



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

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Complete List of Authors:	Cacioppo, John; University of Chicago, Department of Psychology Cacioppo, Stephanie; University of Chicago, Center for Cognitive and Social Neuroscience Cole, Steven; UCLA, Medicine Capitanio, John; University of California, Davis, California National Primate Research Center Goossens, Luc; KULeuven - University of Leuven, School Psychology and Child and Adolescence Boomsma, Dorret; VU University Amsterdam,
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5 **Loneliness Across Phylogeny and**
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7 **A Call for Comparative Studies and Animal Models**
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10
11
12 John T. Cacioppo Stephanie Cacioppo

13
14 University of Chicago

15
16 Steven W. Cole

17
18 University of California, Los Angeles

19
20 John P. Capitanio

21
22 University of California, Davis

23
24 Luc Goossens

25
26 KULeuven - University of Leuven

27
28 Dorret I. Boomsma

29
30 VU University Amsterdam

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45 Address correspondence to the first author at the University of Chicago, Center for
46
47 Cognitive and Social Neuroscience, 940 E. 57th Street, Chicago, IL 60637, or to
48
49 Cacioppo@uchicago.edu. Preparation of this article was supported by the National Institute on
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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 our understanding of loneliness and its underlying principles, mechanisms, consequences, and potential treatments.

Loneliness across Phylogeny and A Call for Comparative Studies and Animal Models

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. When psychologists began studying loneliness, the early work 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., Hawkey 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, this issue). If the scientific construct of "loneliness" is defined solely in terms of a person's phenomenology or complex attributional

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3 processes, it is difficult to dispute this characterization. However, although there likely are
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5 aspects of loneliness that are uniquely human, there also is continuity across species. Our
6
7 evolutionary heritage has shaped our brain and biology to incline us toward certain ways of
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9 feeling, thinking, and acting. A variety of biological mechanisms have evolved that capitalize on
10
11 aversive signals to motivate us to act in ways that are essential for our reproduction or survival.
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13 Hunger is an aversive signal triggered by low blood sugar that motivates us to eat – an important
14
15 early warning system for a species whose hunt for food required much more time and effort than
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17 going to the kitchen cabinet, refrigerator door, or fast food restaurant. Physical pain is an
18
19 aversive signal that alerts us of potential tissue damage and motivates us to take care of our
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21 physical body. The signal of loneliness -- triggered by a discrepancy between an individual's
22
23 preferred and actual social relations-- may similarly be part of a biological warning system that
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25 has evolved to warn us of threats or damage to our social body, which as a member of a social
26
27 species we also need to survive, prosper, and reproduce.
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33 **Loneliness as a Biological Adaptation**

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36 The thesis of this paper is that loneliness is not a uniquely human phenomenon but
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38 instead, as a scientific construct, loneliness represents a generally adaptive predisposition in
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40 response to a discrepancy between an animal's preferred and actual social relations that can be
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42 found across phylogeny. This thesis does not rest on anthropomorphic depictions of nonhuman
43
44 animals but on behavioral measures such as the partner preference assessment in prairie voles
45
46 (Young, Lim, Gingrich, & Insel, 2001) or social preference assessment in monkeys (Capitanio,
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48 Hawkey, Cole, & Cacioppo, in press; Mendoza & Mason, 1986a). Sociality carries costs (e.g.,
49
50 competition for food and mates; increased risk of pathogen transmission) as well as benefits
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52 (e.g., more "eyes and ears" to detect predators; cooperative hunting strategies; mother-infant
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54 attachment). The variations in social structures and behaviors relevant to the benefits of sociality
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3 and to mitigating the costs of sociality have contributed to the diversity in social organization
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5 across species. There may be aspects of loneliness (beyond access to self-report data) that are
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7 unique to humans (e.g., suicidal behavior), but that is an empirical question for comparative
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9 study. The scientific study of other psychological constructs, including hunger, pain, fear, and
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11 depression, has proceeded productively without treating a person's report of experiences as a
12
13 defining attribute. In each case, comparative studies and animal models have advanced our
14
15 understanding of these scientific constructs in human and nonhuman animals.
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18 19 **Consequences of Human Loneliness**

