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Loneliness Across Phylogeny and a Call for Comparative Studies and Animal Models

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Abstract

Loneliness typically refers to the feelings of distress and dysphoria resulting from a discrepancy between a person's desired and achieved levels of social relations, and there is now considerable evidence that loneliness is a risk factor for poor psychological and physical health. Loneliness has traditionally been conceptualized as a uniquely human phenomenon. However, over millions of years of evolution, efficient and manifold neural, hormonal, and molecular mechanisms have evolved for promoting companionship and mutual protection/assistance and for organizing adaptive responses when there is a significant discrepancy between the preferred and realized levels of social connection. We review evidence suggesting that loneliness is not a uniquely human phenomenon, but, instead, as a scientific construct, it represents a generally adaptive predisposition that can be found across phylogeny. Central to this argument is the premise that the brain is the key organ of social connections and processes. Comparative studies and animal models, particularly when integrated with human studies, have much to contribute to the understanding of loneliness and its underlying principles, mechanisms, consequences, and potential treatments.

Keywords

social neuroscience; loneliness; phylogeny; animal models; mechanisms

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Nearly everyone has felt the distress of separation from a loved one, the heartbreak of homesickness, the agony of bereavement, the pain of being shunned, or the anguish of unrequited love. All are variations on the human experience of loneliness that have long been the subject matter of poets, writers, and philosophers. The philosopher Jean-Paul Sartre regarded the experience of loneliness as an inevitable part of the human condition in which people are born alone, they die alone, and in the intervening period they attempt to find validation and meaning in life through their relationships with and acceptance by others (Sartre, 1956). When psychologists began studying loneliness, in their early work they focused on its phenomenology, measurement, and correlates (Peplau, Russell, & Heim, 1979; Russell, Peplau, & Cutrona, 1980). Loneliness was characterized as the aversive feelings of separateness (Lynch & Convey, 1979), alienation (Sadler, 1978), and distress and isolation aroused by the failure to satisfy a human need for intimacy (Weiss, 1973).

Peplau and Perlman (1982) suggested that an emphasis on a human need placed loneliness as a direct consequence of failure to satisfy these needs, ignoring any intervening cognitive processes. Taking an attributional perspective, Perlman and Peplau (1981) conceptualized loneliness as the discrepancy between a person's desired and achieved levels of social relations. The attributional approach helped explain how a person could feel lonely even when among family or friends or when in a crowd, and it contributed to the recognition in the contemporary literature of the importance of a person's judgment of the quality or adequacy of his or her social relationships (e.g., J. T. Cacioppo & Patrick, 2008; Hawkley et al., 2008; Wheeler, Reis, & Nezlek, 1983).

A commonality across these perspectives is the conceptualization of loneliness as a uniquely human phenomenon (see Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015, this issue). If the scientific construct of "loneliness" is defined solely in terms of a person's phenomenology or complex attributional processes, it is difficult to dispute this characterization. However, although there likely are aspects of loneliness that are uniquely human, there also is continuity across species. People's evolutionary heritage has shaped their brain and biology to incline them toward certain ways of feeling, thinking, and acting. A variety of biological mechanisms have evolved that capitalize on aversive signals to motivate people to act in ways that are essential for their reproduction or survival. Hunger is an aversive signal triggered by low blood sugar that motivates people to eat—an important early warning system for a species whose hunt for food required much more time and effort than going to the kitchen cabinet, refrigerator door, or fast food restaurant. Physical pain is an aversive signal that alerts people of potential tissue damage and motivates them to take care of their physical bodies. The signal of loneliness— triggered by a discrepancy between an individual's preferred and actual social relations—may similarly be part of a biological warning system that has evolved to warn a person of threats or damage to his or her social body, which as a member of a social species is also needed to survive, prosper, and reproduce.

