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Social Relationships and Health: The Toxic Effects of Perceived Social Isolation

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Abstract

Research in social epidemiology suggests that the absence of positive social relationships is a significant risk factor for broad-based morbidity and mortality. The nature of these social relationships and the mechanisms underlying this association are of increasing interest as the population gets older and the health care costs associated with chronic disease escalate in industrialized countries. We review selected evidence on the nature of social relationships and focus on one particular facet of the connection continuum – the extent to which an individual feels isolated (i.e., feels lonely) in a social world. Evidence indicates that loneliness heightens sensitivity to social threats and motivates the renewal of social connections, but it can also impair executive functioning, sleep, and mental and physical well-being. Together, these effects contribute to higher rates of morbidity and mortality in lonely older adults.

Individualism and autonomy have long been celebrated in western cultures (e.g., Markus & Kitayama, 1991). People used to think that infants required only their materialistic needs to be addressed, and the view that physical needs (compared to social needs) are of primary importance in older adults remains widely held today. The biological fact remains that we are fundamentally a social species, and our nature is to recognize, interact, and form relationships with conspecifics. Substantial evidence has accumulated to suggest that social relationships are important for mental and physical well-being across the lifespan. Our purpose here is to provide an overview of social relationships and the effects of feeling socially isolated on people's health and welfare.

The ability to discriminate hostile from hospitable external stimuli, and especially friend from foe among conspecifics, is crucial for survival and reproductive success. Social recognition and the formation, orchestration, and maintenance of social relationships represent a surprisingly complicated set of activities. The demands of social living include (a) learning by social observation; (b) recognizing the shifting status of friends and foes; (c) anticipating and coordinating efforts between two or more individuals; (d) using language to communicate, reason, teach, and deceive others; (e) orchestrating relationships, ranging from pair bonds and families to friends, bands, and coalitions; (e) navigating complex social hierarchies, social norms, and cultural developments; (f) subjugating self-interests to the interests of the pair bond or social group in exchange for the possibility of long-term benefits; (g) recruiting support to sanction individuals who violate group norms; and (h) doing all this across time frames that stretch from a person's distant past to multiple possible futures (Dunbar, 2003; Dunbar & Shultz, 2007). The social structures we build as a species have evolved hand in hand with neural, hormonal, genetic, and molecular mechanisms to support them because the consequent social behavior helped us survive, reproduce, and ensure a genetic legacy.

The Conceptualization and Measurement of Social Relationships

Researchers traditionally tended to focus on the physical environment when investigating factors influencing health. This focus has broadened in the last few decades to include the possibility that features of one's social relationships not only impact health behaviors but might also have direct effects on the brain, biology, and health (e.g., Cacioppo, Berntson, Sheridan, & McClintock, 2000; Insel & Fernald, 2004). One of the challenges to investigate the role of social relationships on health is to define and quantify a construct as complicated and varied as "social relationships". We begin this section with a brief review to illustrate approaches to thinking about and quantifying human social relationships.

Social network analyses focus on objective characteristics of a person's relationships. Specifically, each person's social relationships are viewed in terms of network theory, with each individual constituting a node and the relationship between individuals constituting a tie (Scott, 1991). The emphasis is on relational data (how one individual relates to another) rather than attribute data (beliefs, attitudes, perceptions, or characteristics of an individual). Because relational data are defined as characteristics of a system of individuals, not of individuals (Scott, 1991), social network analysis typically ignores a person's perceptions and quantifies the connections between individuals in terms of their objective roles, frequency of contact, or obligatory ties that connect people (cf. Cacioppo, Fowler, & Christakis, 2009). Social network analysis provides a means of measuring (a) local and global arrangements or patterns of individual characteristics, such as homophily (the extent to which connected individuals are similar on some salient attribute such as age, gender, or status); (b) the location of influential individuals, such as centrality (defined in various ways to capture the impact of an individual or group on others in a social network); and (c) network dynamics, such as structural cohesion (the minimum number of people in a social network who would dissolve a group if removed).

Social network analyses can be contrasted with approaches that emphasize attribute data to produce each individual's relational mapping. An early example of this approach is Heider's (1946, 1958) balance theory, which was developed to specify a person's *internal* mapping of the world (i.e., cognitive system), the conditions for equilibrium and disequilibrium among cognitive elements and the effects of disequilibrium on a cognitive system. That is, Heider emphasized a person's internal mapping of elements of knowledge into cognitive systems, including the internal mapping of a person's social systems. For instance, Heider labeled the elements of a triadic system as *p*, which represented the participant or self; *o*, which represented another person; and *x*, which represented some issue, stimulus, event, or another person. Heider described two relations that *p* might perceive as existing between any of the two of these elements. The first he termed a sentiment relation, which reflected the value of the connection. For instance, if *p* liked *o*, then the sentiment relation was positive. The second relation discussed by Heider is the unit relation, which designates the extent to which two elements are perceived as being associated or dissociated. The roles of husband and wife constitute a positive unit relation. As noted, sentiment and unit relations reflect *p*'s perceptions of the connections of *p*, *o*, and *x*. If *p* perceived the marriage to *o* as constituting or requiring a relationship but *p* had grown to dislike *o*, then the bonds between *p* and *o* would consist of a positive unit relation and a negative sentiment relation – an imbalanced state that Heider predicted would constitute a relatively instable and unpleasant connection. A variation of this approach, advanced by Uchino and colleagues (see review by Uchino, 2013), examines the effects on health of a given bivalent sentiment bond (e.g., mild liking) toward a partner that represents either low (e.g., mild positive regard and no negative feelings) or high (e.g., very strong positive regard and strong negative feelings) level of ambivalence toward that partner (cf. Cacioppo & Berntson, 1994).

Alan Fiske (1992) proposed that four elementary relational models exist across human cultures: communal sharing, authority ranking, equality matching, and market pricing. Fiske (1992, p. 689) suggested that

> People construct complex and varied social forms using combinations of these models implemented according to diverse cultural rules. People's chief social conceptions, concerns, and coordinating criteria, their primary purposes and their principles, are usually derived from the four models; they are the schemata people use to construct and construe relationships. This means that people's intentions with regard to other people are essentially sociable, and their social goals inherently relational: People interact with others in order to construct and participate in one or another of the four basic types of social relationships.

A communal sharing relationship is characterized by an equivalence relation and has the properties of reflexivity, symmetry, and transitivity. The individuals in the dyad or group are treated as equivalent and undifferentiated, and the focus is on the similarities between individuals, not on individual identities. The equivalence relation is not fixed, however, and can vary as purposes or goals change.

Fiske characterized an equality matching relationship in terms of the equivalence of the inputs and outputs between individuals. The equality matching relationship is similar to what Clark and Mills (1979) called an exchange relationship, defined by the conferral of a provision or benefit to another that is contingent on specific and timely repayments consisting of benefits of comparable value. As Fiske (1992) noted,

> Acquaintances and colleagues who are not intimate often interact on this basis: They know how far from equality they are, and what they would need to do to even things up (p. 691).

