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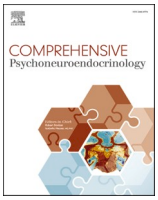

Love and longevity: A Social Dependency Hypothesis☆

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ABSTRACT

Mammals, including humans, are reliant for survival and reproduction on adaptations associated with sociality and physiological investment, which can be linked to interactions with their parents or other bonded adult conspecifics. A wide range of evidence in human and non-human mammal species links social behaviors and relationships - including those characterized by what humans call "love" - to positive health and longevity. In light of this evidence, we propose a Social Dependency Hypothesis of Longevity, suggesting that natural selection has favored longer and healthier adult lives in species or in individuals exhibiting enhanced caregiver responsibilities contributing to the success of the next generation. In highlighting cellular, physiological, and behavioral effects of mammalian reproductive hormones, we examine the specific hypothesis that the neuropeptide oxytocin links longevity to the benefits of parental investment and associated relationships. Oxytocin is a pleiotropic molecule with anti-oxidant and anti-inflammatory properties, capable of regulating the hypothalamic-pituitary-adrenal axis, the parasympathetic nervous system and other systems associated with the management of various challenges, including chronic diseases and therefore may be crucial to establishing the maximum longevity potential of a species or an individual.

1. Introduction

The proximate and ultimate causes for why organisms age and at such different rates across taxa have long puzzled the scientific world. Some species (such as humans, aquatic mammals, tortoises, sea-birds, and sharks) can live for many decades while others (for example, shrews or semelparous marsupials) may live out their life cycle in a number of weeks. Theorists have long pondered these questions of longevity, but still struggle to account for much of the variation in natural aging rates and maximum longevity potentials both within species (individual differences) and across taxa. This may be due, in part, to a lack of integration between approaches to investigating longevity. Longevity has been typically studied from one of two scientific approaches: aging by evolutionary programming or aging due to physiological damage [1]. Concurrent advancements have been made on both fronts with the formulation of the evolutionary theory of aging (Medawar, 1953 [2]; Hamilton 1963), the identification of multiple life history factors that correlate with longevity characteristics (see Refs. [3, 4], and the identification of a number of physiological markers of senescence (see Ref. [5]. However, theorists have struggled to synthesize these ideas and often report contradictory evidence (e.g. Refs. [6–9].

Here we suggest that a new perspective may be required to resolve inconsistencies and provide new directions. Specifically, we offer as an integrative alternative, what we have termed a Social Dependency Hypothesis of Longevity. Following the convention of Tinbergen [10]; this hypothesis begins to merge ultimate and proximate perspectives on patterns of aging, focusing on the importance of both evolutionary programming and the importance of physiological processes at cellular, physiological and behavioral levels that defend against accumulating damage and errors. We propose that this cross-disciplinary perspective helps to resolve some of the unaccounted variation in aging rates observed across taxa, which as has been suggested elsewhere, may vary according to social, parental, and reproductive strategies. We will also directly apply this theory towards issues surrounding human health and longevity. While we focus mainly on the adaptive value and the mechanisms of longevity in mammalian species that exhibit selective social bonds, we recognize that the specific molecular mechanisms hypothesized to moderate this relationship are not restricted to mammals (see

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Ref. [11] and that developmental flexibility and other ontological factors also will also be useful to future cross-taxa models of longevity [12, 13].

The evolutionary theory of aging represents the combined theoretical contributions of biologists Peter Medowar, George C. Williams, and William Hamilton; this theory proposes evolutionary explanations for the absence of complete repair during a life-span (i.e. immortality) and the tendency of organisms to deteriorate at a seemingly predetermined rate. The evolutionary theory of aging posited that the degradation of bodily tissues and processes results from deleterious mutations [14] and/or the consequences of genes with antagonistically pleiotropic characteristics [2] that arise late in the lifespan, thus evading natural selection's ability to eliminate these deleterious effects. These deleterious effects are proposed to worsen over the life span, in part due to the rarity of survival to old age in the wild and the lowered rates of reproductive success late in the lifespan due to extrinsic mortality threats (e.g. predation, disease, parasitism); Hamilton [15] described this as a "selection gradient," capable of hindering the capacity of natural selection to eliminate certain deleterious outcomes, thus resulting in the phenomenon described as "senescence."

In addition to antagonistic pleiotropic effects and deleterious mutations that arise during the lifespan, other cellular and molecular processes such as oxidative stress (see [16], inflammation (see [17], and the degradation of telomeres (see [18], provide additional barriers to the evolution of longer lifespans. This array of internal threats and the various extrinsic mortality factors that suppress selection's ability to eliminate deleterious effects late in the life-span combine to make longevity comparatively rare in the animal kingdom. Among various animal taxa, the distribution of life expectancies is highly skewed to the left, with the vast majority of known species living less than a few decades, while only a very small minority of species (humans among them) are capable of living more over a century.