Loneliness as a Biological Adaptation

The thesis of this article is that loneliness is not a uniquely human phenomenon, but, instead, as a scientific construct, loneliness represents a generally adaptive predisposition in response

to a discrepancy between an animal's preferred and actual social relations that can be found across phylogeny. This thesis does not rest on anthropomorphic depictions of nonhuman animals but on behavioral measures, such as the partner preference assessment in prairie voles (Young, Lim, Gingrich, & Insel, 2001) or social preference assessment in monkeys (Capitanio, Hawkley, Cole, & Cacioppo, 2014; Mendoza & Mason, 1986a). Sociality carries costs (e.g., competition for food and mates; increased risk of pathogen transmission) as well as benefits (e.g., more "eyes and ears" to detect predators; cooperative hunting strategies; mother–infant attachment). The variations in social structures and behaviors relevant to the benefits of sociality and to mitigating the costs of sociality have contributed to the diversity in social organization across species. There may be aspects of loneliness (beyond access to self-report data) that are unique to humans (e.g., suicidal behavior), but that is an empirical question for comparative study. The scientific study of other psychological constructs—including hunger, pain, fear, and depression—has proceeded productively without treating a person's report of experiences as a defining attribute. In each case, comparative studies and animal models have advanced the understanding of these scientific constructs in human and nonhuman animals.

Consequences of human loneliness

Why might the concept of loneliness warrant such study? A substantial literature now shows that loneliness is a major risk factor for adverse physical and mental outcomes (e.g., S. Cacioppo, Grippo, London, Goossens, & Cacioppo, 2015, this issue; Holt-Lunstad et al., 2015). For instance, we determined the association between loneliness and mortality in 2002, and over the subsequent 6 years we investigated social relationships, health behaviors, and morbidity as potential mechanisms through which loneliness affects mortality risk among older Americans (Luo, Hawkley, Waite, & Cacioppo, 2012). Results showed that loneliness was associated with increased mortality risk over the 6-year period and that neither health behaviors nor objective features of social relationships (e.g., marital status, proximity to friends or family) could explain the association between loneliness and mortality. Although researchers using mechanistic studies in humans have identified a variety of biological pathways through which loneliness may produce these effects (cf. J. T. Cacioppo, Cacioppo, Capitanio, & Cole, 2015), experimental and mechanistic studies in which researchers use animal models are needed to better understand the specific neural, hormonal, and molecular mechanisms underlying these various effects and to determine cognitive, behavioral, and pharmacological interventions for dealing with loneliness and its harmful effects on health, social behavior, and well-being.

Relevance of animal studies

To date, there is no animal literature on loneliness per se, but there is a large literature in which animals are randomly assigned to normal social living conditions, to socially isolated living conditions, or to social living conditions separated from a preferred partner. These animal models were developed independently of the human research on loneliness to investigate the effects of environmental enrichment/isolation on brain plasticity, learning, and behavioral organization (e.g., Markham & Greenough, 2004; Mason, 1970; Rosenzweig, Bennett, Hebert, & Morimoto, 1978) or to investigate various behavioral disorders and putative treatments (e.g., depression, anxiety, schizophrenia, aggressive behavior; e.g., Nin,

Martinez, Pibiri, Nelson, & Pinna, 2011; Valzelli, 1973; Wallace et al., 2009). Recent animal models of the effects of social loss on depression (e.g., Bosch, Nair, Ahern, Neumann, & Young, 2009; Nin et al., 2011; Sun, Smith, Lei, Liu, & Wang, 2014) may be especially noteworthy given that social loss represents a discrepancy between an animal's preferred and actual social relations (i.e., loneliness) and that the extant research indicates that loneliness leads to increased depressive behavior (as shown later in the article).

Both human and animal research (cf. J. T. Cacioppo, Capitanio, & Cacioppo, 2014; J. T. Cacioppo & Hawkley, 2009) indicates that loneliness is not equivalent to objective social isolation. The importance of the discrepancy between conspecific preference and realized social condition is nicely illustrated in research in which social preference is tested (e.g., with measures of social distance between cage mates, proximity within arm's reach) among members of two species: the monogamous titi monkeys and the polygynous squirrel monkeys. Following 1 hr of social isolation from their pair mates, the titi monkeys (for whom partner preference is high) showed a significant increase in plasma cortisol, whereas the squirrel monkeys (for whom partner preference is relatively low) did not (Mendoza & Mason, 1986a). In contrast, the titi monkeys did not show hypothalamic– pituitary–adrenocortical (HPA) activation when separated from their infants, whereas the separation of squirrel monkey mothers from their infants produced significant increases in HPA activation (e.g., Mendoza & Mason, 1986b).