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21 Why might the concept of loneliness warrant such study? A substantial literature now
22
23 shows that loneliness is a major risk factor for adverse physical and mental outcomes (e.g., S.
24
25 Cacioppo, Grippo, London, Goosens, & Cacioppo, this issue; Holt-Lunstad & Smith, this issue).
26
27 For instance, we determined the association between loneliness in 2002 on mortality over the
28
29 subsequent 6 years, and we investigated social relationships, health behaviors, and morbidity as
30
31 potential mechanisms through which loneliness affects mortality risk among older Americans
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33 (Luo, Wait, Hawkey, & Cacioppo, 2012). Results showed that loneliness was associated with
34
35 increased mortality risk over the 6-year period and that neither health behaviors nor objective
36
37 features of social relationships (e.g., marital status, proximity to friends or family) could explain
38
39 the association between loneliness and mortality. Although mechanistic studies in humans have
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41 identified a variety of biological pathways through which loneliness may produce these effects
42
43 (cf. Cacioppo, Cacioppo, Capitanio, & Cole, in press), experimental and mechanistic studies
44
45 using animal models are needed to better understand the specific neural, hormonal, and
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47 molecular mechanisms underlying these various effects and to determine cognitive, behavioral,
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49 and pharmacological interventions for dealing with loneliness and its harmful effects on health,
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51 social behavior, and well-being.
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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, and/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, Herbert, & 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 social loss represents a discrepancy between an animal's preferred and actual social relations (i.e., loneliness) and the extant research shows that loneliness leads to increased depressive behavior (see below).

Both the human and animal research (cf. Cacioppo et al., in press; 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 testing social preference (e.g., using 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 monkey. Following 1 hour 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 HPA activation when

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3 separated from their infant, whereas the separation of squirrel monkey mothers from their infant
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5 produces significant increases in HPA activation (e.g., Mendoza & Mason, 1986b).
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8 The diversity in social behavior in animals suggests that loneliness is not merely an
9
10 inevitable consequence of social isolation, but is manifested differently based on the organization
11
12 of the brain and the nature of the relationship of the animal to a conspecific. For example,
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14 montane voles live a solitary lifestyle, and therefore are unlikely to express loneliness-like
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16 physiology and behavior when socially isolated compared to prairie voles. Prairie vole pups, in
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18 contrast to montane vole pups, emit ultrasonic vocalizations when isolated and secrete high
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20 levels of corticosterone (Shapiro & Insel, 1990). Comparative studies in animals with diverse
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22 social organizations might be especially informative. Indeed, comparative studies and animal
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24 models, especially when integrated with human research, have the potential to transform the
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26 literature on the construct of loneliness. In many cases, the adaptations of other social animals
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28 and our own adaptations share similarities, suggesting that much of what we thought was unique
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30 to being human may not be quite as unique as was thought. This is not to say there is nothing
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32 unique about our species, but only that we may be largely naïve about or unaware of much of
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34 what governs our behavior on a daily basis because significant aspects of the underlying neural
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36 structures and processes may have evolved long before humans walked the earth.
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43 In addition, understanding how other social species negotiate their environments can help
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45 us understand adaptations that are different from our own and advance our understanding of our
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47 own adaptations. For instance, a well-characterized response to maternal separation in a variety
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49 of species, including rats, voles, and our own, is the separation cry. In the rat, the separation cry
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51 is in the ultrasonic range. As Hofer (2009) notes:
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55 The evolution of such a response is clarified by the finding that infant rat [ultrasonic vocalization]
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57 is a powerful stimulus for the lactating rat, capable of causing her to interrupt an ongoing nursing
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59 bout, initiate searching outside the nest, and direct her search toward the source of the calls...The
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3 mother's retrieval response to the pup's vocal signals then results in renewed contact between pup
4 and mother. This contact, in turn, quiets the pup (Hofer, 2009, p. 20).