An authority ranking relationship is characterized in terms of an asymmetry among individuals who are ordered along some linear, hierarchical social dimension. Authority relationships are reflexive, transitive, and antisymmetric. Individuals higher in rank have status, prerogatives, and privileges, whereas subordinates are typically entitled to protection and care. Fiske's(1992) formulation provides a detailed depiction of social relationships that is pan-cultural and predictive of certain aspects of interpersonal behavior, but more work is needed to determine to what extent (and, if so, specifically how) these different types of relationships have direct effects on people's brain, biology, and health.

To summarize thus far, social relationships have objective and subjective characteristics, and each aspect of social relationships is complex and varied. Among the most fundamental characteristics of social relationships are the extent to which an individual is socially isolated (objective isolation) and the extent to which the individual feels socially isolated (subjective isolation). Animal studies have focused on the former, whereas studies in humans have quantified both (Cacioppo, Hawkley, Norman, & Berntson, 2011). In animal studies, participants are randomly assigned to social isolation or normal social conditions. In studies of people, participants typically are not randomly assigned to social isolation or normal conditions but rather measurements are made of their objective and perceived social isolation. That is, people exert some choice and control over the extent to which they are objectively socially isolated.

Various measures have been developed to assess objective and subjective social isolation in humans. Objective isolation, for instance, has been measured by assigning one point for each of the following: (a) unmarried/not-cohabiting; (b) had less than monthly contact (including face-to-face, telephone, or written/e-mail contact) with one's children; (c) had less than monthly contact with other family members; (d) had less than monthly contact (including

face-to-face, telephone, or written/e-mail contact) with friends; and (e) did not participate in organizations such as social clubs or resident groups, religious groups, or committees (e.g., Steptoe et al., 2013). Scores range from 0 to 5, with higher scores indicating greater objective social isolation.

Perceived social isolation, known more colloquially as loneliness, was characterized in early scientific investigations as "a chronic distress without redeeming features" (Weiss, 1973, p. 15). Various questionnaire measures of loneliness exist, most of which avoid the word "lonely" or "loneliness" and instead rely on statements that have been found to differentiate between lonely and nonlonely individuals, such as "My social relationships are superficial" (see Russell, 1996; Russell, Peplau, & Cutrona, 1980). A variety of events in the social environment – ranging from homesickness, bereavement, and unrequited love to social rejection or isolation over which one has little or no control – can affect a person's feelings of loneliness (Cacioppo & Patrick, 2008).

Each conceptualization and measurement of social relationships described above highlights a specific aspect of the connection between conspecifics. There is also some overlap among these depictions. For instance, Fiske's (1992) communal sharing relationship has much in common with what Clark and Mills (1979) called a communal relation, defined as the noncontingent (or relatively noncontingent) conferral of a provision or benefit to another based on a concern for the other's welfare (cf. Clark & Mills, 2012). Objective and subjective isolation are also related, especially when a person has little or no control over the social environment, as when an older adult becomes disabled (Hawkley et al., 2008). Although both objective and subjective isolation have been found to impact health, the pathways through which such effects occur are somewhat different. In the remainder of this review, we focus on work showing that the extent to which an individual *feels* socially isolated (i.e., loneliness) predicts not only morbidity and mortality but also several specific deleterious physiological processes above and beyond what can be predicted by objective isolation.

Perceived Absence of Social Connection (Loneliness) and Health

The presence of stable bonds among conspecifics is a defining characteristic of social species. It should perhaps not be surprising that the absence of these connections threatens the health, life, and genetic legacy of members of many different social species. For instance, social isolation has been shown to decrease the lifespan of the fruit fly, *Drosophilia melanogaster* (Ruan & Wu, 2008); promote the development of obesity and type 2 diabetes in mice (Nonogaki, Nozue, & Oka, 2007); exacerbate the infarct size and edema and decrease post-stroke survival rate following experimentally induced stroke in mice (Karelina et al., 2010); delay the positive effects of running on adult neurogenesis in rats (Stranahan, Khalil, & Gould, 2006); increase the activation of the sympathetic adrenomedullary response to acute stressors in rats (Dronjak, Gavrilovic, Filipovic, & Radojcic, 2004); decrease the expression of genes regulating glucocorticoid response in the frontal cortex of piglets (Poletto, Steibel, Siegford, & Zanella, 2006); decrease open field activity, increase basal cortisol concentrations, and decrease lymphocyte proliferation to mitogens in pigs (Kanitz, Tuchscherer, Puppe, Tuchschere, & Stabenow, 2004); increase morning rises in cortisol in squirrel monkeys (Lyons, Ha, & Levine, 1995); and elevate 24 hr urinary catecholamines and oxidative stress in the Watanabe heritable hyperlipidemic rabbit (Nation et al., 2008).

Humans are born to one of the longest periods of dependency of any species and are dependent on conspecifics across the lifespan to survive and prosper. Perhaps not surprisingly, humans do not fare well, either, whether they are confined to solitary living or they simply *perceive* that they live in relative isolation. In a nationally representative sample of 2010 US adults aged 50 years and over from the 2002 to 2008 waves of the health and retirement

study, we estimated the effect of loneliness at one time point on *mortality* over the subsequent 6 years and investigated social relationships, health behaviors, and morbidity as potential mechanisms through which loneliness affects mortality risk among older Americans (Luo, Hawkley, Waite, & Cacioppo, 2012). We operationalized morbidity as depressive symptoms, self-rated poor health, and functional limitations; and we conceptualized the relationships between loneliness and each measure of morbidity as reciprocal and dynamic. We found that feelings of loneliness were associated with increased mortality risk over a 6-year period. Importantly, the association between loneliness and mortality was not explained by objective features of social relationships (e.g., marital status) or by health behaviors. In cross-lagged panel models that tested the reciprocal prospective effects of loneliness and morbidity, loneliness both affected and was affected by depressive symptoms and functional limitations over time, and it had marginal effects on later self-rated health. Higher rates of morbidity and mortality in lonely than nonlonely older adults have also been reported by other investigators (e.g., Caspi, Harrington, Moffitt, Milne, & Poulton, 2006; Eaker, Pinsky, & Castelli, 1992; Holt-Lunstad, Smith, & Layton, 2010; Olsen, Olsen, Gunner-Svensson, & Waldstrom, 1991; Patterson & Veenstra, 2010; Perissinotto, Stijacic, & Covinsky, 2012; Seeman, 2000; Thurston & Kubzansky, 2009).

Loneliness makes people feel sad (Cacioppo et al., 2006), and loneliness and depressive symptomatology have sometimes been conflated (cf. Booth, 2000; Cacioppo, Hawkley, & Thisted, 2010). We investigated the prospective associations between loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study (CHASRS), a population-based, ethnically diverse sample of 229 men and women who were 50–68 years old at study onset (Cacioppo et al., 2010). Cross-lagged panel models were used in which the criterion variables were loneliness and depressive symptoms, considered simultaneously. We used variations on this model to evaluate the possible effects of gender, ethnicity, education, physical functioning, medications, social network size, neuroticism, stressful life events, perceived stress, and social support on the observed associations between loneliness and depressive symptoms. Cross-lagged analyses indicated that loneliness predicted subsequent changes in depressive symptomatology, but not vice versa, and that this temporal association was not attributable to demographic variables, objective social isolation, dispositional negativity, stress, or social support.