The diversity in social behavior in animals suggests that loneliness is not merely an inevitable consequence of social isolation but is manifested differently on the basis of the organization of the brain and the nature of the relationship of the animal to a conspecific. For example, montane voles live a solitary lifestyle and, therefore, are unlikely to express loneliness-like physiology and behavior when socially isolated compared with prairie voles. Prairie vole pups, in contrast to montane vole pups, emit ultrasonic vocalizations when isolated and secrete high levels of corticosterone (Shapiro & Insel, 1990). Comparative studies in animals with diverse social organizations might be especially informative. Indeed, comparative studies and animal models, especially when integrated with human research, have the potential to transform the literature on the construct of loneliness. In many cases, the adaptations of other social animals and people's own adaptations share similarities, suggesting that much of what researchers thought was unique to being human may not be quite as unique as they thought. This is not to say that there is nothing unique about the human species but only that people may be largely naïve about or unaware of much of what governs their behavior on a daily basis because significant aspects of the underlying neural structures and processes may have evolved long before humans walked the earth.

In addition, understanding how other social species negotiate their environments can help people understand adaptations that are different from their own and advance their understanding of their own adaptations. For instance, a well-characterized response to maternal separation in a variety of species—including rats, voles, and humans—is the separation cry. In the rat, the separation cry is in the ultrasonic range. As Hofer (2009) noted,

> The evolution of such a response is clarified by the finding that infant rat [ultrasonic vocalization] is a powerful stimulus for the lactating rat, capable of causing her to interrupt an ongoing nursing bout, initiate searching outside the nest, and direct her search toward the source of the calls … The mother's retrieval response to the pup's vocal signals then results in renewed contact between pup and mother. This contact, in turn, quiets the pup. (p. 20)

The same ultrasonic vocalizations that guide the mother to the infant can also lead predators to the infant. Ultrasonic vocalizations, therefore, may be beneficial or deleterious depending on the presence of predators in the environment. As a consequence, no single level of intensity of ultrasonic vocalizations to isolation is universally best, and heritable individual differences in this predisposition exist in the population (Hofer, 2009). In contrast, there is no separation cry in the baby Komodo dragon because adult Komodo dragons are cannibals: "Advertising vulnerability makes sense only for those animals whose brains can conceive of a parental protector" (Lewis, Amini, & Lannon, 2000, p. 26).

The human and animal literatures are large, and the size and complexity of these literatures are magnified when considering the effects of social isolation from conception to death. Given researchers' focus on loneliness in an aging U.S. population as a risk factor for poor wellbeing, morbidity, and mortality, we focus here on the literature on adults. For a review of loneliness in children and adolescents, see Qualter et al. (2015, this issue).

Causes of Loneliness

Behavioral genetic analyses indicate that loneliness has a sizeable heritable component, consistent with the notion that loneliness represents an evolutionary development (J. T. Cacioppo, Cacioppo, & Boomsma, 2014; see Goossens et al., 2015, this issue). Strong environmental influences on loneliness have also been identified. For instance, lower levels of loneliness are associated with marriage (Hawkley, Browne, & Cacioppo, 2005; Pinquart & Sőrensen, 2003) as well as higher education and income (Savikko, Routasalo, Tilvis, Strandberg, & Pitkala, 2005), whereas higher levels of loneliness are associated with living alone (Routasalo, Savikko, Tilvis, Strandberg, & Pitkala, 2006), infrequent contact with friends and family (Bondevik & Skogstad, 1998; Hawkley et al., 2005; Mullins & Dugan, 1990), physical health symptoms (Hawkley et al., 2008), chronic work or social stress (Hawkley et al., 2008), small social network (Hawkley et al., 2005; Mullins & Dugan, 1990), lack of a spousal confidant (Hawkley et al., 2008), marital or family conflict (Segrin, 1999), poor quality social relationships (Hawkley et al., 2008; Mullins & Dugan, 1990; Routasalo et al., 2006), and divorce and widowhood (Dugan & Kivett, 1994; Samuelsson, Andersson, & Hagberg, 1998).

Although related to factors such as marital status, frequency of contact with friends and family, and participation in voluntary organizations, loneliness is not reducible to these social factors or to simply being alone (e.g., J. T. Cacioppo et al., 2000; Hawkley et al., 2008; Wheeler et al., 1983). Solitude expresses the glory of being alone, whereas loneliness expresses the pain of feeling alone (Tillich, 1959). The consequences of objective and perceived social isolation (i.e., loneliness) can differ in part because of individual differences

in the extent to which individuals choose to form and maintain social relationships—variations that have often been characterized in terms of introversion. Whereas introversion refers to the preference for low levels of social involvement (Eysenck, 1947), loneliness refers to the perception that one's social relationships are inadequate in light of his or her preferences for social involvement, and it is stochastically and functionally distinct from introversion (J. T. Cacioppo, Hawkley, et al., 2006).