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

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

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Causes of Loneliness

Behavioral genetic analyses indicate that loneliness has a sizeable heritable component, consistent with the notion that loneliness represents an evolutionary development (Cacioppo, Cacioppo, & Boomsma, 2014; see Goossens et al., 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; Pinqart & Sørensen, 2003), and 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.,

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3 2008), chronic work and/or social stress (Hawkley et al., 2008), small social network (Hawkley
4 et al., 2005; Mullins & Dugan, 1990), lack of a spousal confidant (Hawkley et al., 2008), marital
5 or family conflict (Segrin, 1999), poor quality social relationships (Hawkley et al., 2008; Mullins
6 & Dugan, 1990; Routasalo et al., 2006), and divorce and widowhood (Dugan & Kivett, 1994;
7 Samuelsson, Andersson, & Hagberg, 1998).

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15 Although related to factors such as marital status, frequency of contact with friends and
16 family, and participation in voluntary organizations, loneliness is not reducible to these social
17 factors or to simply being alone (e.g., Cacioppo et al., 2000; Hawkley et al., 2008; Wheeler et al.,
18 1983). Solitude expresses the glory of being alone, whereas loneliness expresses the pain of
19 feeling alone (Tillich, 1959). The consequences of objective and perceived social isolation (i.e.,
20 loneliness) can differ in part due to individual differences in the extent to which individuals
21 choose to form and maintain social relationships –variations that have often been characterized
22 in terms of introversion. Whereas introversion refers to the preference for low levels of social
23 involvement (Eysenck, 1947), loneliness refers to the perception that one's social relationships
24 are inadequate in light of their preferences for social involvement and is stochastically and
25 functionally distinct from introversion (Cacioppo et al., 2006a).

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

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17 There may be a variety of processes that favor the aversive state of loneliness across
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19 phylogeny (e.g., the rewarding nature of pair bonding/monogamy and the aversive nature of
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21 partner loss), with self-preservation exerting an especially powerful selective pressure. Consider,
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23 for instance, the absence of companionship and mutual protection/assistance – of being on the
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25 social perimeter – as a signal for danger. For mammals, the absence of a caregiver early in life
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27 threatens the survival of the infant. Even as adults, a chief threat to reproductive success and
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29 survival in many species comes from other members of that species. In this context, an aversive
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31 signal–triggered by the perception that companionship and mutual protection/assistance are
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33 absent or at risk – may be highly adaptive. Loneliness can be conceptualized as an aversive
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35 signal that motivates individuals to take action that minimizes damage to their social body to
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37 promote short-term self-defense and self-preservation.
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43 Self-preservation is used here, not in reference to an explicit (i.e., conscious) goal, but as
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45 the probabilistic outcome of a behavioral predisposition orchestrated by the brain. Fish on the
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47 edge of a group are more likely to be attacked by predators. This is not due to their being the
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49 slowest or weakest, but to the ease of isolating and preying upon those on the social perimeter.
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51 As a result, fish have evolved to swim to the middle of the group when a predator attacks
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53 (Ioannou, Guttal, & Couzin, 2012). The behavioral expression of self-preservation by fish when
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55 on the social perimeter illustrates a more general principle: perceived social isolation – detecting
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3 a discrepancy between an animal's preferred and actual social relations – activates neural,
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5 neuroendocrine, and behavioral responses that promote short-term survival.
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8 Social isolation from a preferred partner has been shown to increase vigilance for
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10 predatory threats in mammals as well as fish. For instance, prairie voles when isolated from their
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12 pair-bonded partner and subsequently placed in an open field, show less exploratory behavior
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14 and more predator evasion than prairie voles who have been housed with their partner (Grippe et
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16 al., in press). These behaviors reflect an increased emphasis on self-defense when on the social
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18 perimeter, an emphasis that increases the likelihood of surviving to leave a genetic legacy.
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20 However adaptive loneliness might be in an evolutionary sense, chronic loneliness may be
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22 maladaptive in contemporary society given the increase in human longevity, social mobility, and
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24 the transience of our social interactions and relationships.
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28 **Social Withdrawal, Anxiety and Depressive Symptomatology**