Loneliness has also been found to be a risk factor for increased vascular resistance and blood pressure (Cacioppo, Hawkley, Crawford, et al., 2002; Hawkley, Burleson, Berntson, & Cacioppo, 2003; Hawkley, Masi, Berry, & Cacioppo, 2006; Hawkley, Thisted, Masi, & Cacioppo, 2010), metabolic syndrome (Whisman, 2010), fragmented sleep (Cacioppo, Hawkley, Berntson, et al., 2002; Hawkley, Preacher, & Cacioppo, 2010; Jacobs, Cohen, Hammerman-Rozenberg, & Stessman, 2006; Kurina et al., 2011), increased hypothalamic pituitary adrenocortical activity (Adam, Hawkley, Kudielka, & Cacioppo, 2006; Cacioppo, Ernst, et al., 2000; Doane & Adam, 2010; Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004), altered gene expression indicative of decreased inflammatory control and increased glucocorticoid insensitivity (Cole, Hawkley, Arevalo, & Cacioppo, 2011; Cole et al., 2007), diminished immunity (Dixon et al., 2006; Glaser, Evandrou, & Tomassini, 2005; Kiecolt-Glaser et al., 1984; Pressman et al., 2005; Straits-Troester, Patterson, Semple, & Temoshok, 1994), and diminished impulse control (cf. Cacioppo & Hawkley, 2009). Included in the documentation of these associations are longitudinal as well as cross-sectional studies and evidence that the association with loneliness holds even when controlling for other risk factors such as marital status, frequency of contact with friends and family, depression, and social support.

For instance, we used data from CHASRS to test the hypothesis that the effect of loneliness accumulates to produce greater increases in systolic blood pressure (SBP) over years

than are observed in less lonely individuals (Hawkley, Thisted, et al., 2010). Cross-lagged panel analyses revealed that loneliness at study onset predicted increases in SBP 2, 3, and 4 years later. These increases were cumulative such that higher initial levels of loneliness were associated with greater increases in SBP over a 4-year period. The effect of loneliness on SBP was independent of age, gender, race or ethnicity, cardiovascular risk factors, medications, health conditions, and the effects of depressive symptoms, social support, perceived stress, and hostility.

Given the danger involved in a social animal being on the social perimeter, the brain has evolved to monitor the status of one's social body just as it monitors the status of one's physical body (Cacioppo, Cacioppo, & Boomsma, 2013; Cacioppo & Patrick, 2008). Like physical pain serves as a signal to draw attention and respond to threats or damage to one's physical body, the feelings of loneliness serve as a figural signal to draw attention to and motivate responses to threats or damage to one's social body (Cacioppo et al., 2013; Cacioppo & Hawkley, 2009). Early in our history as a species, we survived and prospered by banding together – in couples, in families, in tribes – to provide mutual protection and assistance. The aversive feeling of loneliness serves to prompt us to renew the connections we need to insure survival and to promote social trust, cohesiveness, and collective action. Hunger, thirst, and physical pain, if ignored, ultimately reduce a person's ability in the wild to find and capture food. Loneliness, too, if ignored, can have damaging effects that contribute to deleterious mental and physical health.

The fact that social isolation has similar neurological and behavioral consequences across phylogeny demonstrates the importance of the social environment for social species (Cacioppo, Cacioppo, & Boomsma, 2013; Cacioppo, Cacioppo, & Capitanio, 2013). The deep evolutionary roots of tilting our brain and biology toward self-preservation also suggests that much of what is triggered when we feel socially isolated may be nonconscious. For instance, feeling socially isolated increases our motivation to connect with others, but it also produces an implicit (nonconscious) hypervigilance for social threats (Cacioppo & Hawkley, 2009). This, in turn, leads to attentional, confirmatory, and memory biases that lead us to think and act toward others in a more negative fashion, which in turn can increase negative interactions with others and fuel our feelings of isolation (Cacioppo, Cacioppo, & Boomsma, 2013). If so, why might such patterns have evolved?

The effect of loneliness on one's explicit attention to social stimuli and one's implicit attention to social threats has a counterpart in hunger. Hunger increases one's explicit attention to and motivation to find food. Not everything that appears edible is safe to eat by humans, however. Over an evolutionary timescale, our taste buds have developed to be much more sensitive to bitter (e.g., concentrations on the order of 1:2,000,000) than to sweet (e.g., concentrations on the order of 1:200). Poisons tend to have a bitter taste, so this difference in sensitivity has evolved to protect the individual from dangers that arise as a result of the drive to find food. Interactions with people can also be figuratively poisonous or nutritious. Becoming more sensitive to social threats when on the social perimeter may make it more difficult to form better relationships, but it is also more costly to fall victim to a fatal assault than to forego a friendship that can be pursued another day (Cacioppo, Cacioppo, & Boomsma, 2013).

Based on this formulation, we reasoned that the end of the day does not necessarily bring an end to the lonely brain's high alert state. If it is dangerous to fend off wild beasts with a stick by oneself, imagine how dangerous it is to lay down to sleep at night when predators are out and an individual does not have a safe social surround. We therefore investigated whether lonely days invade the night and found that lonely, compared to nonlonely, college students showed more microawakenings and less restful sleep. These results could not be

explained in terms of differences in sleep duration, depressive symptomatology, or other risk factors (Cacioppo, Hawkley, Berntson, et al., 2002) but instead reflected the lonely brain remaining relatively vigilant during sleep.

To assess the prospective association between daily feelings of loneliness and subsequent feelings of daytime dysfunction indicative of poor sleep quality, we tested the older adults from CHASRS (Hawkley, Preacher, et al., 2010). Specifically, three consecutive end-of-day diaries were completed by our CHASRS sample. Diary questions probed sleep duration, daytime dysfunction (e.g., fatigue, low energy, and sleepiness), loneliness, physical symptoms, and depressed affect experienced that day. Chronic health condition data and body mass index were also obtained. Autoregressive cross-lagged panel models were used to examine the magnitude of reciprocal prospective associations between loneliness and daytime dysfunction. Unstandardized path coefficients adjusted for race/ethnicity, sleep duration, marital status, household income, chronic health conditions, and health symptom severity. Analyses revealed that daily variations in loneliness predicted subsequent feelings of daytime dysfunction, and daytime dysfunction predicted subsequent loneliness, adjusted for covariates. Loneliness continued to significantly predict subsequent daytime dysfunction when depressive symptomatology was held constant. The effect of loneliness on daytime dysfunction was independent of sleep duration, indicating that the same amount of sleep was less salubrious when individuals felt relatively socially isolated (Hawkley, Preacher, et al., 2010).

The research on loneliness and poor sleep has used adults across a wide range of ages, but all have been from urban environments. Our theoretical framework is cast within an evolutionary context, however (Cacioppo, Cacioppo, & Boomsma, 2013). We therefore investigated the extent to which loneliness is associated with sleep fragmentation in a traditional 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 (but no differences in sleep duration) even after controlling for age, sex, body mass index, risk of sleep apnea, depression, anxiety, and perceived stress.