In addition, the brain is the key organ for forming, monitoring, maintaining, repairing, and replacing salutary connections with others as well as for regulating physiological processes relevant to morbidity and mortality. The human brain does not simply respond to stimuli in an invariant fashion; instead, it categorizes, abstracts, interprets, and evaluates incoming stimuli in light of current states and goals as well as prior knowledge and predispositions. Consequently, an individual may perceive the same objective social relationship (e.g., a sibling) as caring and protective or as callous and threatening on the basis of a host of factors, including the individual's prior experiences, current attributions, and overall preference for social contact. Although physical/objective social isolation may increase the risk for loneliness, individuals can also feel lonely in a marriage, friendship, family, schoolyard, or congregation. The idea that the brain is the key organ of social connections and processes should be true for other species for which companionship (e.g., attachment, pair bonding) and mutual protection and support have been central features of life for millions of years.

Loneliness and Self-Preservation

There may be several processes that favor the aversive state of loneliness across phylogeny (e.g., the rewarding nature of pair bonding/monogamy and the aversive nature of partner loss), with self-preservation exerting an especially powerful selective pressure. Consider, for instance, the absence of companionship and mutual protection/assistance—of being on the social perimeter—as a signal for danger. For mammals, the absence of a caregiver early in life threatens the survival of the infant. Even as adults, a chief threat to reproductive success and survival in many species comes from other members of that species. In this context, an aversive signal—triggered by the perception that companionship and mutual protection/assistance are absent or at risk—may be highly adaptive. Loneliness can be conceptualized as an aversive signal that motivates an individual to take action that minimizes damage to his or her social body to promote short-term self-defense and self-preservation.

Self-preservation is used here, not in reference to an explicit (i.e., conscious) goal but as the probabilistic outcome of a behavioral predisposition orchestrated by the brain. Fish on the edge of a group are more likely to be attacked by predators. This is not due to their being the slowest or weakest but to the ease of isolating and preying on those on the social perimeter. As a result, fish have evolved to swim to the middle of the group when a predator attacks (Ioannou, Guttal, & Couzin, 2012). The behavioral expression of self-preservation by fish when on the social perimeter illustrates a more general principle: Perceived social isolation—detecting a discrepancy between an animal's preferred and actual social relations—activates neural, neuroendocrine, and behavioral responses that promote short-term survival.

Social isolation from a preferred partner has been shown to increase vigilance for predatory threats in mammals as well as fish. For instance, prairie voles, when isolated from their pair-bonded partner and subsequently placed in an open field, show less exploratory behavior and more predator evasion than prairie voles that have been housed with their partner (Grippo et al., 2014). These behaviors reflect an increased emphasis on self-defense when on the social perimeter, an emphasis that increases the likelihood of surviving to leave a genetic legacy. However adaptive loneliness might be in an evolutionary sense, chronic loneliness may be maladaptive in contemporary society given the increase in human longevity, social mobility, and the transience of people's social interactions and relationships.

Social withdrawal, anxiety, and depressive symptomatology

Loneliness in humans has been shown to increase dysphoria, anxiety, and social withdrawal. In an experimental study in which loneliness was manipulated in a sample of young adults, for instance, participants expressed higher levels of depressed affect, anxiety, shyness, and fear of negative evaluation in the lonely, rather than nonlonely, condition (J. T. Cacioppo, Hawkley, et al., 2006). Similarly, longitudinal studies, including those in which researchers used population-based samples of adults, have shown that loneliness predicts increases in depressive symptomatology beyond what can be explained by prior levels of depressive symptomatology (J. T. Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006; Heikkinen & Kauppinen, 2004; VanderWeele, Hawkley, Thisted, & Cacioppo, 2011; Wei, Russell, & Zakalik, 2005) and beyond what can be predicted by associated psychosocial variables, such as objective stress, perceived stress, social network size, neuroticism, and social support (J. T. Cacioppo, Hawkley, & Thisted, 2010; see S. Cacioppo et al., 2015).