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31 Loneliness in humans has been shown to increase dysphoria, anxiety, and social
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33 withdrawal. In an experimental study in which loneliness was manipulated in a sample of young
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35 adults, for instance, participants expressed higher levels of depressed affect, anxiety, shyness,
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37 and fear of negative evaluation in the lonely than nonlonely condition (Cacioppo et al., 2006a).
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39 Similarly, longitudinal studies, including those using population-based samples of adults, have
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41 shown that loneliness predicts increases in depressive symptomatology above and beyond what
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43 can be explained by prior levels of depressive symptomatology (Cacioppo, Hughes, Waite,
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45 Hawkley, & Thisted, 2006b; Heikkinen & Kauppinen, 2004; VanderWeele et al., 2011; Wei,
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47 Russell, & Zakalik, 2005) and beyond what can be predicted by associated psychosocial
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49 variables such as objective stress, perceived stress, social network size, neuroticism, and social
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51 support (Cacioppo, Hawkley, & Thisted, 2010; see S. Cacioppo et al., this issue).
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3 Among the early animal models of depression were those based on maternal separation
4 and social isolation in early life (e.g., Sanchez, Ladd, & Plotsky, 2001). Importantly, social
5 separation in adulthood also produces behavioral indicators of depression, anxiety, and/or social
6 withdrawal in a number of species, including the monogamous prairie vole (e.g., Grippo,
7 Cushing, & Carter, 2007a; Sun et al., 2014), the Sprague-Dawley rat (e.g., Barrot et al., 2005;
8 Wallace et al., 2009), the Wistar rat (e.g., Evans, Sun, McGregor, & Connor, 2012), the
9 C57BL/6J mouse (Martin & Brown, 2009), and the rhesus monkey (Suomi, Eisele, Grady, &
10 Harlow, 1975). Chronic social isolation in many of these species now serves as an animal model
11 for studying depression and anxiety and treatment responses (e.g., Martin & Brown, 2010; Nin et
12 al., 2011).
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26 Depression may be adaptive for animals (Allen & Badcock, 2003; Bosch et al., 2009),
27 and the influence of loneliness on depression is easily incorporated into this line of reasoning.
28 For instance, depression and social withdrawal resulting from loneliness diminish the likelihood
29 that an individual encounters foes from which there is no escape, attempts to force its way back
30 into a group from which it was excluded, and the likelihood of the transmission of an infectious
31 disease to others (Cacioppo et al., 2014). By acting on depressive symptomatology, loneliness
32 also increases the likelihood that an individual will exhibit facial displays, postural displays, and
33 acoustic signals that may serve as a call for others to come to its aid to provide companionship
34 and support. Whether this passive strategy succeeds and benefits the individual depends on the
35 social environment, such as the likelihood that a caring conspecific will see and be willing and
36 able to respond to the distress cues before predators or foes take advantage of the affected
37 individual.
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54 **Attention**

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3 If fish and rodents that lack companionship and mutual protection/assistance show an
4 increased vigilance for predatory threats, what effects does loneliness have on attention in
5 humans? In many contexts across human history, a chief threat to a person's survival and
6 reproductive success has come from other humans. There is growing evidence that loneliness
7 increases certain aspects of attention toward negative social stimuli (e.g., social threats, rejection,
8 and exclusion). Correlational research shows that lonely, compared to nonlonely, individuals
9 worry more about being evaluated negatively and feel more threatened in social situations (even
10 when they are not more likely to be rejected; Jones, Freemon, & Goswick, 1981), and similar
11 differences have been found when loneliness is manipulated experimentally (Cacioppo et al.,
12 2006a).