Not all forms of social relationships have comparable effects on human loneliness, of course (Cacioppo & Cacioppo, 2012). For instance, the noncontingent (or relatively noncontingent) conferral of a provision or benefit to another based on a concern for the other's welfare may be an important marker of the extent to which an individual feels relatively safe and connected to, or isolated and under threat from, others in the social environment. Social network characteristics are related to loneliness, but people can feel lonely in a marriage, while leading a company or sitting in a central position in a social network. For instance, research using relational and attribute data as predictors of the extent to which an individual feels lonely has shown that relational variables, such as marital status, group memberships, and frequency of contact with friends and family, are significant predictors, but the association between these objective relational variables and loneliness have generally been found to be mediated by an individual's perceptions of relationship quality (e.g., Hawkley et al., 2008; Wheeler, Reis, & Nezlek, 1983).

In sum, humans are fundamentally social organisms. When an individual feels socially isolated, there is a tendency for the brain to go into a self-preservation mode, with a range of biological, cognitive, behavioral, and social consequences (see Figure 1). These effects may have served short-term survival in evolutionary time, but they contribute to morbidity and mortality in contemporary society in which normal lifespans extend well into the eighth decade of life.

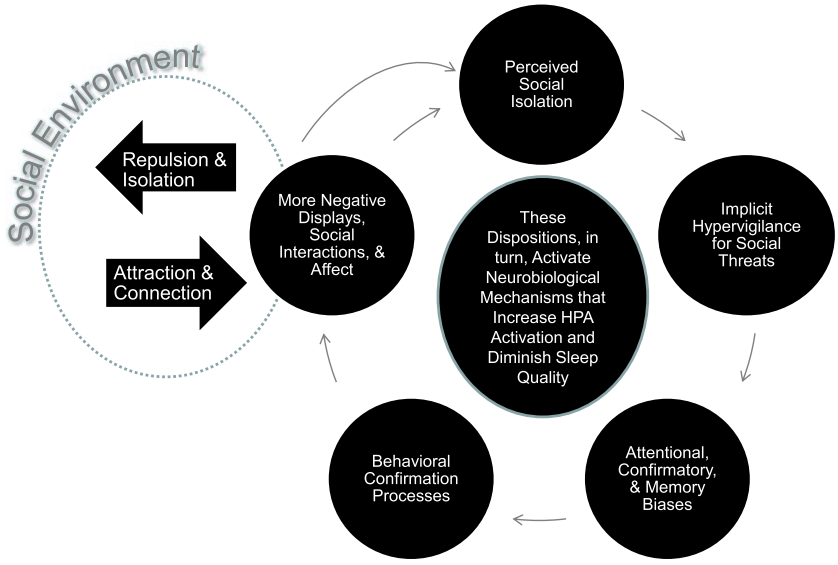

Figure 1. The effects of loneliness on attention, cognition, and social behavior. From Cacioppo and Hawkley (2009).

Concomitants of Loneliness

There is considerable variation in the extent to which individuals form and maintain salutary social relationships (Cacioppo et al., 2006). In this section, we review evidence that loneliness is separable from other individual difference predictors. Individual differences in loneliness have often been analyzed in terms of broad personality traits such as shyness or introversion (cf. Dill & Anderson, 1999). 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 one's preferences for social involvement. The frequency of time spent alone or social network size, therefore, may reflect low sociability (introversion) rather than loneliness per se, especially when a person has control over their relationships (Hawkley et al., 2008). The big five traits and anxiety are also related to loneliness but are not sufficient to explain the associations outlined above between loneliness and mental or physical health in population-based samples (Cacioppo et al., 2006).

Social support, which has received considerable attention in studies of social relationships and health, is sometimes thought to be synonymous with or to subsume loneliness. However, social support and loneliness are also functionally and stochastically distinct (Cacioppo et al., 2006). Social support refers to having family, friends, or other people to whom one can turn in times of need. One can be the recipient of emotional, tangible, informational, and belonging support, but if being the recipient of such support reflects an exchange relationship or brings with it a sense of indebtedness, such encounters may do little to make the person feel less lonely (Cacioppo et al., 2006). People may have access to considerable support from others, but the support may have nothing to do with sharing good times together, it may come at a cost (as in an exchange relationship), or it may come from someone other than the person with whom an individual aspires connection. A bereaved spouse, for instance, can feel lonely even though family and friends provide emotional, tangible, informational, and belonging support. Accordingly, even after statistically controlling for social support, loneliness has been found to be a risk factor for a host of mental and physical health problems including depressive symptomatology (Cacioppo et al., 2006, 2010;

VanderWeele, Hawkley, Thisted, & Cacioppo, 2011), impaired cognitive performance and cognitive decline (Gow, Pattie, Whiteman, Whalley, & Deary, 2007; Tilvis et al., 2004; Wilson et al., 2007), progression of Alzheimer's disease (Wilson et al., 2007), fragmented sleep (Cacioppo, Hawkley, Berntson, et al., 2002; Hawkley, Preacher, et al., 2010; Kurina et al., 2011), morning rise in cortisol (Adam et al., 2006), elevated blood pressure (Hawkley et al., 2006; Hawkley, Thisted, et al., 2010), and morbidity and mortality (Luo et al., 2012).

Longitudinal studies have found that loneliness is temporally stable (e.g., Bartels, Cacioppo, Hudziak, & Boomsma, 2008; Cacioppo, Ernst, et al., 2000; Cacioppo et al., 2010), and studies of twins indicate that loneliness is moderately heritable (Bartels et al., 2008; Boomsma, Cacioppo, Muthen, Asparouhov, & Clark, 2007; Boomsma, Willemsen, Dolan, Hawkley, & Cacioppo, 2005; McGuire & Clifford, 2000). To address concerns that heritability estimates for loneliness from twin studies might not be generalized to the general population, Distel et al. (2010) examined the genetic architecture of loneliness in an extended twin-family design. The presence of assortative (nonrandom) mating, genetic nonadditivity, vertical cultural transmission, and gene-environment interactions were modeled. Results indicated the presence of positive assortative mating for loneliness – people who are similar in their trait loneliness tend to mate. Distel et al. (2010) also confirmed that loneliness is moderately heritable but interestingly found a significant contribution of nonadditive genetic variation. No evidence was found for vertical cultural transmission, which suggests that parents may pass on genes for loneliness but not socialize this state.

Studies also indicate that there are environmental influences on loneliness. For instance, freshmen who leave family and friends behind often feel increased social isolation when they arrive at college even though they are surrounded by large numbers of other young adults (e.g., Cutrona, 1982; Russell et al., 1980). Lower levels of loneliness are associated with marriage (Hawkley, Browne, & Cacioppo, 2005; Pinquart & Sőrensen, 2003), higher education (Savikko, Routasalo, Tilvis, Strandberg, & Pitkala, 2005), and higher income (Andersson, 1998; Savikko et al., 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), dissatisfaction with living circumstances (Hector-Taylor & Adams, 1996), physical health symptoms (Hawkley et al., 2008), disabilities (Hawkley et al., 2008; Perissinotto et al., 2012), chronic work and/or social stress (Hawkley et al., 2008), a small social network (Hawkley et al., 2005; Mullins & Dugan, 1990), lack of a spousal confidant (Hawkley et al., 2008), marital or family conflict (Jones, 1992; Segrin, 1999), poor quality social relationships (Hawkley et al., 2008; Mullins & Dugan, 1990; Routasalo et al., 2006), and divorce and widowhood (Dugan & Kivett, 1994; Dykstra & de Jong, 1999; Holmen, Ericsson, Andersson, & Winblad, 1992; Samuelsson, Andersson, & Hagberg, 1998). To summarize, situations that appear to increase a person's risk for loneliness include those in which the person has little control over their social relationships, or perceives s/he is merely an instrumental means to the other person's extrinsic, nonsocial ends.