Although most animal species can survive and effectively reproduce with relatively short life cycles, some have evolved longer lives for reasons that remain to be understood. However, some of the mechanisms by which longer lifespans may have evolved are being discovered. Among the mechanisms associated with longer life spans are a variety of defensive systems that protect against the internal and external risks that lead to mortality and aging (Fig. 1). For example, endogenous antioxidants protect against oxidative stress and anti-inflammatory agents protect against the deleterious effects of chronic inflammation. The enzyme telomerase is capable of rebuilding and maintaining chromosomal caps and thereby protecting against genetic deterioration if activated or re-activated in cells. Physical defenses (i.e. spines/shells) and neuroendocrine stress response systems that mobilize the organism can protect against ecological threats. Finally, an array of social defenses also exists in some species with the capacity to protect against various external mortality threats such as predation (i.e. social warning), parasitism (i.e. social grooming), and famine (i.e. cooperative hunting/foraging). These various defensive systems were previously thought to be independently regulated. However, here we postulate that a central neurohormonal mechanism, involved in the expression of reproductive and selective social bonds in mammals, might be involved in coordinating most if not all of these defensive pathways, thus interacting to reduce both intrinsic and extrinsic mortality threats and alter the pace of aging.

2. Longevity as an adaptive trait for the next generation

Humans, as a species, exhibit all of the defensive traits shown in Fig. 1 and also have the capacity to live nearly a century longer than expected by our body size, at least when.

compared to other mammals (Fig. 2). Particularly difficult to explain in evolutionary terms is the rare but relevant phenomenon of significant post-reproductive lifespans found in some mammals (including humans) [19,20]. In humans, this phenomenon has been discussed in several theories of aging including the "grandmother hypothesis" [21,22] and the "embodied capital model" [23–25]. These theories converge in emphasizing the reproductive or otherwise adaptive roles that older individuals provide their community by "nonreproductive" means. Consistent with these theories, longevity itself becomes adaptive because of the role of older individuals in caring for the younger generation, which is the central concept in this Social Dependency Hypothesis.

Among human hunter-gatherer cultures grandmothers represent the most obvious example of caregiving late in the lifespan [22], but other adults will also expend considerable time and energy to support the developing generation in important ways (such as provisioning and protection). As argued elsewhere [23–25,157], the high level of intellectual knowledge and skills that benefit human populations depend on

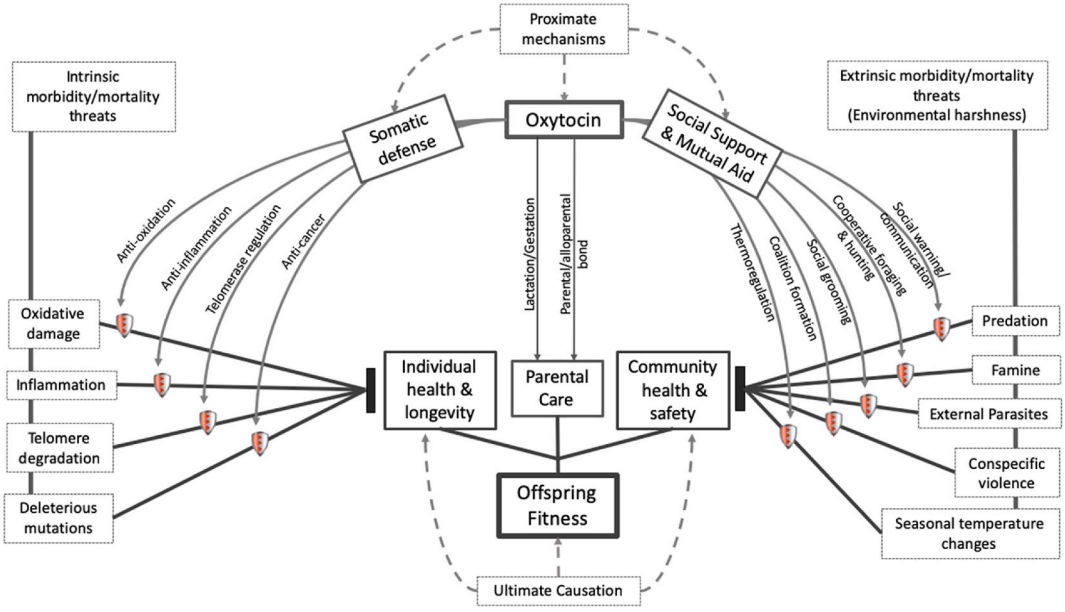

Fig. 1. Interactions and the hypothesized mediating mechanism between intrinsic and extrinsic mortality factors, parental care, parental longevity, and offspring fitness in socially dependent species: a Social Dependency Hypothesis.

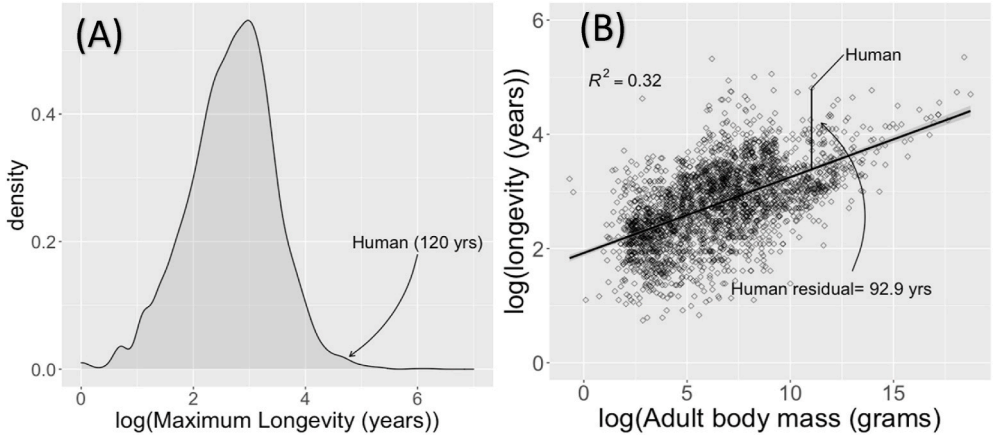

Fig. 2. (A) Density distribution of maximum longevity across 3776 animal species (log transformed). (B) Allometric scaling of maximum longevity across 2560 species of chordate (log transformed). Data are from AnAge database [4].

