Jones et al. 2001; Hotta and Uchida 2010). Aging also leads to alterations in the balance of parasympathetic and sympathetic tone. Sympathetic activity increases, despite decreased adrenergic receptor expression in the cardiovascular system, and parasympathetic tone decreases, which are linked to reduced cardiac vagal suppression of heart rate and cardiac output (Seals and Esler 2000). These changes affect heart rate, blood pressure, and risk for cardiovascular morbidity (Jones et al. 2001; Seals and Esler 2000; Hotta and Uchida 2010). Heart rate variability (HRV), a measure of autonomic health, declines with age, a change that has been correlated

with various markers of cognitive function and that can be reversed by interventions that extend lifespan, such as caloric restriction (Stein et al. 2012; Frewen et al. 2013).

Evidence from human studies suggests that affective states associated with different social contexts are accompanied by distinct patterns of ANS activity (Pasquini et al. 2022; Quintana et al. 2012; Shahrestani et al. 2015). For example, HRV is associated with measures of social cognition, like emotion recognition accuracy, and decreases in the context of negative dyadic social interactions in humans (Quintana et al. 2012; Shahrestani et al. 2015). Further, activity across functional brain networks that mediate social cognition in humans and that map to circuitry for social behavior in animal models, such as the salience network, may coordinate ANS function (Pasquini et al. 2022; Seeley et al. 2007). The cognitive systems that may be impacted by aging, specifically memory and reward as described above, are also intimately tied to the regulation of physiology in response to stress (Ulrich-Lai and Herman 2009). Understanding these changes in the context of pair bonding in animal models may have bearing on the changes to broader healthspan, particularly cardiometabolic health, that are significantly impacted by attachment status in humans.

Pair bonding in prairie voles has been linked to improved cardiovascular function, specifically decreased heart rate, mean arterial blood pressure (MAP), and increased HRV when compared to isolated animals (Grippo et al. 2011b). Bonded voles are generally more aggressive towards an opposite sex intruder and exhibit increased heart rate and MAP (Lewis et al. 2017). Such adaptive, state- and stimulus-specific changes in ANS activity may be disrupted with social stress. Social isolation in male prairie voles following loss of a female partner results in increased heart rate, autonomic imbalance characterized by increased sympathetic and decreased parasympathetic drive to the heart, and elevation of adrenocorticotropic hormone and CORT (McNeal et al. 2014). Similar effects on heart rate and HRV have been seen with isolation from a same-sex conspecific (Grippo et al. 2018). In voles, OXT treatment prevents alterations in cardiovascular consequences and depression-like behaviors induced by social isolation in female prairie voles (Grippo et al. 2009). OXTR is expressed throughout the body, in multiple organ systems that regulate cardiovascular and metabolic function, smooth muscle contraction, as well as fluid homeostasis and food intake (Quintana and Guastella 2020). The oxytocinergic system may thus mediate aspects of both central and peripheral changes associated with pair bonding.

Studies have primarily focused on the actions of CRF signaling and glucocorticoids in mediating the impacts of social buffering and bond disruption (Avitsur, Stark, and Sheridan 2001; Bosch et al. 2009; Peen, Duque-Wilckens, and Trainor 2021). However, attachment has been conceptualized as both a behavioral and *physiological* system that dynamically adapts to meet the needs of the environment, resulting in centrally modulated peripheral processes aiming to regulate stress responses (Mikulincer and Shaver 2010; Quintana and Guastella 2020). Such dynamic changes to attachment relationships over the course of the lifespan as well as the different types of social and environmental stressors encountered likely engage the HPA axis and ANS regulation in different ways (McEwen et al. 2015; McNeal et al. 2017; Mumtaz et al. 2018; Yang et al. 2016). Social stressors may also have common or divergent consequences depending on when in the life course a stress is encountered. Early life stress has been studied in the context of juvenile and adult

attachment in prairie voles and other species, but may have continued effects on behavior and health into late age (Perkeybile, Griffin, and Bales 2013; Sailer et al. 2022). Further, the two physiological systems discussed here are not meant to be exhaustive, and other important processes, including epigenetic regulation and immune function, likely play important roles in the integration of social function and healthy aging (Chiou et al. 2022; Siracusa et al. 2022; Snyder-Mackler et al. 2016; 2019). Identifying the differential response to varying types of social stress as well as to other environmental and physiological stressors with age will be important for developing specific and effective interventions for diseases impacting healthspan.