Among the early animal models of depression were those based on maternal separation and social isolation in early life (e.g., Sanchez, Ladd, & Plotsky, 2001). Social separation in adulthood also produces behavioral indicators of depression, anxiety, or social withdrawal in a number of species, including the monogamous prairie vole (e.g., Grippo, Cushing, & Carter, 2007; Sun et al., 2014), the Sprague–Dawley rat (e.g., Barrot et al., 2005; Wallace et al., 2009), the Wistar rat (e.g., Evans, Sun, McGregor, & Connor, 2012), and the rhesus monkey (Suomi, Eisele, Grady, & Harlow, 1975). Chronic social isolation in many of these species now serves as an animal model for studying depression and anxiety as well as treatment responses (e.g., Martin & Brown, 2010; Nin et al., 2011).

Depression may be adaptive for animals (Allen & Badcock, 2003; Bosch et al., 2009), and the influence of loneliness on depression is easily incorporated into this line of reasoning. For instance, depression and social withdrawal resulting from loneliness diminish the likelihood that an individual encounters foes from which there is no escape, the likelihood that an individual attempts to force his or her way back into a group from which he or she was excluded, and the likelihood of the transmission of an infectious disease to others (J. T. Cacioppo et al., 2014). By acting on depressive symptomatology, loneliness also increases the likelihood that an individual will exhibit facial displays, postural displays, and acoustic signals that may serve as a call for others to come to his or her aid to provide companionship and support. Whether this passive strategy succeeds and benefits the individual depends on the social environment, such as the likelihood that a caring conspecific will see and be

willing and able to respond to the distress cues before predators or foes take advantage of the affected individual.

Attention

If fish and rodents that lack companionship and mutual protection/assistance show an increased vigilance for predatory threats, what effects does loneliness have on attention in humans? In many contexts across human history, a chief threat to a person's survival and reproductive success has come from other humans. There is growing evidence that loneliness increases certain aspects of attention toward negative social stimuli (e.g., social threats, rejection, and exclusion). Correlational research shows that lonely, compared with nonlonely, individuals worry more about being evaluated negatively and feel more threatened in social situations (even when they are not more likely to be rejected; Jones, Freemon, & Goswick, 1981), and similar differences have been found when loneliness is manipulated experimentally (J. T. Cacioppo, Hawkley, et al., 2006).

Several studies suggest that the effect of loneliness on attention to potential social threats may be largely implicit, perhaps reflecting its deep evolutionary roots on brain structures and processes (S. Cacioppo, Capitanio, & Cacioppo, 2014). First, using a modified emotional Stroop task, we have shown that lonely participants, relative to nonlonely participants, exhibit greater Stroop interference for negative social, relative to negative nonsocial, words (Egidi, Shintel, Nusbaum, & Cacioppo, 2008)—consistent with the idea that loneliness is associated with a heightened accessibility of negative social information. Second, the results of an investigation of the effects of subliminal priming on the detection of painful facial expressions showed that loneliness was associated with greater sensitivity to the presence of pain in dislikable faces, as gauged by the sensitivity index, d', from signal detection theory (Yamada & Decety, 2009). Third, in an eye-tracking study, lonely and nonlonely young adults viewed various positive and negative social scenes and exhibited different fixation patterns. Individuals high in loneliness were more likely to first fixate on and to spend a greater proportion of their initial viewing time looking at socially threatening stimuli in a social scene, whereas individuals low in loneliness were more likely to first fixate on and to spend a greater proportion of their initial view time looking at positive stimuli in a social scene (Bangee, Harris, Bridges, Rotenberg, & Qualter, 2014). Finally, functional magnetic resonance imaging research is also consistent with a heightened attention to social threats in the lonely brain. For instance, loneliness is associated with greater activation of the visual cortex in response to negative social images, in contrast to negative nonsocial images (J. T. Cacioppo, Norris, Decety, Monteleone, & Nusbaum, 2009).