the maturation of the human nervous system. This perspective emphasizes the exceptional altriciality of human offspring and the extensive parental and alloparental support structure required to sustain human young to an age of maturity and/or independence. While the evolutionary reasons for the human species' altricial nature are debated [155], there seems little doubt concerning the ecological and evolutionary relevance to human evolution of this highly derived life history trait. In the wild, human neonates and juveniles require the long-term recruitment of maternal investment (as in other mammals), but also the involvement an extensive alloparental support structure including fathers, grandparents, aunts, uncles, older offspring and even unrelated community members [157]. Although the collective metabolic cost of this life history strategy is large, the tradeoff has documented reproductive value. The human brain enables humans to master our environment and to replicate our genome in a manner not found in other species. In accord with these earlier hypotheses of human longevity, we consider the success of the human species in part as an outcome of the enhanced caregiving resources provided to the highly altricial developing generation made possible by exceptionally long-lived adult caregivers.

Evidence supporting these ideas is gradually emerging. For example, social bonding and positive social engagements are associated with health and vitality of a human life (e.g. Refs. [26–31]. Some studies have proposed a more direct link between social interactions and mortality rates (e.g. Refs. [32,33]. A meta-analysis across 148 human studies including 308,849 participants revealed a 50% increased likelihood of survival for those reporting stronger social relationships [34]. Also, in support of the grandmother hypothesis, a recent study in elderly people found a positive correlation between longevity and the level of caregiving exhibited by the elderly towards related and unrelated dependents in the final decades of life [35]. These and other studies reveal that caregiving relationships and the mechanisms therein may play a crucial role in facilitating longevity characteristics among adults engaged in those behaviors.

3. A Social Dependency Hypothesis of Longevity

Although the human species represents an outlier of longevity among mammals and other animal species, the biological mechanisms that enable the neurophysiology of caregiving relationships in humans originated deep in the evolutionary history of life on this planet and are expressed in other selectively-social mammal species but also non-mammalian vertebrates (see Refs. [11,36,37]. As proposed here, this Social Dependency Hypothesis suggests a specific link between the physiological pathways required for selective social bonds and certain aspects of longevity (including the post-reproductive lifespan common in humans). We examine this hypothesis in light of features of mammalian physiology related to the oxytocin system (Fig. 1).

We specifically suggest that the longevity-related benefits of social interactions and dependency, as regulated in part by the oxytocin system, may be more common in species that have evolved to depend heavily on caregiving by conspecifics for survival. In mammals, as also in birds, caregiving from mothers, and in some cases allomothers, fathers and other related conspecifics facilitates successful reproduction [38,157]. However, as articulated below this hypothesis emphasizes the effects of caregiving not only in relation to early life experiences [13], but also the overall health of adults as critical factors in fitness and survivorship; this is especially the case in species for which high levels of social or parental dependency exist throughout the life-history. In other words, when adult support is required for surviving development, the overall longevity and/or survivorship of those adults can be considered as an adaptive trait for the ultimate benefit of the individuals that depend on them (reference Fig. 1). Evidence for this pattern is found in the multitude of positive health and longevity-enhancing effects of the oxytocin system at the cellular and behavioral levels (see Ref. [39] and below). We specifically hypothesize that the expression of the mammalian caregiver phenotype, mediated in part by oxytocin signaling throughout the brain and body, is a key life history factor in establishing the long-term health and eventual longevity. Although untested at this time, the oxytocin system, including the oxytocin receptor, through its effects on parental bonding, parental physiological changes, and parental/adult longevity, could have been a specific target of natural selection towards offspring fitness particularly during development (Fig. 1).

4. Mammalian parental care and oxytocin

The principles of this Social Dependency Hypothesis as detailed in this review are not limited to mammals [40] or even vertebrates (for example in bees; [12,41]. The genes that encode for oxytocin, its paralog vasopressin, and their various orthologous forms (i.e. vasotocin, mesotocin, isotocin) are all thought to be derived from the same ancestral vertebrate gene. Similarly, their receptors are also homologous across vertebrates and therefore it has been argued that the same orthologous names should be adopted across vertebrates and paralogous names relative to each other [11]. In other words, oxytocin and vasopressin are thought to be universal among vertebrates with the exception of the jawless fish (agnathans), a class of vertebrate only thought to have vasopressin orthologs since the gene-duplication event that gave rise to oxytocin is thought to have occurred sometime after the first emergence of jawed fishes (see Yamashita & Kitano, 2013). This finding suggests that while some of the specific effects of oxytocin in the mammalian

physiology may be derived, oxytocin-like molecules are not exclusive to mammals, but are expressed in most, if not all jawed vertebrates in one form or another. We will focus here on mammals not because we suspect oxytocin nor its receptor to be novel to the class, but because of the highly conserved nature of selective social bonding in the mammalian life history, a feature for which the conserved oxytocin system is thought to play a crucial role. Additionally, the availability of knowledge regarding the physiology of mammalian selective social bonds, including the importance of oxytocin [42], provides a specific pathway that could contribute to the role of social dependency in longevity.