Loneliness is typically investigated as an individual factor, but because perceived and objective isolation can be differentiated, loneliness can also vary within and across groups. For instance, we used network linkage data from the population-based Framingham Heart Study to trace the topography of loneliness in social networks and the path through which loneliness spreads through these networks (Cacioppo et al., 2009). Results indicated that loneliness occurs in clusters within social networks, is disproportionately represented at the periphery of social networks, extends up to three degrees of separation, and is stronger for women than men.

Several features of the Framingham study pointed to loneliness spreading through a contagious process and moving lonely individuals closer to the edge of social networks over

time. Contagion is defined as the transmission of a state by direct or indirect contact, and virulence is determined, in part, by exposure (i.e., dose). Longitudinal analyses indicated that loneliness in one individual at Time 1 was followed by increased loneliness in others in that individual's social network by Time 2. Second, the closer the friend or contact was physically to this individual at Time 1, the lonelier the friend or contact became at Time 2. Third, loneliness was transmitted from the individual at Time 1 through friends and contacts to others beyond the individual's circle of contacts by Time 2. Fourth, the transmission of loneliness was stronger when the friendship between the individual who was lonely at Time 1 and others in the social network was reciprocal rather than asymmetric. Importantly, these results were unchanged when controlling for depressive symptomatology, indicating that the contagion of loneliness was not merely a function of depression levels (Cacioppo et al., 2009).

As noted above, loneliness has been shown to lead to, but is distinguishable from, depressive symptomatology (Cacioppo et al., 2010). A person made to feel lonely not only feels unhappy but also feels unsafe, feelings that activate an anachronistic survival mechanism that heightens sensitivity to threats from all sides (Cacioppo & Patrick, 2008). Consequently, people who feel lonely may reach out to connect with others but unknowingly emphasize the negative, or *perceive* negative, features of the interaction (e.g., Cacioppo & Hawkley, 2005; Hawkley, Preacher, & Cacioppo, 2007). Data from the Framingham study do not permit detailed investigation of the means by which loneliness is transmitted, but this contagion may occur through at least three different mechanisms: automatic emotional contagion (Hatfield, Cacioppo, & Rapson, 1994), coextensive self-other overlap and the attendant susceptibility of shared states (Slotter & Gardner, 2009), and quality of social interactions (Hawkley et al., 2007). For instance, in an experience sampling study of everyday behavior, we found loneliness to be associated with more negative affect and more negative social interactions, the quality of social interactions predicted subsequent affective states and vice versa, and more negative social interactions had longer lasting effects on affect than positive social interactions (Hawkley et al., 2007). These data are consistent with the notion that the contagion of loneliness can occur through negative social cognition and the interpersonal interactions it engenders, but more definitive research is needed to delineate the mechanisms by which loneliness spreads through social networks. This question gains additional importance as our social networks have expanded digitally.

Conclusion

Early in our history as a species, we survived and prospered by banding together to provide mutual protection and assistance (cf. Cacioppo & Patrick, 2008). People may think of feeling lonely as a sad condition, but as is the case for other social species, finding oneself on the social perimeter is not just sad but also dangerous. The brains of social species, including our own, have evolved to emphasize self-preservation when on the social perimeter (Cacioppo, Cacioppo, & Boomsma, 2013). This brings with it some unwanted and unrecognized effects on a person's thoughts and behaviors toward others.

The aversion of loneliness increases people's awareness of the deficits in their social relationships and motivates the person to attend to and connect with others. The emphasis on self-preservation may be largely nonconscious, however, increasing the likelihood that a person who feels lonely will act in a more defensive and self-protective fashion (Cacioppo & Hawkley, 2005, 2009). This, in turn, can undermine the achievement of the goal to form better connections with others.

Feeling socially isolated activates *neurobiological* mechanisms that may promote self-preservation in the short-term but take a toll on health and well-being in the long-term. As outlined above, among these effects are higher vascular resistance in young adults, the putative consequence of the brain's hypervigilance for social threats (e.g., Cacioppo, Hawkley, Crawford, et al., 2002); larger morning rises in cortisol, a powerful stress hormone, the consequence of the brain's preparation for another dangerous day (e.g., Adam et al., 2006); increased prepotent responding, which means that behaviors high in the response hierarchy are more likely even though this includes impulsive (including poor health) behaviors (e.g., Cacioppo, Ernst, et al., 2000; Hawkley, Thisted, & Cacioppo, 2009); altered gene expression, for instance, increasing inflammatory biology to deal with assaults (Cole et al., 2007, 2011); and the decreased salubriousness of sleep, the consequence of the brain's high alert state (Cacioppo, Hawkley, Berntson, et al., 2002; Hawkley, Preacher, et al., 2010). Together, these processes can contribute to early morbidity and mortality.

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Short Biography

John Cacioppo is the Tiffany and Margaret Blake Distinguished Service Professor and Director of the Center for Cognitive and Social Neuroscience at the University of Chicago. Cacioppo is a pioneer in the field of social neuroscience and the author of more than 400 scientific articles and 20 books. Among the awards he has received are the Troland Award from the National Academy of Sciences, the Distinguished Scientific Contribution Award from APA, a MERIT Award from NIH, the Scientific Impact Award from the SESP, the Award for Distinguished Scientific Contributions from SPR, and the Campbell Award and the Theoretical Innovation Prize from SPSP. He is a past-president of several scientific societies, including the Society for Social Neuroscience; the Association for Psychological Science, the Society for Personality and Social Psychology, the Society for Psychophysiological Research, and the Society for Consumer Psychology; and the Psychology Section of AAAS. He is the Chair of the Board of Behavioral, Cognitive, and Sensory Sciences at the National Research Council and a member of the NSF Advisory Committee for the SBE Division and a former member of the Council for the NIH Center for Scientific Review and of the Council for the National Institute on Aging.

Stephanie Cacioppo (nee Ortigue) recently became a research assistant professor of psychology at the University of Chicago, where she directs the high-performance electrical neuroimaging laboratory (https://hpenlaboratory.uchicago.edu). Author of over 80 scientific articles (current h-index: 19), her general research area is at the intersection of psychology and social and cognitive neuroscience in health and neurological disease. Combining different high-resolution brain imaging techniques with psychophysics, her research focuses on body language, unconscious effects of pair-bonding (such as love) and other biological drives on embodied cognition, and the role of the mirror neuron system in understanding desires, intentions, and actions of other people while in social settings. Among the awards she has received are the ESSM Award of Excellence (2011), the Tom Slick's Award from the Mind Science Foundation (2010), the University Maurice Chalumeau Award (2007), the annual ESSM award for best oral presentation (2007), and the "Volker Henn" Award from the Swiss Society for Neuroscience (2002). In September 2011, Ortigue was named a "rising star" by the scientific Association for Psychological Science.