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26 Several studies suggest that the effect of loneliness on attention to potential social threats
27 may be largely *implicit*, perhaps reflecting its deep evolutionary roots on brain structures and
28 processes (S. Cacioppo, Capitano, & Cacioppo, in press). Using a modified emotional Stroop
29 task, lonely participants, relative to nonlonely participants, show greater Stroop interference for
30 negative social, relative to negative non-social, words (Egidi, Shintel, Nusbaum, & Cacioppo,
31 2008), consistent with the idea that loneliness is associated with a heightened accessibility of
32 negative social information. Second, the results of an investigation of the effects of subliminal
33 priming on the detection of painful facial expressions showed that loneliness was associated with
34 greater sensitivity to the presence of pain in dislikable faces, as gauged by the sensitivity index,
35 d' , from signal detection theory (Yamada and Decety (2009). Third, in an eye tracking study,
36 lonely and nonlonely young adults viewed various positive and negative social scenes and
37 exhibited different fixation patterns. Individuals high in loneliness were more likely to first
38 fixate on and to spend a greater proportion of their initial viewing time looking at socially
39 threatening stimuli in a social scene, whereas individuals low in loneliness were more likely to
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3 first fixate on and spend a greater proportion of their initial view time looking at positive stimuli
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5 in a social scene (Bangee, Harris, Bridges, Rotenberg, & Qualter, 2014). Finally, functional
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7 magnetic resonance imaging (fMRI) research is also consistent with a heightened attention to
8
9 social threats in the lonely brain. For instance, loneliness is associated with greater activation of
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11 the visual cortex in response to negative social images, in contrast to negative nonsocial images
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13 (Cacioppo et al., 2009).
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17 A possible consequence of loneliness and the implicit hypervigilance for social threats
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19 and self-defense is that lonely, compared to nonlonely, individuals may be less likely to focus on
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21 the needs of others and more likely to focus on their own self-preservation in adverse situations.
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23 Activation in the temporoparietal junction (TPJ) has been found previously to be associated with
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25 the performance of tasks involving empathy, theory of mind, and perspective taking. Although
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27 loneliness was positively related to visual cortical activation in response to negative social, in
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29 contrast to nonsocial, stimuli, loneliness was inversely related to amount of activation observed
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31 in the TPJ – as would be expected if social threats, even when directed toward others, were
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33 especially likely to promote self-preservation in the lonely brain (Cacioppo et al., 2009).¹
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38 Sleep

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40 If it is dangerous to fend off predatory threats with a stick by oneself, then it should be
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42 especially dangerous to lay down to sleep at night when predators are out and an individual does
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44 not have a safe social surround. We therefore reasoned that the end of the day might not bring an
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50 ¹ Although it may seem counterintuitive that loneliness would both motivate an individual to repair or replace social
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52 connections and implicitly bias the individual to be more suspicious of others, consider the basic motivational state
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54 of hunger, which increases an organism's attention to and drive for food. Not everything that appears edible is safe
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56 to eat, and taste buds have evolved to be much more sensitive to bitter than to sweet. Poisons tend to have a bitter
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58 taste, so this difference in sensitivity is thought to have evolved to protect the individual from dangers that arise as
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60 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 while
loneliness also explicitly increases attention to positive and negative social stimuli in the environment.