Among the social bonds exhibited by mammals, the maternal-offspring relationship is the most conserved and fundamental to the mammalian life history. Mammals are phylogenetically distinguished from other animals, in part by lactation, but also due to their long periods of gestation and high levels of interactions between mothers and their offspring. Although these traits are not exclusive to mammals, the degree to which mammals have integrated them into the life history strategy is remarkable. For example, milk-like secretions to sustain offspring have been found in arachnids [43], insects [44], and several species of birds [45,46]. Also, gestation (including viviparity and in some cases even the formation of a placenta) is present in some squamate reptiles (see Ref. [47]. What makes mammals truly unique is not the mere existence of these maternal physiological traits, but the total conservation of this mother-offspring relationship and the physiological innovations that support it. Every known mammal species exhibits a lasting maternal investment in which the mother provides, at a minimum, specialized nutrition (in the form of milk), protection, and warmth during the developmental stage of life.

Importantly, in contrast to some other phyla, where males are also integrated into the caregiving strategy (e.g. birds), in most mammalian species the female bears the vast majority of the burden of offspring investment during early development. Mammalian males and alloparents also can contribute to offspring nurture and survival directly and indirectly, including by offering protection and resources [157]. However, it is comparatively rare among mammalian species for males to contribute directly to the childrearing process [48]. Exceptions do exist, including socially monogamous species of rodents and New World primates as well as humans, in which males are actively involved in parenting [49,50]. However, as detailed elsewhere these apparent exceptions may be associated with the physiological and behavioral effects of hormones such as oxytocin, which affect behavior in both males and females [51–55]. In addition, oxytocin interacts with the consequences of androgens and androgen-dependent hormones (such as vasopressin and testosterone), especially during early development [13,42]. Furthermore, during stress, androgens and vasopressin can influence systems associated with oxytocin with possible benefits for males [56] but may also lead to long-term health consequences such as immune-incompetence [57], inflammation, chronic disease, and more (reviewed [58].

The distinguishing physiological traits of mammalian maternal phenotype are gestation and lactation. These derived evolutionary innovations provide unique adaptive advantages for mammal offspring and are thought to be responsible, in part, for the adaptive radiation of mammals over the last 100 million years (e.g. Refs. [59–61]. These traits also result in a novel and often irreplaceable dependency between early life caretakers, typically the biological mother, and their neonates. In nature no mammal will survive without a sufficient gestational period and access to milk, most often provided by the biological mother, and sometimes supplemented by an alloparent [157]. These features of female reproduction also are associated with selective social behaviors directed to the offspring, creating a biological basis for perceived safety and, secure social bonds, and what humans sometimes call “love” [62].

In light of this fundamental importance of maternal investment among mammals, we hypothesize that a process may have evolved linking the traits associated with caregiving with survivorship of adult females (especially mothers). The same physiological systems that nurture the offspring, also appear necessary for establishment and maintenance of the bonds of dependency that arise during the vulnerable stages of offspring development. In mammals, early development is a time when death or illness of the mother would typically result in the subsequent death of the offspring. Only a living and healthy mother (or other caregiver) with a strong bond to her young is able to provide the specialized environment necessary for the slow developmental requirements common among mammals. Mammals are known to take far more time than many other vertebrates to develop, often emphasizing immunologic and neurologic development in early life over locomotor function or speed of sexual maturation. This tradeoff is consistent with a “slow” life history strategy (e.g. Ref. [63]; primates [64]; bats [13]; humans) which in mammals generally requires sustained support from the biological mother. This process shares a physiology with the biological relationship between mothers and their offspring; that same physiology may be activated in other adults such as allomothers, grandmothers, fathers, or other community members [52,53]. Thus, the possible health benefits brought about by the physiological processes surrounding motherhood (as described below and in Ref. [39] may have also been extended to other caregivers, with more benefits in species described as showing social monogamy [42] or cooperative breeding [38], that experience the health and longevity benefits of sociality. One prominent example among rodents is the eusocial, naked mole rat that exhibits exceptional longevity, with breeding females of this species living in captivity up to 30 years [65]. Importantly, oxytocin has been shown to mediate at least some of the components of naked mole-rat eusociality (e.g. [66,67,160]).

Physiological processes can be highly conserved and often co-opted for multiple purposes. However, due to the fundamental importance of maternal health in the success of offspring the physiology contained within the maternal phenotype is one place to search for clues regarding possible mechanisms linking caregiving to health and longevity. Caretaking in mammals or a parental phenotype emerges through a series of adaptive transformative processes influenced by developmental, social and environmental conditions [68]. The maternal phenotype is a distinct psychophysiological state that can arise periodically during the female life-history after successful insemination by a male. It is identifiable by distinctive neurological, hormonal, and morphological changes which can be understood as a type of mammalian “metamorphosis.” These changes prepare females for the sometimes extreme physiological, behavioral, and energetic demands of motherhood.

Among many maternal changes associated with reproduction are the development of added fat stores [69], significant remodeling of the uterus to enable gestation for developing fetus [70,71], modifications to the cervix and uterus near the time of delivery to enable parturition [72,73], remodeling of mammary glands to enable lactation after birth [158], and the development of a novel and temporary maternal bodily organ, the placenta, specifically designed to provide nutrients to the developing fetus during gestation [74]. There is also evidence of “rewiring” of the maternal brain [75,76], including distinct changes to axonal projections from hypothalamic magnocellular neurons responsible for transporting oxytocin throughout the central nervous system which takes place near the time of birth [77].