Note

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References

Adam, E. K., Hawkley, L. C., Kudielka, B. M., & Cacioppo, J. T. (2006). Day-to-day dynamics of experience-cortisol associations in a population-based sample of older adults. *Proceedings of the National Academy of Sciences*, **103**, 17058–17063.

Andersson, L. (1998). Loneliness research and interventions: A review of the literature. *Aging & Mental Health*, **2**, 264–274.

Bartels, M., Cacioppo, J. T., Hudziak, J. J., & Boomsma, D. I. (2008). Genetic and environmental contributions to stability in loneliness throughout childhood. *American Journal of Medical Genetic Part B: Neuropsychiatric Genetics*, **147B**, 385–391.

Bondevik, M., & Skogstad, A. (1998). The oldest old, ADL, social network, and loneliness. *Western Journal of Nursing Research*, **20**, 325–343.

Boomsma, D. I., Cacioppo, J. T., Muthen, B., Asparouhov, T., & Clark, S. (2007). Longitudinal genetic analysis for loneliness in Dutch twins. *Twin Research and Human Genetics*, **10**, 267–273.

Boomsma, D. I., Willemsen, G., Dolan, C. V., Hawkley, L. C., & Cacioppo, J. T. (2005). Genetic and environmental contributions to loneliness in adults: The Netherlands Twin Register Study. *Behavior Genetics*, **35**, 745–752.

Booth, R. (2000). Loneliness as a component of psychiatric disorders. *Medscape General Medicine*, **2**, 1–7.

Cacioppo, J. T., & Berntson, G. G. (1994). Relationship between attitudes and evaluative space: A critical review, with emphasis on the separability of positive and negative substrates. *Psychological Bulletin*, **115**, 401–423.

Cacioppo, S., & Cacioppo, J. T. (2012). Decoding the invisible forces of social connections. *Frontiers in Integrative Neuroscience*, **6**(Article 51), 1–7.

Cacioppo, J. T., Cacioppo, S., & Boomsma, D. (2013). Evolutionary mechanisms for loneliness. *Cognition and Emotion*. DOI: 10.1080/02699931.2013.837379

Cacioppo, S., Cacioppo, J. T., & Capitanio, J. (2013). Neurology of social isolation from fruit flies to patients. Manuscript under review.

Cacioppo, J. T., & Hawkley, L. C. (2005). People thinking about people: The vicious cycle of being a social outcast in one's own mind. In K. D. Williams, J. P. Forgas, & W. von Hippel (Eds.), *The Social Outcast: Ostracism, Social Exclusion, Rejection, and Bullying* (pp. 91–108). New York: Psychology Press.

Cacioppo, J. T., & Hawkley, L. C. (2009). Perceived social isolation and cognition. *Trends in Cognitive Sciences*, **13**, 447–454.

Cacioppo, J. T., Hawkley, L. C., Berntson, G. G., Ernst, J. M., Gibbs, A. C., Stickgold, R., et al. (2002). Lonely days invade the nights: Social modulation of sleep efficiency. *Psychological Science*, **13**, 384–387.

Cacioppo, J. T., Hawkley, L. C., Crawford, L. E., Ernst, J. M., Burleson, M. H., Kowalewski, R. B., et al. (2002). Loneliness and health: Potential mechanisms. *Psychosomatic Medicine*, **64**, 407–417.

Cacioppo, J. T., & Patrick, B. (2008). *Loneliness: Human Nature and the Need for Social Connection*. New York: W. W. Norton & Company.

Cacioppo, J. T., Berntson, G. G., Sheridan, J.F., & McClintock, M. K. (2000). Multi-level integrative analyses of human behavior: Social neuroscience and the complementing nature of social and biological approaches. *Psychological Bulletin*, **126**, 829–843.

Cacioppo, J. T., Ernst, J. M., Burleson, M. H., McClintock, M. K., Malarkey, W. B., Hawkley, L. C., et al. (2000). Lonely traits and concomitant physiological processes: The MacArthur Social Neuroscience Studies. *International Journal of Psychophysiology*, **35**, 143–154.

Cacioppo, J. T., Fowler, J. H., & Christakis, N. A. (2009). Alone in the crowd: The structure and spread of loneliness in a large social network. *Journal of Personality and Social Psychology*, **97**, 977–991.

Cacioppo, S., Frum, C., Asp, E., Weiss, R., Lewis, J. W., & Cacioppo, J. T. (2013). A quantitative meta-analysis of functional imaging studies of social rejection. *Scientific Reports*, **3**, 2027. DOI: 10.1038/srep02027

Cacioppo, J. T., Hawkley, L. C., Ernst, J. M., Burleson, M., Berntson, G. G., Nouriani, B., et al. (2006). Loneliness within a nomological net: An evolutionary perspective. *Journal of Research in Personality*, **40**, 1054–1085.

Cacioppo, J. T., Hawkley, L. C., Norman, G. J., & Berntson, G. G. (2011). Social isolation. *Annals of the New York Academy of Sciences*, **1231**, 17–22.

Cacioppo, J. T., Hawkley, L. C., & Thisted, R. A. (2010). Perceived social isolation makes me sad: Five year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. *Psychology and Aging*, **25**, 453–463.

Caspi, A., Harrington, H., Moffitt, T. E., Milne, B. J., & Poulton, R. (2006). Socially isolated children 20 years later: Risk of cardiovascular disease. *Archives of Pediatrics and Adolescent Medicine*, **160**, 805–811.

Clark, M. S., & Mills, J.R, (1979). Interpersonal attraction in exchange and communal relationships. *Journal of Personality and Social Psychology*, **37**, 12–24.

Clark, M. S., & Mills, J. R. (2012). A theory of communal (and exchange) relationships. In P. Van Lange, A. Kruglanski, & E. T. Higgins (Eds.), *Handbook of Theories of Social Psychology* (Volume **1**, pp. 232–250). Thousand Oaks, CA: Sage Press.

Cole, S. W., Hawkley, L. C., Arevalo, J. M. G., & Cacioppo, J. T. (2011). Transcript origin analysis identifies antigen presenting cells as primary targets of socially regulated leukocyte gene expression. *Proceedings of the National Academy of Sciences*, **108**, 3080–3085.

Cole, S. W., Hawkley, L. C., Arevalo, J. M., Sung, C. Y., Rose, R. M., & Cacioppo, J. T. (2007). Social regulation of gene expression in human leukocytes. *Genome Biology*, **8**, R189.

Cutrona, C. E. (1982). Transition to college: Loneliness and the process of social adjustment. In L. A. Peplau, & D. Perlman (Eds.), *Loneliness: A Sourcebook of Current Theory, Research, and Therapy* (pp. 291–309). New York: John Wiley & Sons.

Dill, J. C., & Anderson, C. A. (1999). Loneliness, shyness, and depression: The etiology and interrelationships of everyday problems in living. In T. Joiner, & J. C. Coyne (Eds.), *The Interactional Nature of Depression: Advances in Interpersonal Approaches* (pp. 93–125). American Psychological Association: Washington, DC.

Distel, M. A., Rebollo-Mesa, I., Abdellaoui, A., Derom, C. A., Willemsen, G., Cacioppo, J. T., et al. (2010). Familial resemblance for loneliness. *Behavior Genetics*, **40**, 480–494.