5. Future directions and conclusions

As studies of social aging develop, many open questions related to pair bonding and attachment and their intersection with age-related health remain. Among these is the overarching question of how attachment behavior, both in the context of long-term established pair bonds as well as the formation of new pair bonds, and the underlying neurobiology evolves into late age. We have presented several aspects of cognitive and social behavioral change with age in humans and their potential correlates in voles, suggesting behavioral constructs that may be operationalized as readouts of aging dynamics. We advocate for comprehensive behavioral profiling to fully assess such cognitive domains, both in social and non-social contexts. Furthermore, formal lifespan analyses of socially monogamous and closely related polygamous species will clarify the relationship between mating strategy and lifespan determination.

In order to address the effects of aging on molecular mechanisms related to pair bonding, advances in molecular genetics, genomics, and the use of well annotated genomes for vole species will continue to be useful. The question of whether certain cellular and molecular “hallmarks of aging” are present with age in various tissues in the vole and how they are altered with pair bonding or mate loss is also of interest (López-Otín et al. 2013; 2023). One study has approached epigenetic regulation with age and pair bonding by developing an “epigenetic clock” or DNA methylation-based estimator in voles based on conserved mammalian CpGs, representing a promising approach for comparing chronological and biological age (Sailer et al. 2020). Further, cellular aging, as measured by oxidative damage and telomere degradation in peripheral blood cells in voles is associated with chronic isolation, and these effects are ameliorated by injection of oxytocin (Stevenson et al. 2019). Enrichment for conserved risk genes for age-related disease in molecular profiles from specific populations of neurons linked to social attachment behavior will further identify molecular pathways and vulnerable cell populations in which these genes act. Examining such conserved markers of aging in prairie voles and varying bonding contexts will allow for the identification of reliable predictors of social aging processes.

In addition to studies of molecular and cellular aging, altered activity across specific neural populations and defined circuits will be particularly relevant to understanding changes in behavior with age and their impacts on health. The neural circuits underlying pair bond behavior and their evolution in terms of activity can now be labeled and mapped, and the dynamics of activity therein monitored and manipulated using methods for viral

mediated labeling, transsynaptic tracing, calcium imaging, opto- and chemo-genetic as well as CRISPRa/i approaches, all of which are now feasible in voles. Further, molecular tools, such as *Fos* responsive Targeted Recombination in Active Populations (FosTRAP), allow the labeling of neurons active during specific behavioral contexts for later transcriptional and activity profiling (Guenthner et al. 2013). The recent adaptation of CRISPR-based approaches in voles allows us to now mechanistically examine the resilience of neural systems to aging processes (Berendzen et al. 2023; Horie et al. 2019). Such tools will identify active neuronal populations that encode bonded partner information and can be used to determine how the identity and function of these cells evolves over time with various perturbations. The response of peripheral physiological systems to stress conditions and where in the brain this information is encoded are also particularly open areas of study.

It is abundantly clear that our social lives influence our lifespan, as well as our health into late age. Fundamental to social aging are the attachments and bonds formed with others, close partners in particular. Among species that form such long-term, selective bonds, the influence of age and effects on health may be conserved, as evidence from prairie voles and other species suggests (Powell et al. 2022; Grippo et al. 2021a; Robles et al. 2014). In recent years, the call for the expansion of model systems to explore behavioral and physiological phenomena across the lifespan has been resounding (Henry, Grainger, and von Hippel 2023; Kensinger and Gutchess 2017; Snyder-Mackler et al. 2020). Prairie voles and other species that form relationships that endure throughout life give us a path forward towards understanding one of the most fundamental of human social behaviors and the health impacts of our bonds and losses into late life.