Many of these changes, including the neurological and physiological changes that facilitate parturition and lactation, are known to be mediated by hormonal processes that include the hormone oxytocin (Tai, et al., 2021). Without oxytocin lactation is impossible [78], and stereotypical maternal behavior post-partum is found to be significantly impaired [79]. Oxytocin, and its receptor, therefore represent critical components in the development of the maternal phenotype in mammals. In addition, in mammals to enabling the maternal phenotype, as we will see, oxytocin is also central to the overall health of the mother thereby serving as a possible mechanism through which caregiving may relate to health and longevity [39].

5. Maternal longevity

All of the aforementioned changes that comprise the maternal phenotype benefit offspring but require significant energy and time investments from the mother. As only one example, the energetic demands of lactation are enormous, increasing nearly 2-fold above pre-pregnancy levels in some species (e.g. Ref. [80]. Surprisingly, despite these added physiological challenges encountered by mammalian females, females remain remarkably resilient to both the internal and external mortality risks that threaten survival during adulthood. As one example, despite the high metabolic costs of reproduction, including elevated levels of oxidative stress [81], women who have more children are more likely to live to old age than those who have fewer [163] and may age more slowly as measured by telomere length [82].

Another example is found in the consistent sex difference in longevity across mammalian species, such that females tend to live significantly longer than males who generally bear little of the physiological burden of childcare. This observation has long puzzled evolutionary biologists [83–85]. Some researchers have speculated that this putative sex difference may be attributable to differences in vulnerabilities or exposures to various environmental hazards [2]. Mammalian males experience higher levels of mortality even in embryological life and other factors, such as genetic dissimilarities in sex-chromosome content (i.e. the "heterogametic sex hypothesis") and/or asymmetric inheritance of mitochondrial DNA, which might contribute to some of the variation in longevity between the sexes [86,87].

An alternative explanation argues that the burden of defensive behaviors and risky sexually selected traits, such as male-male aggression, could leave males at a longevity disadvantage [88,89]. Along these same lines, the "immunocompetence handicap hypothesis" (ICHH [57,90]; states that increased levels of testosterone required for the male life history strategy and to increase male reproductive potential might also function as an immunosuppressant leading to decreased immunocompetence and subsequent health consequences, thus ultimately impairing male health and longevity. For example, evidence of an inhibitory effect of testosterone on oxytocin signaling and parental behavior in mice [91] suggests that mammalian males face a fitness trade-off not encountered by their female counterparts which may help explain some of the variation in longevity between the sexes. Here we build on these lines of thinking by focusing on another key difference in life history strategies between male and female mammals – investment in offspring. The prolonged exposure in females to certain hormones, including oxytocin, associated with the female reproductive strategy (including gestation, lactation, and parental investment) may also function to facilitate long-term health in the adult phenotype [39].

Support for this idea can be found in a notable exception to the pattern of female-biased longevity among mammals which relates mating behavior. Unlike polygynous species which tend to conform to the general rule, significant sex differences in survivorship and longevity are less apparent among socially monogamous species [84]. One explanation for this observation that has been tested in anthropoid primate species is the parental care hypothesis. Allman and associates [92] have proposed that female mammals may live longer lives than their male counterparts because of an obligate reproductive role as caregivers. In support of this hypothesis, they reported that among anthropoid primates, in those species that exhibit uncommonly high levels of paternal care (such as Owl and Titi monkeys) males actually carry the longevity advantage [92]. However, whether males of such species live comparably longer lives as a direct result of caregiving traits and behaviors or whether their longevity advantage is due to another factor associated with this derived male life history (e.g. a lowered likelihood of engaging in certain risky and damaging behaviors such as male-male aggression) is still debated. Regardless, parenting behaviors (both maternal and paternal) in Titi monkeys have been shown to be directly regulated in part by oxytocin receptor binding in the brain, and parents (of either sex) exhibit higher oxytocin receptor binding levels than non-parents [93]. Given the emerging link between oxytocin and health [39]; and below), it is plausible that caregiving, via oxytocin signaling pathways, might explain a significant proportion of the variance in longevity among animal classes that exhibit varying levels of caregiving in the species' life histories.

The Social Dependency Hypothesis thus extends the parental care hypothesis beyond anthropoid primates and to all animal taxa where a subset of species have evolved to rely on caregiving from bonded conspecifics for survival. In this essay we focus on mammals, where conserved physiological processes, including the oxytocin system, that enable caregiving from mothers, allomothers, in even fathers and other related conspecifics are of particular importance. We further hypothesize that the expression of the mammalian caregiver phenotype (by any mature adult, male or female) and the various social, behavioral, and physiological changes that come with it, as mediated in part by oxytocin signaling throughout the brain and body, could be a key life history factor in establishing the long-term health and longevity of an individual during adulthood.

6. Oxytocin as a mechanism underlying mammalian longevity and the Social Dependency Hypothesis

Physiological and behavioral mechanisms that act to influence all forms of social support and create a context of psychological and emotional safety hold the potential to improve the quality of life and extend the lifespan [31]. As summarized below, oxytocin and its unique receptor, are particularly attractive candidates for central factors in social dependency and love [39,62,94] and the physiology of longevity [95]. Alternatively, factors such as early life stress, which hold the capacity to reduce the effects of the oxytocin system and epigenetically upregulate the vasopressin system, the hypothalamic-pituitary-adrenal axis and immune system may have the opposite consequences (reviewed [13,58,96].