Dixon, D., Cruess, S., Kilbourn, K., Klimas, N., Fletcher, M. A., Ironson, G., et al. (2006). Social support mediates loneliness and human herpesvirus type 6 (HHV-6) antibody titers. *Journal of Applied Social Psychology*, **31**, 1111–1132.

Doane, L. D., & Adam, E. K. (2010). Loneliness and cortisol: Momentary, day-to-day, and trait associations. *Psychoneuroendocrinology*, **35**, 430–41.

Dronjak, S., Gavrilovic, L., Filipovic, D., & Radojcic, M. B. (2004). Immobilization and cold stress affect sympatho-adrenomedullary system and pituitary-adrenocortical axis of rats exposed to long-term isolation and crowding. *Physiology and Behavior*, **81**, 409–415.

Dugan, E., & Kivett, V. R. (1994). The importance of emotional and social isolation to loneliness among very old rural adults. *Gerontologist*, **34**, 340–346.

Dunbar, R. I. M. (2003). The social brain: Mind, language, and society in evolutionary perspective. *Annual Review of Anthropology*, **32**, 163–181.

Dunbar, R. I. M., & Shultz, S. (2007). Evolution in the social brain. *Science*, **317**, 1344–1347.

Dykstra, P. A., & de Jong, G. J. (1999). Differential indicators of loneliness among elderly. The importance of type of partner relationship, partner history, health, socioeconomic status and social relations. *Tijdschrift Voor Gerontologie En Geriatrie*, **30**, 212–225.

Eaker, E. D., Pinsky, J., & Castelli, W. P. (1992). Myocardial infarction and coronary death among women: Psychosocial predictors from a 20-year follow-up of women in the Framingham Study. *American Journal of Epidemiology*, **135**, 854–864.

Eysenck, H. J. (1947). *Dimensions of Personality*. London: Paul, Trench, Trubner & Co., Ltd.

Fiske, A. P. (1992). The four elementary forms of sociality: Framework for a unified theory of social relations. *Psychological Review*, **99**, 689–723.

Glaser, K., Evandrou, M., & Tomassini, C. (2005). The health consequences of multiple roles at older ages in the UK. *Health and Social Care in the Community*, **13**, 470–477.

Glaser, R., Kiecolt-Glaser, J. K., Speicher, C. E., & Holliday, J. E. (1985). Stress, loneliness, and changes in herpesvirus latency. *Journal of Behavioral Medicine*, **8**, 249–260.

Gow, A. J., Pattie, A., Whiteman, M. C., Whalley, L. J., & Deary, I. J. (2007). Social support and successful aging. *Journal of Individual Differences*, **28**, 103–115.

Hatfield, E., Cacioppo, J. T., & Rapson, R. L. (1994). *Emotional Contagion*. New York: Cambridge University Press.

Hawkley, L. C., Browne, M. W., & Cacioppo, J. T. (2005). How can I connect with thee? Let me count the ways. *Psychological Science*, **16**, 798–804.

Hawkley, L. C., Burleson, M. H., Berntson, G. G., & Cacioppo, J. T. (2003). Loneliness in everyday life: Cardiovascular activity, psychosocial context, and health behaviors. *Journal of Personality and Social Psychology*, **85**, 105–120.

Hawkley, L. C., Hughes, M. E., Waite, L. J., Masi, C. M., Thisted, R. A., & Cacioppo, J. T. (2008). From social structural factors to perceptions of relationship quality and loneliness: The chicago health, aging, and social relations study. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, **63**, S375–384.

Hawkley, L. C., Masi, C. M., Berry, J. D., & Cacioppo, J. T. (2006). Loneliness is a unique predictor of age-related differences in systolic blood pressure. *Psychology and Aging*, **21**, 152–164.

Hawkley, L. C., Preacher, K. J., & Cacioppo, J. T. (2007). Multilevel modeling of social interactions and mood in lonely and socially connected individuals: The MacArthur social neuroscience studies. In A. D. Ong, & M. van Dulmen (Eds.), *Oxford Handbook of Methods in Positive Psychology* (pp. 559–575). New York: Oxford University Press.

Hawkley, L. C., Preacher, K. J., & Cacioppo, J. T. (2010). Loneliness impairs daytime functioning but not sleep duration. *Health Psychology*, **29**, 124–129.

Hawkley, L. C., Thisted, R. A., & Cacioppo, J. T. (2009). Loneliness predicts reduced physical activity: Cross-sectional and longitudinal analyses. *Health Psychology*, **28**, 354–363.

Hawkley, L. C., Thisted, R. A., Masi, C. M., & Cacioppo, J. T. (2010). Loneliness predicts increased blood pressure: Five-year cross-lagged analyses in middle-aged and older adults. *Psychology and Aging*, **25**, 132–141.

Hector-Taylor, L., & Adams, P. (1996). State versus trait loneliness in elderly New Zealanders. *Psychological Reports*, **78**, 1329–1330.

Heider, F. (1946). Attitudes and cognitive organization. *Journal of Psychology*, **21**, 107–112.

Heider, F. (1958). *The Psychology of Interpersonal Relations*. New York: Wiley.

Holmen, K., Ericsson, K., Andersson, L., & Winblad, B. (1992). Subjective loneliness--a comparison between elderly and relatives. *Vard i Norden*, **12**, 9–13.

Holt-Lunstad, J., Smith, T.B., & Layton, J.B. (2010) Social relationships and mortality risk: A meta-analytic review. *PLOS Medicine* **7**, e1000316.

Insel, T., & Fernald, R. (2004). How the brain processes social information: Searching for the social brain. *Annual Review of Neuroscience*, **27**, 697–722.

Jacobs, J. M., Cohen, A., Hammerman-Rozenberg, R., & Stessman, J. (2006). Global sleep satisfaction of older people: The Jerusalem cohort study. *Journal of the American Geriatrics Society*, **54**, 325–329.

Ones, D. C. (1992). Parental divorce, family conflict and friendship networks. *Journal of Social and Personal Relationships*, **9**, 219–235.

Kanitz, E., Tuchscherer, M., Puppe, B., Tuchschere, A., & Stabenow, B. (2004). Consequences of repeated early isolation in domestic piglets (Sus scrofa) on their behavioural, neuroendocrine, and immunological responses. *Brain, Behavior, and Immunity*, **18**, 35–45.

Karelina, K., Norman, G. J., Zhang, N., Morris, J. S., Peng, H., & DeVries, A. C. (2010). Social isolation alters neuroinflammatory response to stroke. *Proceedings of the National Academy of Sciences*, **106**, 5895–5900.

Kiecolt-Glaser, J. K., Garner, W., Speicher, C., Penn, G. M., Holliday, J., Glaser, R., et al. (1984). Psychosocial modifiers of immunocompetence in medical students. *Psychosomatic Medicine*, **46**, 7–14.

Kurina, L. M., Knutson, K. L., Hawkley, L. C., Cacioppo, J. T., Lauderdale, D. S., & Ober, C. (2011). Loneliness is associated with sleep fragmentation in a communal society. *Sleep*, **34**, 1519–1526.

Luo, Y., Hawkley, L. C., Waite, L., & Cacioppo, J. T. (2012). Loneliness, health, and mortality in old age: A national longitudinal study. *Social Science & Medicine*, **74**, 907–914.