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3 end to the lonely brain's high alert state. In the first test of this reasoning in lonely versus
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5 nonlonely young adults, we investigated sleep efficiency as measured by objective Nightcap
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7 recordings and the Pittsburgh Sleep Quality Inventory. Results indicated that loneliness was
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9 related to more microawakenings and less restful sleep (e.g., higher reports of daytime fatigue).
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11 These results could not be explained in terms of differences in sleep duration, depressive
12
13 symptomatology, or other risk factors (Cacioppo et al., 2002a).
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18 To examine whether the lonely brain remains relatively vigilant during sleep or people
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20 who show less restful sleep are more likely to become lonely, older adults in the Chicago Health,
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22 Aging, and Social Relations Study were asked to complete end-of-day diaries on three
23
24 consecutive days (Hawley et al., 2010a). Diary questions probed sleep duration, daytime
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26 dysfunction (e.g., fatigue, sleepiness), loneliness, physical symptoms, and depressed affect
27
28 experienced that day. Cross-lagged panel models were used to examine the magnitude of
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30 reciprocal prospective associations between loneliness and daytime dysfunction, and statistical
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32 controls were introduced for race/ethnicity, sleep duration, marital status, household income,
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34 chronic health conditions, health symptom severity, and depressive symptomatology. Analyses
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36 revealed that daily variations in loneliness predicted feelings of daytime dysfunction the next
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38 day, whereas daytime dysfunction did not significantly predict subsequent loneliness (Hawley
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40 et al., 2010a).
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46 The research on loneliness and poor sleep has used adults across a wide range of ages,
47
48 but all have been from urban environments. We therefore investigated the extent to which
49
50 loneliness was associated with sleep fragmentation in a communal, agrarian society living in
51
52 South Dakota (Kurina et al., 2011). Ninety five participants wore a wrist actigraph for one week
53
54 to measure sleep fragmentation and sleep duration, and self-reports were used to measure
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56 loneliness, depression, anxiety, stress, and subjective aspects of sleep. Results showed that
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3 loneliness was associated with significantly higher levels of sleep fragmentation even after
4
5 controlling for covariates such as age, sex, depression, anxiety, and perceived stress.
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8 To our knowledge, there has been only one study investigating the effects of social
9
10 isolation on sleep in adult animals. Adult male (C57BL/6J) mice who were socially isolated for 5
11
12 weeks, compared to pair-housed, showed a marked reduction in EEG delta power in NREM
13
14 sleep during baseline conditions. The socially isolated, compared to pair-housed, mice also
15
16 showed a blunted homeostatic sleep response to acute sleep deprivation. Both isolated and pair-
17
18 housed mice showed increases in EEG delta power in NREM sleep following sleep deprivation,
19
20 but this increase in EEG delta power did not persist throughout the dark period in socially
21
22 isolated mice, indicating less deep sleep and poorer sleep quality compared to matched pair-
23
24 housed mice. This difference was still evident 18 hours after deprivation (Kaushal, Nair, Gozal,
25
26 & Ramesh, 2012).
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30 31 **Physiological Activation** 32