The oxytocin molecule and its unique receptor were initially thought to be only involved in the processes of birth and lactation. While both processes are important functions of the oxytocin system, the belief that oxytocin was only relevant to one sex (females) and in one context (reproduction) led to a misconception that significantly hampered research into the various evolutionary and developmental functions of this pleiotropic molecule.

As described above, the fundamental role of this hormonal system in enabling maternal processes offers support for this Social Dependency Hypothesis of Longevity. But natural selection has not limited the functionality of oxytocin to the maternal phenotype. Oxytocin is expressed and active in males, infants, and reproductively naïve adults, and in all known bodily systems. For reasons summarized here briefly, and in more detail elsewhere, oxytocin is implicated in essentially all aspects of mammalian life from conception to death [97–100]. Building on these and many other discoveries, oxytocin has become a focal point for investigations into biological basis for reproduction, social behavior and good health, promoting us to ask "Is oxytocin 'Nature's' medicine?" [39].

Despite a rich literature now directly linking oxytocin to positive mental and physical health outcomes (described below and reviewed elsewhere by Refs. [39,101,102] and many others), less attention has been directed toward an explicitly proposed anti-aging role of oxytocin in either an evolutionary or medical context. [However, see Lussier et al. [95] and Stevenson, et al. [103]]. This health-focused perspective on oxytocin lends directly to a new evolutionary framework conceptualizing oxytocin's effects on sociality and social bonding, as central to adaptive calibration in mammalian life histories [13], but also toward elongating the adult lifespan in support of those bonds. A synthesis of both ultimate and proximate functions implicates oxytocin as an evolved mechanism capable of supporting caregiving-related outcomes including longevity (see Fig. 1).

Specifically, as briefly reviewed below, oxytocin has now been

directly implicated in defending against some of the established "hallmarks of aging" (see [5], including oxidative stress, inflammation, oncogenetic mutations, and telomere shortening (also see Refs. [39, 103]. Via its neurobehavioral consequences, oxytocin is further involved in defending against external threats related to environmental harshness such as parasitism, conspecific violence, predation, seasonal temperature changes, and famine. As summarized in Fig. 1 and below, all of these threats can be related to aging both within (individual differences) and across species.

Protection from oxidative damage. Oxytocin, along with several other neuropeptides synthesized in the mammalian brain, is a potent antioxidant [161]. Not only is the molecule itself an antioxidant, but oxytocin also the capacity to upregulate the activity of other endogenous antioxidants [104,105]. Oxidative stress is known to be particularly prevalent during periods of high metabolic demand and is most damaging to tissues and organs with high metabolic rates (such as the heart). It is therefore notable that oxytocin has specifically been found to decrease oxidative stress in cardiac tissue in mothers [106]. Also noteworthy are the findings that oxytocin is released in response to increases in body temperature and fever [107], and in response to physical activity, exercise, and some forms of physiological stress [108], particularly in the late stages of pregnancy and labor [109]; Sala et al., 1974; Soloff et al., 1979). A growing literature indicates that oxytocin functions, in part, to provide protection against oxidative damage particularly during periods of high metabolic demand, including pregnancy and lactation (see Refs. [39,110].

Inflammation and healing. Oxytocin has also been recently established as a central mediator of the homeostatic inflammatory protein response, both by dampening inflammatory pathways and also managing some of the deleterious after-effects of inflammation [111]. Specifically, during parturition it has been discovered that oxytocin acts as a potent anti-inflammatory molecule in the neonatal gut and brain which may protect both the fetus and the mother from the high levels of oxidative stress associated with birth [110]. Furthermore, due to its known role in managing adrenal-cortical responses, oxytocin is able to suppress inflammation and other damage caused by psychophysiological stress (e.g. Ref. [112]. In rats, oxytocin administration reduces the infarct size after an experimentally-induced heart attack [113]; reviewed [114], or stroke [115], suggesting both cardioprotective and neuroprotective properties of the molecule. In humans, high levels of oxytocin were correlated with faster wound healing [116]. Oxytocin administration also enhanced wound-healing abilities in rats that experienced burn wounds [117]. Importantly in the latter experiment a comparable, enhanced wound-healing ability was observed simply by socializing the burned rats rather than isolating them. Oxytocin also has been implicated in the management of chronic pain (including pain from chronic inflammation) and aging [95]. These and many other studies support a link between sociality and the healing power of oxytocin [39].

Telomere length. Recent evidence suggests that oxytocin also may play a role in managing telomere length in cells in a context-dependent manner. In both rats [118] and prairie voles [103], oxytocin administration prevented accelerated telomere shortening caused by social isolation. In humans, a growing literature is linking maternal characteristics to telomere length. A study of indigenous mothers of the Kaqchikel people in Guatemala suggested a link between lifetime parity and telomere length such that women with more surviving children reported longer telomeres [82]. Although oxytocin was not directly considered as a proximate mechanism in this finding, it is possible that the increased exposure to the maternal effects of oxytocin over the lifespan in these higher-fecundity human mothers may have played a role. Oxytocin is also now implicated in developmental programming in response to early life stress (reviewed [13]. In one example of this, trauma-exposed mothers with higher oxytocin levels were found to have longer telomeres in memory cytotoxic T immune cells than those with lower oxytocin [119]. These findings offer yet another mechanism, the protection of telomeres, through which oxytocin might slow down aging.