Lyons, D., Ha, C., & Levine, S. (1995). Social effects and circadian rhythms in squirrel monkey pituitary-adrenal activity. *Hormones and Behavior*, **29**, 177–190.

Markus, H. R., & Kitayama, S. (1991). Culture and the self: Implications for cognition, emotion, and motivation. *Psychological Review*, **98**, 224–253.

McGuire, S., & Clifford, J. (2000). Genetic and environmental contributions to loneliness in children. *Psychological Science*, **11**, 487–491.

Mullins, L. C., & Dugan, E. (1990). The influence of depression, and family and friendship relations, on residents' loneliness in congregate housing. *Gerontologist*, **30**, 377–384.

Nation, D. A., Gonzales, J. A., Mendez, A. J., Zaias, J., Szeto, A., Brooks, L. G., et al. (2008). The effect of social environment on markers of vascular oxidative stress and inflammation in the Watanabe heritable hyperlipidemic rabbit. *Psychosomatic Medicine*, **70**, 269–275.

Nonogaki, K., Nozue, K., & Oka, Y. (2007). Social isolation affects the development of obesity and type 2 diabetes in mice. *Endocrinology*, **148**, 4658–4666.

Olsen, R. B., Olsen, J., Gunner-Svensson, F., & Waldstrom, B. (1991). Social networks and longevity: A 14 year follow-up study among elderly in Denmark. *Social Science & Medicine*, **33**, 1189–1195.

Patterson, A. C., & Veenstra, G. (2010). Loneliness and risk of mortality: A longitudinal investigation in Alameda County, California. *Social Science & Medicine*, **71**, 181–186.

Perissinotto, C. M., Stijacic, C. I., & Covinsky, K. E. (2012). Loneliness in older persons: A predictor of functional decline and death. *Archives of Internal Medicine*, **172**, 1078–1083.

Pinquart, M., & Sőrensen, S. (2003). Risk factors for loneliness in adulthood and old age – A meta-analysis. In S. P. Shohov (Ed.), *Advances in Psychology Research* (Vol. **19**, pp. 111–143). Hauppauge, NY: Nova Science Publishers, Inc.

Poletto, R., Steibel, J. P., Siegford, J. M., & Zanella, A. J. (2006). Effects of early weaning and social isolation on the expression of glucocorticoid and mineralocorticoid receptor and 11beta-hydroxysteroid dehydrogenase 1 and 2 mRNAs in the frontal cortex and hippocampus of piglets. *Brain Research*, **1067**, 36–42.

Pressman, S. D., Cohen, S., Miller, G. E., Barkin, A., Rabin, B. S., Treanor, J. J., et al. (2005). Loneliness, social network size, and immune response to influenza vaccination in college freshmen. *Health Psychology*, **24**, 297–306.

Routasalo, P. E., Savikko, N., Tilvis, R. S., Strandberg, T. E., & Pitkala, K. H. (2006). Social contacts and their relationship to loneliness among aged people – a population-based study. *Gerontology*, **52**, 181–187.

Ruan, H., & Wu, C. F. (2008). Social interaction-mediated lifespan extension of Drosophila Cu/Zn superoxide dismutase mutants. *Proceedings of the National Academy of Sciences*, **105**, 7506–7510.

Russell, D. (1996). UCLA loneliness scale (version 3): Reliability, validity, and factor structure. *Journal of Personality Assessment*, **66**, 20–40.

Russell, D., Peplau, L. A., & Cutrona, C. E. (1980). The revised UCLA Loneliness Scale: Concurrent and discriminant validity evidence. *Journal of Personality & Social Psychology*, **39**, 472–480.

Samuelsson, G., Andersson, L., & Hagberg, B. (1998). Loneliness in relation to social, psychological and medical variables over a 13-year period: A study of the elderly in a Swedish rural district. *Journal of Mental Health and Aging*, **4**, 361–378.

Savikko, N., Routasalo, P., Tilvis, R. S., Strandberg, T. E., & Pitkala, K. H. (2005). Predictors and subjective causes of loneliness in an aged population. *Archives of Gerontology and Geriatrics*, **41**(3), 223–233.

Scott, J. (1991). *Social Network Analysis: A Handbook*. London: Sage.

Seeman, T. E. (2000). Health promoting effects of friends and family on health outcomes in older adults. *American Journal of Health Promotion*, **14**, 362–370.

Segrin, C. (1999). Social skills, stressful events, and the development of psychosocial problems. *Journal of Social & Clinical Psychology*, **18**, 14–34.

Slotter, E. B., & Gardner, W. L. (2009). Where do you end and I begin? Evidence for anticipatory, motivated self-other integration between relationship partners. *Journal of Personality and Social Psychology*, **96**, 1137–1151.

Steptoe, A., Owen, N., Kunz-Ebrecht, S. R., & Brydon, L. (2004). Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. *Psychoneuroendocrinology*, **29**, 593–611.

Steptoe, A., Shankar, A., Demakakos, P., et al. (2013). Social isolation, loneliness, and all-cause mortality in older men and women. *Proceedings of the National Academy of Sciences*, **110**, 5797–5801.

Straits-Troester, K., Patterson, T. L., Semple, S. J., & Temoshok, L. (1994). The relationship between loneliness, interpersonal competence, and immunologic status in HIV-infected men. *Psychology and Health*, **9**, 205–219.

Stranahan, A. M., Khalil, D., & Gould, E. (2006). Social isolation delays the positive effects of running on adult neurogenesis. *Nature Neuroscience*, **9**(4), 526–533.

Thurston, R. C., & Kubzansky, L. D. (2009). Women, loneliness, and incident coronary heart disease. *Psychosomatic Medicine*, **71**, 836–842.

Tilvis, R. S., Kähönen-Väre, M. H., Jolkkonen, J., Valvanne, J., Pitkala, K. H., Strandberg, T. E., et al. (2004). Predictors of cognitive decline and mortality of aged people over a 10-year period. *Journal of Gerontology Series A Biological Sciences and Medical Sciences*, **59**, 268–274.

Uchino, G. N. (2013). Understanding the links between social ties and health. *Journal of Social and Personal Relationships*, **30**, 155–162.

VanderWeele, T. J., Hawkley, L. C., Thisted, R. A., & Cacioppo, J. T. (2011). A marginal structural model analysis for loneliness: Implications for intervention trials and clinical practice. *Journal of Clinical and Consulting Psychology*, **79**, 225–235.

Weiss, R. (1973). *Loneliness: The experience of Emotional and Social Isolation*. Cambridge, MA: MIT Press.

Wheeler, L., Reis, H., & Nezlek, J. (1983). Loneliness, social interaction, and sex roles. *Journal of Personality and Social Psychology*, **45**, 943–953.

Whisman, M. A. (2010). Loneliness and the metabolic syndrome in a population-based sample of middle-aged and older adults. *Health Psychology*, **29**, 550–554.

Wilson, R. S., Krueger, K. R., Arnold, S. E., Schneider, J. A., Kelly, J. F., Barnes, L. L., et al. (2007). Loneliness and risk of Alzheimer disease. *Archives of General Psychiatry*, **64**, 234–240.