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34 Loneliness may activate neurobiological mechanisms that promote self-preservation in
35
36 the short-term, but the heightened vigilance for social threats brings with it a heightened
37
38 preparatory response for responding to potential assaults and a toll on health and well-being in
39
40 the long-term. Elevated resistance to blood flow through the cardiovascular system (i.e., vascular
41
42 resistance) has served as a marker of threat surveillance in humans (Mendes, Blascovich, Lickel,
43
44 & Hunter, 2002), and loneliness has been associated with higher tonic levels of vascular
45
46 resistance in laboratory studies (Cacioppo et al., 2002b) and during the course of a normal day
47
48 (Hawkley, Burleson, Berntson, & Cacioppo, 2003). Consistent with this effect in humans,
49
50 research in socially isolated, compared to socially housed, prairie voles indicates that chronic
51
52 isolation of these typically monogamous animals induces alterations in cellular functioning in the
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3 vasculature (e.g., the release of vascular contracting factors in endothelial cells) that contribute to
4
5 higher levels of vascular resistance (Peuler, Scotti, Phelps, McNeal, & Grippo, 2012).
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7
8 Elevated vascular resistance in young adults is a risk factor for higher blood pressure later
9
10 in life. In cross-sectional (Cacioppo et al., 2002b) and longitudinal studies (Hawkey et al.,
11
12 2010b) of older adults, loneliness has been associated with higher blood pressure. Interestingly,
13
14 an experimental study of cardiovascular activity in adult male baboons contrasted three social
15
16 housing conditions: (a) individual housing (social isolation), (b) the standard housing with a
17
18 social companion, and (c) housing with a social stranger. These conditions made it possible to
19
20 evaluate the effects of the loss of companionship and mutual protection/assistance, and the
21
22 effects of social isolation per se. Social isolation per se was not the important factor: solitary
23
24 housing and housing with an unfamiliar animal were associated with higher blood pressure than
25
26 housing with a social companion (Coelho, Carey, & Shade, 1991).
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31
32 Loneliness in human adults has also been associated with alterations in neuroendocrine
33
34 functioning (for a review, see Cacioppo, Cacioppo, Capitanio, & Cole, 2015). For instance, the
35
36 hypothalamic pituitary adrenocortical (HPA) axis is an important component of the
37
38 neuroendocrine system that regulates reactions to stress as well as physiological functions
39
40 including metabolism, digestion, immunity, and energy storage and expenditure. Among the
41
42 major hormones produced in the HPA axis are glucocorticoids (e.g., cortisol in humans,
43
44 corticosterone in rodents), which act on glucocorticoid receptors. Loneliness has been associated
45
46 with larger morning rises in cortisol (e.g., Adam et al., 2006), higher circulating glucocorticoid
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48 levels (e.g., Doane & Adam, 2010), and decreased glucocorticoid receptor sensitivity (Cole,
49
50 2008; Cole et al., 2007), indicating higher levels of HPA activation. Various species of rodents
51
52 and nonhuman primates similarly show increased activation of the HPA axis when chronically
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54 isolated as an adult from a preferred partner (e.g., a pair bond). For instance, studies in prairie
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3 voles show that animals that are chronically isolated from their pair-bonded partner show
4
5 increased corticosterone levels (e.g., Bosch et al., 2009; McNeal et al., 2014; Sun et al., 2014)
6
7 and higher corticosterone levels after a resident-intruder test (Grippe et al., 2007a), whereas
8
9 prairie voles that are chronically isolated from a conspecific for whom partner preference is low
10
11 (e.g., same sex sibling) show no such increase in corticosterone levels (e.g., Bosch et al., 2009;
12
13 Grippe et al., 2007b). As noted above, similar effects have been found in other monogamous
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15 species, including non-human primates (e.g., Mendoza & Mason, 1986ab).
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18 19 **Complexities**

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21 Although a number of similarities in the effects of social isolation from a preferred
22
23 partner have been found in the extant human and animal literatures, there are also important
24
25 inconsistencies (cf. Cacioppo et al., in press). Small sample sizes and underpowered studies,
26
27 coupled with an emphasis on null hypothesis testing, likely have contributed to some of these
28
29 inconsistencies (see Button et al., 2013). In addition, the complexity of social life within and
30
31 across species and sex makes it challenging to define the loss of salutary social bonds in other
32
33 species. An animal model should have face validity (isomorphism), predictive validity
34
35 (correlated outcome), and construct validity (homology and similarity in the underlying
36
37 neurobiological mechanisms) (Willner, 1991; Fuchs & Flügge, 2006). What constitutes face
38
39 validity can vary as a function of expertise, however, and one often does not know enough about
40
41 the underlying neurobiological mechanism in humans for this criterion to be particularly useful
42
43 when evaluating the results of animal research (Fuchs & Flügge, 2006). Advances in our
44
45 understanding of recent ancestry and similarity in underlying neuroanatomy may point towards
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47 some models being more useful than others for certain functional outcomes.
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55 The most appropriate animal model may depend on the specific mechanism under
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57 scrutiny as well as the nature of the relationship between conspecifics. For example, social
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3 isolation of male adult rodents is generally associated with a substantial reduction in physical
4
5 activity and a notable decrease in fighting and other overtly aggressive behavior. Once
6
7 reintroduced into social settings, isolated male rodents often display a greater propensity for
8
9 aggressive behavior (Blanchard et al., 2001), which has parallels in the increased negativity and
10
11 hostility observed in lonely individuals (Cacioppo et al., 2006a). In small rodent models,
12
13 repeated social threat from an aggressive conspecific may provide a model for important aspects
14
15 of the chronic sense of social threat and hostility seen in lonely humans. The animal model for
16
17 repeated social threat activates neuroendocrine responses and cellular glucocorticoid resistance
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19 (Hanke et al., 2012; Powell et al., 2013) similar to those observed in lonely humans (Cole et al.,
20
21 2007, 2011; Cole 2008). Experimental molecular studies in mice using this paradigm suggest
22
23 that the pro-inflammatory gene regulation dynamics are also similar to those observed in lonely
24
25 humans (Cole et al., 2007, 2011). These results suggest that a variety of animal models may be
26
27 usefully employed to examine the mechanisms underlying different loneliness-related processes.
28
29 Consideration of “loneliness” as a biological adaptation common to many social species makes it
30
31 possible to take full advantage of the toolkit available from animal research, and expand our
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33 understanding of psychological, physiological, and genetic underpinnings of this construct.
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40 **Conclusion**