Deleterious mutations. Oxytocin also may have anti-tumor properties and therefore could serve as a defense against oncogenetic mutations leading to cancer (e.g. Ref. [120]; for review see Ref. [121] which is a mortality risk factor that increases dramatically in older age. Notably, these findings are most apparent in female-specific forms of cancer. Increases in oxytocin have been directly associated with attenuation of breast and ovarian tumors (Alizedah et al., 2018; [122]. In humans, treatment of breast cancer cells with oxytocin results in significant growth inhibition and enhances the inhibitory effect of tamoxifen (a hormone therapy used to treat breast cancer) on cell proliferation [123]. [In contrast, oxytocin does not protect and may actually facilitate the development of prostate cancers in men [121].] The discovery of these anti-cancer properties of oxytocin that specifically target organs and tissues necessary for maternal investment may be significant in linking oxytocin to female longevity. Cancers of reproductive tissues and organs, at a minimum, tend to leave females in a condition of sterility or could inhibit a female's capacity to care for an infant. The evidence that oxytocin protects against these negative effects further substantiates the link between caregiving, oxytocin, and long-term health.

Ecological threats. Although a high proportion of modern humans die of or in old age, wild animals rarely live long enough to die of such causes, but are often eliminated by a combination of intrinsic and extrinsic threats before the onset of senescence. The same is assumed of our hunter-gatherer ancestors living in the environment of evolutionary adaptiveness (see Ref. [124]. As posited by the evolutionary theory of aging (briefly discussed above), an assembly of extrinsic threats (sometimes conceptualized as "environmental harshness" [125]; are thought to limit the ability for natural selection to eliminate deleterious internal risks (such as deleterious somatic mutations) that arise late in the lifespan and therefore can be directly associated to aging. Some of these external threats include the hazards of predation, parasitism, famine, dramatic seasonal temperature changes, and conspecific violence (Fig. 1).

A recent review by Lucas & Keller (2019) has outlined an important role of sociality as an influence affecting senescence and longevity as these threats are related to environmental harshness. They identify social defense, social vigilance, social cooperation among the mechanisms through which extrinsic mortality threats can be reduced in social species, thereby enabling selection for reduced rates of aging. Although not specifically implicated in this theoretical framework, oxytocin is known to be involved in most of the social and behavioral traits that help social communities defend against environmental harshness. These include social grooming or preening behaviors which can be protective against parasitism and infection (e.g. Refs. [36,126–128], group favoritism which can be protective against conspecific violence (e.g. Refs. [129, 130], social communication [131], social attachments [62,132], and seasonal behavioral changes that enable enhanced thermoregulatory abilities, for example as is seen in some species of birds (e.g. seasonal flocking in sparrows, see Ref. [133] and in mammals (e.g. seasonal group-living in meadow voles, see Ref. [134]; huddling in mice, [135]. On the topic of thermoregulation, there is also evidence that oxytocin, in conjunction with multiple other hormones in the hypothalamo-pituitary axis, is involved in thermogenesis [136–139]. Thermoregulation is a particularly notable oxytocin-mediated innovation for survival in a harsh environment as it is thought to have been elemental to the evolution of mammals and is fundamental to the parental strategies of endothermic animals [140–142], such as mammals, birds, and some species of reptile (e.g. female pythons, Van Mierop and Barnard, 1978; tegu lizards, Tattersall et al., 2016; for review see Farmer, 2016).

All of the behavioral traits mentioned above represent novel social solutions to adaptive problems that are not seen in many other classes of animal. However, it is important to note that these various oxytocin-mediated socio-defensive abilities are found not just in humans [143], but across mammals [94,128,144], and importantly also in birds (e.g. Refs. [36,131,133], suggesting that the longevity-enhancing effects of oxytocin and sociality, as proposed here and by others (e.g. Lucas &

Keller, 2019), may exist elsewhere in the vertebrate tree of life.

7. A theoretical paradigm for the oxytocin system

The emerging body of evidence, sampled briefly above, directly implicates oxytocin in the defense against many of the most well-established properties of aging, granting a window into a mechanism through which mammals and other vertebrates manage health and survive later into adulthood. Due to the conservation of oxytocin pathways throughout the vertebrate lineage (see Ref. [11], this mechanism may not only account for some of the individual differences in aging rates within species, but also species-level variation in longevity at multiple levels of phylogenetic organization. Oxytocin not only offers a possible mechanism for maternal, socio-behavioral, or emotional effects relevant to the role of caretaking in aging (e.g. Ref. [30], it also contributes to health and resilience across the lifespan [13,39]. The discovery and/or rediscovery of environmental contexts and stimuli that engage the oxytocin system, resulting in a natural upregulation of oxytocin pathways and increased exposure to this natural "medicine" provides an exciting new direction for medical and gerontological research (e.g. Ref. [95].

Although many of the intricacies of the workings of the oxytocin system are still emerging, evidence already exists revealing a number of natural stimuli that can either up or downregulate oxytocin pathways by neuroendocrine or epigenetic processes which thus may serve to modulate human health outcomes. This may be accomplished in the early stages of life by developmental programming (see Ref. [13], but also by certain exposures in adulthood (e.g. Refs. [145,146]. A parallel rodent literature further supports this developmental plasticity of oxytocin as a function of stress-exposures throughout the mammalian lifespan (for review see Ref. [96].