A possible consequence of loneliness and the implicit hypervigilance for social threats and self-defense is that lonely, compared with nonlonely, individuals may be less likely to focus on the needs of others and may be more likely to focus on their own self-preservation in adverse situations. Activation in the temporoparietal junction has been found previously to be associated with the performance of tasks involving empathy, theory of mind, and perspective taking. Although loneliness was positively related to visual cortical activation in response to negative social, in contrast to nonsocial, stimuli, loneliness was inversely related to amount of activation observed in the temporoparietal junction—as would be expected if

social threats, even when directed toward others, were especially likely to promote self-preservation in the lonely brain (J. T. Cacioppo et al., 2009).[1]

Sleep

If it is dangerous to fend off predatory threats with a stick by oneself, then it should be especially dangerous to lay down to sleep at night when predators are out and an individual does not have a safe social surround. We therefore reasoned that the end of the day might not bring an end to the lonely brain's high alert state. In the first test of this reasoning in lonely versus nonlonely young adults, we investigated sleep efficiency as measured by objective Nightcap recordings and the Pittsburgh Sleep Quality Inventory (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Results indicated that loneliness was related to more microawakenings and less restful sleep (e.g., higher reports of daytime fatigue). These results could not be explained in terms of differences in sleep duration, depressive symptomatology, or other risk factors (J. T. Cacioppo, Hawkley, Berntson, et al., 2002).

To examine whether the lonely brain remains relatively vigilant during sleep or whether people who show less restful sleep are more likely to become lonely, we asked older adults in the Chicago Health, Aging, and Social Relations Study to complete end-of-day diaries on 3 consecutive days (Hawkley, Preacher, & Cacioppo, 2010). Diary questions probed sleep duration, daytime dysfunction (e.g., fatigue, sleepiness), loneliness, physical symptoms, and depressed affect experienced that day. Cross-lagged panel models were used to examine the magnitude of reciprocal prospective associations between loneliness and daytime dysfunction, and statistical controls were introduced for race/ethnicity, sleep duration, marital status, household income, chronic health conditions, health symptom severity, and depressive symptomatology. Analyses revealed that daily variations in loneliness predicted feelings of daytime dysfunction the next day, whereas daytime dysfunction did not significantly predict subsequent loneliness (Hawkley, Preacher, & Cacioppo, 2010).

Researchers on loneliness and poor sleep have used adults across a wide range of ages, but all the participants have been from urban environments. We therefore investigated the extent to which loneliness was associated with sleep fragmentation in a communal, agrarian society living in South Dakota (Kurina et al., 2011). Ninety-five participants wore a wrist actigraph for 1 week to measure sleep fragmentation and sleep duration, and self-reports were used to measure loneliness, depression, anxiety, stress, and subjective aspects of sleep. Results showed that loneliness was associated with significantly higher levels of sleep fragmentation even after controlling for covariates such as age, sex, depression, anxiety, and perceived stress.

[1]Although it may seem counterintuitive that loneliness would both motivate an individual to repair or replace social connections and implicitly bias the individual to be more suspicious of others, consider the basic motivational state of hunger, which increases an organism's attention to and drive for food. Not everything that appears edible is safe to eat, and taste buds have evolved to be much more sensitive to bitter than to sweet. Poisons tend to have a bitter taste, so this difference in sensitivity is thought to have evolved to protect the individual from dangers that arise as a result of the drive to find food. Consequently, individuals are more likely to forego edible bitter foods than edible sweet foods. Interactions with people can also be figuratively poisonous or nutritious. Given it is more costly to fall victim to a fatal assault at the hands of another than to forego a friendship that one may pursue later, becoming more sensitive to social threats may also be adaptive, especially in environments populated by dangerous foes, even though loneliness also explicitly increases attention to positive and negative social stimuli in the environment.

To our knowledge, there has been only one study in which researchers investigated the effects of social isolation on sleep in adult animals. Adult male (C57BL/6J) mice that were socially isolated for 5 weeks, compared with pair-housed mice, showed a marked reduction in electroencephalography (EEG) delta power in nonrapid eye movement sleep during baseline conditions. The socially isolated, compared with pair-housed, mice also showed a blunted homeostatic sleep response to acute sleep deprivation. Both isolated and pair-housed mice showed increases in EEG delta power in nonrapid eye movement sleep following sleep deprivation, but this increase in EEG delta power did not persist throughout the dark period in socially isolated mice, indicating less deep sleep and poorer sleep quality compared with matched pair-housed mice. This difference was still evident 18 hr after deprivation (Kaushal, Nair, Gozal, & Ramesh, 2012).