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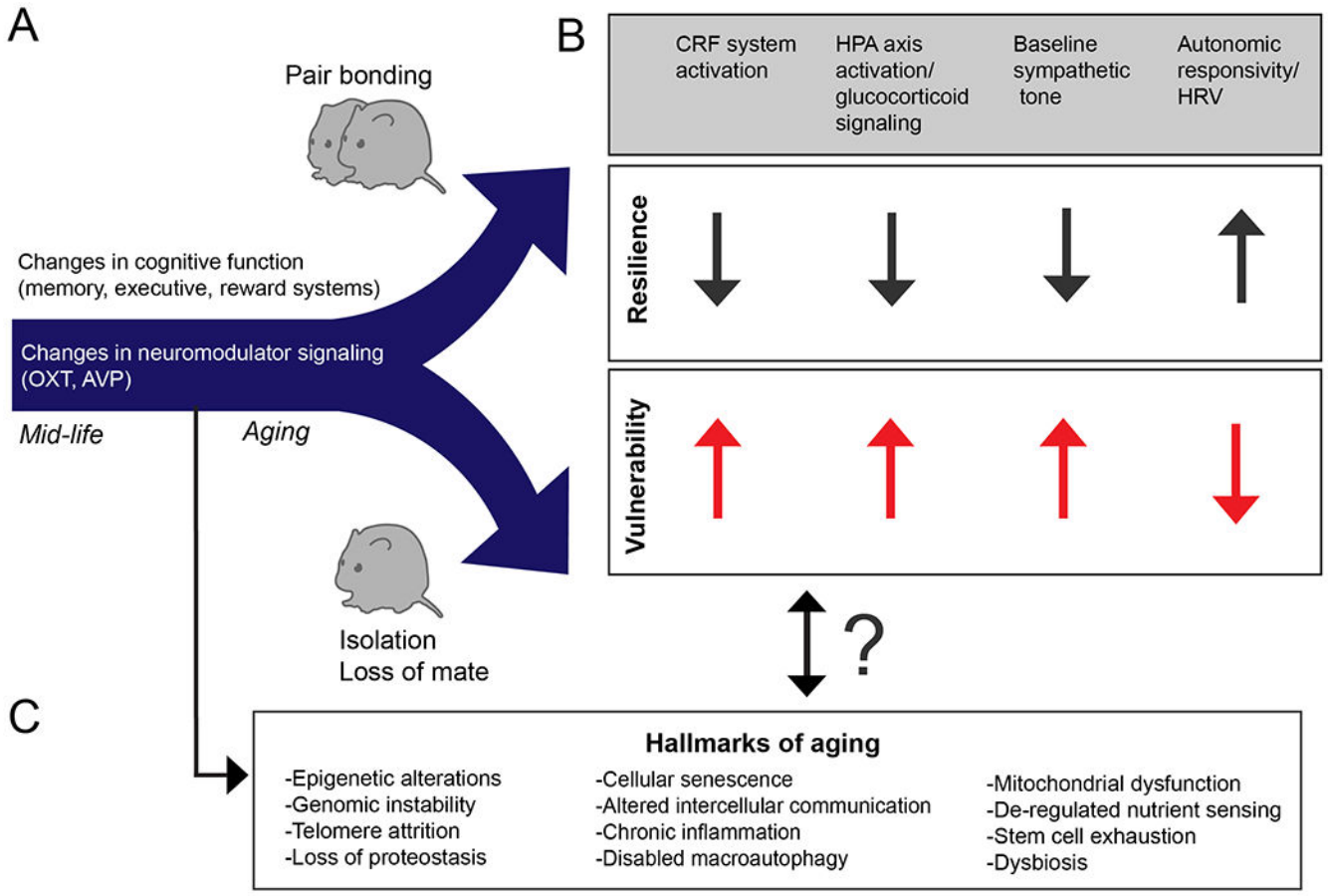

Figure 1. Model illustrating potential interactions of attachment and aging.

A) Changes in neuromodulator signaling and/or cognitive function with age may influence the demonstration of pair bonding and related behaviors, including the response to social isolation or loss of a mate in late life (Leal and Yassa 2015; Kenkel et al. 2019b; Powell et al. 2022; Cacioppo and Hawkley 2009). B) Experiencing attachments, isolation, or other bonding states through mid-life and aging may contribute to resilience or vulnerability to age-related stress. HPA/glucocorticoid/CRF signaling and autonomic system regulation are implicated in the response to stress throughout the lifespan (Aguilera 2011b; Sapolsky et al. 1987a; Stein et al. 2012; Hotta and Uchida 2010). Central regulation of these processes is thought to occur partially through neuromodulator signaling (Grippo et al. 2009; Quintana and Guastella 2020; Bosch et al. 2016b). C) Defined biological hallmarks of aging (López-Otín et al. 2013; 2023) may be modulated by bonding state in model systems. Furthermore, inter-individual variability in such cellular functions may mediate bonding state-dependent differences in resilience or vulnerability to age-related stressors and pathological processes. Experiments probing the mutual influences of sociality and aging will enhance our understanding of these processes and inform interventions promoting healthy aging.