For the purposes of this paper, the most relevant context by which oxytocin pathways are altered throughout life are in the changes associated with the mother-offspring bond. Female mammals, upon entering the maternal stage of life, are exposed to increases in circulating oxytocin (e.g. Ref. [109]; Sala et al., 1974; Soloff et al., 1979) and typically experience an upregulation of oxytocin receptors throughout the brain and body (Fuchs et al., 1984). Increased numbers of oxytocin neurons and neuronal fibers extending from the hypothalamus have also been reported in lactating vs sexually naïve rat dams [77].

This robust upregulation of the oxytocin system has previously been thought to function in support of the physiological attributes of parturition and lactation (e.g. uterine contractions, milk ejection). Although oxytocin may be directly involved in these processes, it also possible that this upregulation functions indirectly to boost maternal immunity, relieve oxidative stress levels, and improve overall health and longevity. This offers yet another perspective regarding how and why oxytocin may be so crucial for maternal behavior and physiology. Without oxytocin, mothers not only may be unable to express many of the key physiological requirements of motherhood, but also may be left at significantly greater risk of morbidity or mortality thus damaging the potential for reproductive success of their offspring. From this perspective childbearing and childrearing, which is normally dependent on an intact oxytocin system, may help explain the overall female advantage in longevity in humans and in other mammals.

Unlike most other mammal species where males lack participation in the childrearing effort, human males play an important role in facilitating the success of offspring. Interestingly, while in some species there are notable sex differences in oxytocin activity, in humans and other highly social mammals such as prairie voles, sex differences are less pronounced (reviewed [42,147]. Although most mammalian males do not experience the dramatic upregulation to the oxytocin system in reproductive and neural tissues that is experienced by females during birth, exceptions such as the human species exist where emerging evidence suggests a similar, albeit lesser upregulation of oxytocin signaling in the transition to human fathering and provides support for the importance of oxytocin in fathers and other male caregivers [51].

As described elsewhere, males have the capacity to produce and use oxytocin, but they also may be more reliant on a more evolutionarily ancient and androgen-dependent molecule, vasopressin [54,94,147,148]. Interestingly, in direct contrast to oxytocin, vasopressin has been implicated in chronic inflammation, diabetes, hypertension, osteoporosis, and more (reviewed [58]. In addition to the advantages associated with oxytocin, an asymmetric male dependence on vasopressin could provide insights regarding the observed sex differences in longevity. Still, it is notable that during the early period of offspring development, during parent-child interactions, human fathers expressed levels of salivary oxytocin comparable to those in mothers [149]. As reviewed in Ref. [51]; increases in plasma oxytocin levels paired with decreases in salivary testosterone levels (and other changes) coincide with the transition into a caregiving/fatherly role among humans. It is possible that due to the derived evolutionary role as male caregivers, in relation to most other mammalian males, human males might also carry a large capacity for oxytocin upregulation when placed in an explicit caregiving role. For example, testosterone metabolites may upregulate oxytocin [56]. This in turn could enable the at least some of the health and longevity benefits experienced by their female counterparts.

If human males have evolved the capacity for upregulation of oxytocin pathways during fatherhood, then what other human experiences might enable this hypothesized longevity and health-enhancing physiological change? If we look beyond direct parenting roles and consider the many other caregiving roles available to humans, we find that healthy humans of both sexes have the innate capacity to care for and provide love and support to others. These roles can be directed to juveniles or to society as a whole (i.e. social work, civil service, military service, etc.). Love, both given and received, is now known to be one of the most crucial components associated with a long and healthy life [31]. The evidence described above places the oxytocin system at the center of a biobehavioral system linking the expression of love to both our individual health and longevity.

8. A Social Dependency Hypothesis and modern human society

Unlike ancestral human societies, where a long life was synonymous with a healthy life, modern humans in developed countries have become increasingly dependent on medical or technological solutions. The past century was marked by a decline in overall physical and mental health in developed countries [150]. In the 20th century more Americans than ever died from physical health problems such as cardiovascular disease [151] and cancer [159], or from mental health problems including suicide [152].

This decline in overall human health has been obscured in part by a simultaneous improvement in medical technology. While beneficial to our overall life expectancy, this technology is associated with a great economic cost. For example, in the United States, medical care now costs a staggering $3.8 trillion per year, or more than $11,000 per citizen – roughly 18% of our national GDP (according to CMS.gov). The state of mental and physical illness in our modern world is further underscored by the estimated 48.3 million surgical procedures that take place every year in the U.S. and the fact that ~50% of Americans rely on prescription medication [153].

Evolution has already endowed humans with the biological substrates needed to live in a state of physical and mental health more than 100 years (Figs. 1 and 2). However, until now, our medical systems have often failed to recognize the importance of socio-environmental and behavioral contexts that permit this exceptional longevity. Of course, the oxytocin system does not act alone, but it may offer insight into an evolved and comparatively modern physiological mechanism that lends to an appreciation of mammalian, and especially human sociality, and indirectly lead us towards improved health and longevity. Here we suggest that the greatest tools we have towards fulfilling the evolved limit of human survivorship may not be found in drugs or surgery, but

rather in the natural "medicines" associated with the evolved human instinct to love and care for one another.

Declaration of competing interest

The authors Alex Horn and Sue Carter have no competing interests to declare.

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