Physiological activation

Loneliness may activate neurobiological mechanisms that promote self-preservation in the short-term, but the heightened vigilance for social threats brings with it a heightened preparatory response for responding to potential assaults and a toll on health and well-being in the long-term. Elevated resistance to blood flow through the cardiovascular system (i.e., vascular resistance) has served as a marker of threat surveillance in humans (Mendes, Blascovich, Lickel, & Hunter, 2002), and loneliness has been associated with higher tonic levels of vascular resistance in laboratory studies (J. T. Cacioppo, Hawkley, Crawford, et al., 2002) and during the course of a normal day (Hawkley, Burleson, Berntson, & Cacioppo, 2003). Consistent with this effect in humans, research in socially isolated, compared with socially housed, prairie voles indicates that chronic isolation of these typically monogamous animals induces alterations in cellular functioning in the vasculature (e.g., the release of vascular contracting factors in endothelial cells) that contribute to higher levels of vascular resistance (Peuler, Scotti, Phelps, McNeal, & Grippo, 2012).

Elevated vascular resistance in young adults is a risk factor for higher blood pressure later in life. In cross-sectional (J. T. Cacioppo, Hawkley, Crawford, et al., 2002) and longitudinal studies (Hawkley, Thisted, Masi, & Cacioppo, 2010) of older adults, loneliness has been associated with higher blood pressure. In an experimental study of cardiovascular activity in adult male baboons, Coelho, Carey, and Shade (1991) contrasted three social housing conditions: (a) individual housing (social isolation), (b) the standard housing with a social companion, and (c) housing with a social stranger. These conditions made it possible to evaluate the effects of the loss of companionship and mutual protection/assistance as well as the effects of social isolation per se. Social isolation per se was not the important factor: Solitary housing and housing with an unfamiliar animal were associated with higher blood pressure than housing with a social companion (Coelho et al., 1991).

Loneliness in human adults has also been associated with alterations in neuroendocrine functioning (for a review, see J. T. Cacioppo, Cacioppo, Capitanio, & Cole, 2015). For instance, the HPA axis is an important component of the neuroendocrine system that regulates reactions to stress as well as physiological functions, including metabolism, digestion, immunity, as well as energy storage and expenditure. Among the major hormones produced in the HPA axis are glucocorticoids (e.g., cortisol in humans, coricosterone in

rodents), which act on glucocorticoid receptors. Loneliness has been associated with larger morning rises in cortisol (e.g., Adam, Hawkley, Kudielka, & Cacioppo, 2006), higher circulating glucocorticoid levels (e.g., Doane & Adam, 2010), and decreased glucocorticoid receptor sensitivity (Cole, 2008; Cole et al., 2007), indicating higher levels of HPA activation. Various species of rodents and nonhuman primates similarly show increased activation of the HPA axis when chronically isolated as an adult from a preferred partner (e.g., a pair bond). For instance, studies show that prairie voles that are chronically isolated from their pair-bonded partner show increased corticosterone levels (e.g., Bosch et al., 2009; McNeal et al., 2014; Sun et al., 2014) and higher corticosterone levels after a resident–intruder test (Grippo, Cushing, & Carter, 2007), whereas prairie voles that are chronically isolated from a conspecific for whom partner preference is low (e.g., same sex sibling) show no such increase in corticosterone levels (e.g., Bosch et al., 2009; Grippo, Gerena, et al., 2007). As noted earlier, similar effects have been found in other monogamous species, including nonhuman primates (e.g., Mendoza & Mason, 1986a, 1986b).

Complexities

Although several similarities in the effects of social isolation from a preferred partner have been found in the extant human and animal literatures, there are also important inconsistencies (cf. J. T. Cacioppo et al., 2014, 2015). Small sample sizes and underpowered studies, coupled with an emphasis on null hypothesis testing, likely have contributed to some of these inconsistencies (see Button et al., 2013). In addition, the complexity of social life within and across species and sex makes it challenging to define the loss of salutary social bonds in other species. An animal model should have face validity (isomorphism), predictive validity (correlated outcome), and construct validity (homology and similarity in the underlying neurobiological mechanisms; Fuchs & Flügge, 2006; Willner, 1991). What constitutes face validity can vary as a function of expertise, however, and one often does not know enough about the underlying neurobiological mechanism in humans for this criterion to be particularly useful when evaluating the results of animal research (Fuchs & Flügge, 2006). Advances in the understanding of recent ancestry and similarity in underlying neuroanatomy may point toward some models being useful than others for certain functional outcomes.