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42 Social species, by definition, create emergent organizations beyond the individual–
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44 structures ranging from dyads and families to societies. These social structures and associated
45
46 behaviors evolved hand in hand with neural, hormonal, and genetic mechanisms to support them
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48 because their net effect helped these organisms survive and reproduce. One of the benefits of
49
50 sociality is mutual protection and assistance, and being isolated or on the social perimeter can
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52 represent a dangerous circumstance. The cumulative research suggests that the brain has evolved
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54 to put individuals into a short-term self-preservation mode when they find themselves without
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3 companionship or mutual protection/assistance. As noted in this review, among the range of
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5 neural and behavioral effects are: (a) increased implicit vigilance for social threats and self-
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7 defense along with increased anxiety, hostility, and social withdrawal to avoid predation; (b)
8
9 increased sleep fragmentation to avoid predation during sleep; (c) elevated vascular activity and
10
11 heightened HPA activity to deal with potential assaults that may arise; and (d) increased
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13 depressive symptomatology, for instance, as nonverbal means of signaling the need for support
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15 and connection. These effects extend beyond early developmental periods through mechanisms
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17 in the adult brain that permit adaptation to the functional demands of a fluid social environment.
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19 Although these neural and behavioral responses may increase the likelihood of short-term
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21 survival, they also carry long-term costs especially when the normal lifespan is extended and
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23 isolation becomes chronic.
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29 If there are deep evolutionary roots tilting the human brain and biology toward short-term
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31 self-preservation when a person feels socially isolated, then at least part of what is triggered
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33 when individuals feel lonely should be nonconscious and should be evident in nonhuman
34
35 animals under comparable social conditions for that species. We have reviewed evidence that
36
37 loneliness increases the explicit desire to connect with others but it also appears to produce an
38
39 implicit hypervigilance for social threats – perhaps an adaptation of the predator evasion and
40
41 aggressiveness documented previously in socially isolated rodents (Hofer, 2009; Kaushal et al.,
42
43 2012). This priming for social threats, in turn, can lead to attentional, confirmatory, and memory
44
45 biases that lead an individual to think and act toward others in a more negative fashion than
46
47 otherwise would be the case, which in turn can increase negative interactions with others (e.g.,
48
49 Duck, Pond, & Leatham, 1994) – all while leaving the lonely individual unaware of their
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51 contributions to or control over the hostile interactions with others (Rotenberg, 1994).
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3 Studies of the influence of environmental and genetic factors on loneliness in humans
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5 still have much to contribute to our understanding of the antecedents and consequences of
6
7 loneliness across the lifespan and to the development of effective social, cognitive, and
8
9 behavioral treatments. However, comparative studies and animal models, especially when
10
11 integrated with this human literature, have an important role in advancing our understanding of
12
13 longer-term origins of the antecedents and consequences of loneliness, the adaptive and
14
15 maladaptive aspects of loneliness within specific ecological niches, the neurobiological and
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17 molecular mechanisms underlying loneliness, and potential social, behavioral, and
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19 pharmacological treatments to address the deleterious effects of loneliness on health and well-
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21 being.
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