The most appropriate animal model may depend on the specific mechanism under scrutiny as well as the nature of the relationship among conspecifics. For example, social isolation of male adult rodents is generally associated with a substantial reduction in physical activity and a notable decrease in fighting and other overtly aggressive behavior. Once reintroduced into social settings, isolated male rodents often display a greater propensity for aggressive behavior (Blanchard, McKittrick, & Blancard, 2001), which has parallels in the increased negativity and hostility observed in lonely individuals (J. T. Cacioppo, Hawkley, et al., 2006). In small rodent models, repeated social threat from an aggressive conspecific may provide a model for important aspects of the chronic sense of social threat and hostility seen in lonely humans. In the animal model for repeated social threat, neuroendocrine responses and cellular glucocorticoid resistance are activated (Hanke, Powell, Stiner, Bailey, & Sheridan, 2012; Powell et al., 2013), similar to those observed in lonely humans (Cole, 2008; Cole, Hawkley, Arevalo, & Cacioppo, 2011; Cole et al., 2007). Experimental

molecular studies in mice in which this paradigm was used suggest that the proinflammatory gene regulation dynamics are also similar to those observed in lonely humans (Cole et al., 2011, 2007). These results suggest that a variety of animal models may be productively used to examine the mechanisms underlying different loneliness-related processes. Consideration of loneliness as a biological adaptation common to many social species makes it possible to take full advantage of the toolkit available from animal research and to expand the understanding of psychological, physiological, and genetic underpinnings of this construct.

Conclusion

Social species, by definition, create emergent organizations beyond the individual—structures ranging from dyads and families to societies. These social structures and associated behaviors evolved hand in hand with neural, hormonal, and genetic mechanisms to support them because their net effect helped these organisms survive and reproduce. One of the benefits of sociality is mutual protection and assistance, and being isolated or on the social perimeter can represent a dangerous circumstance. The cumulative research suggests that the brain has evolved to put individuals into a short-term, self-preservation mode when they find themselves without companionship or mutual protection/assistance. As noted in this review, the range of neural and behavioral effects includes the following: (a) increased implicit vigilance for social threats and self-defense along with increased anxiety, hostility, and social withdrawal to avoid predation; (b) increased sleep fragmentation to avoid predation during sleep; (c) elevated vascular activity and heightened HPA activity to deal with potential assaults that may arise; and (d) increased depressive symptomatology, for instance, as nonverbal means of signaling the need for support and connection. These effects extend beyond early developmental periods through mechanisms in the adult brain that permit adaptation to the functional demands of a fluid social environment. Although these neural and behavioral responses may increase the likelihood of short-term survival, they also carry long-term costs, especially when the normal life span is extended and when isolation becomes chronic.

If there are deep evolutionary roots tilting the human brain and biology toward short-term self-preservation when a person feels socially isolated, then at least part of what is triggered when individuals feel lonely should be nonconscious and should be evident in nonhuman animals under comparable social conditions for that species. We have reviewed evidence that loneliness increases the explicit desire to connect with others, but it also appears to produce an implicit hypervigilance for social threats—perhaps an adaptation of the predator evasion and aggressiveness documented previously in socially isolated rodents (Hofer, 2009; Kaushal et al., 2012). This priming for social threats, in turn, can lead to attentional, confirmatory, and memory biases that lead an individual to think and act toward others in a more negative fashion than otherwise would be the case, which, in turn, can increase negative interactions with others (e.g., Duck, Pond, & Leatham, 1994)—all while leaving the lonely individual unaware of his or her contributions to or control over the hostile interactions with others (Rotenberg, 1994).

Studies of the influence of environmental and genetic factors on loneliness in humans still have much to contribute to the understanding of the antecedents and consequences of

loneliness across the life span and to the development of effective social, cognitive, and behavioral treatments. However, comparative studies and animal models—especially when integrated with this human literature—have an important role in advancing the understanding of longer term origins of the antecedents and consequences of loneliness; the adaptive and maladaptive aspects of loneliness within specific ecological niches; the neurobiological and molecular mechanisms underlying loneliness; and potential social, behavioral, and pharmacological treatments to address the deleterious effects of loneliness on health and well-being.

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