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Social isolation, cognitive decline, and cardiovascular disease risk

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Some of the first observations in early psychology regarding human nature involved the importance of social connections to mental health. Humans are hypothesized to have a fundamental need to belong, which includes having meaningful, affectionate bonds from close relationships. Without such bonds humans are susceptible to psychological consequences, including negative affect and stress. Recently, research has begun to consider additional consequences of an unmet need to belong, including those impacting physiology, neurology, and physical health. Research employing animal models and human participants has provided converging evidence that social isolation is robustly and negatively associated with cognitive and cardiovascular function. In this review, we examine that evidence, review the possible mechanisms by which those associations form, and close by proposing avenues for future research to help elucidate these associations.

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'*If no one turned round when we entered, answered when we spoke, or minded what we did, but if every person we met 'cut us dead,' and acted as if we were non-existing things, a kind of rage and impotent despair would ere long well up in us, from which the cruelest bodily tortures would be a relief; for these would make us feel that, however bad might be our plight, we had not sunk to such a depth as to be unworthy of attention at all.*' *(pp. 293–294; James, 1890)*

Observations such as that above, made by William James at the dawn of psychology as a scientific discipline [1], have forecasted a large body of empirical literature aimed at understanding the consequences of social isolation. Much ado has been made of the sequela of social isolation, most notably the isolated engaging in prosocial (e.g. ingratiation [2]) or antisocial (e.g. aggression; [3,4]) behaviors, as well as experiencing internal states, such as stress and negative mood [5•]. Not every instance of social isolation is as intentional as that depicted in the quote above, but nevertheless, research indicates that threats to individuals' perceived relational value exert similar levels of social threat, whether those threats be in the form of ostracism, exclusion, isolation, discrimination, loneliness, social pain, stigmatization, or dissolution of a relationship, to name a few [6].

Theoretically, why should social isolation have such deleterious consequences for individuals? Humans, being social animals, are hypothesized to have a fundamental need to belong, as basic to human survival and functioning as their needs for food, water, and shelter [7••]. As such, humans have evolved mechanisms to detect and respond to instances in which the need to belong may fail to be sated [8••]. In other words, the neurological, physiological, and psychological reactions to both social pain and physical pain rely on shared neurological substrates in humans [9•,10•]. This system is highly sensitive, designed to detect first, then assess [11•]. As functional as this is in warding off potential social death, the consequences of the activation of this system on the health of the individual should not be ignored. Both cognitive functioning and cardiovascular health are impacted by the activation of threat-detection systems, so it stands to reason that the presence of social isolation may also tax these systems and lead to downstream consequences including cognitive decline and cardiovascular disease risk. Here we review the existing literature that links social isolation with cognitive and cardiovascular decline, and point to important future directions for understanding the mental and physical health consequences of isolation.

Social isolation and cognitive impairments

Although feelings of isolation can have an adaptive social value [12] there is robust evidence that social isolation negatively impacts both cognitive and neural functioning [13••]. In rodent and animal studies, social isolation is typically induced by removing the animals from the social environment for extended periods of the day. Such studies have demonstrated that isolation negatively impacts brain function, leading to reduced volume and long-term potentiation in the hippocampus [14•], including the CA1 region [15], as well as increased

levels of brain-derived neurotrophic factor, a protein that is critical for supporting the growth and differentiation of new neurons and synapses [16]. The increased levels of neurotrophic factor in the medial prefrontal cortex are thought to be associated with impairments in emotional regulation [16]. Overall, the changes in neural functioning listed above are accompanied by deficits in a range of cognitive processes, including latent learning [17], inhibition [16], and contextual fear memory [15].

Studies of social isolation in humans have likewise shown strong evidence of cognitive and neural impairments. One method to investigate the effects of social isolation in humans is correlational: quantifying an individual's existing level of social integration and comparing isolated adults to included ones. Older adults who have lower social integration demonstrate accelerated memory decline relative to those with high social integration [18•], as well as lower performance on memory recall and verbal fluency tasks [19]. Longitudinal studies of perceived isolation have similarly shown detrimental effects on cognitive function, IQ, and later development of Alzheimer's Disease [20,21•]. fMRI studies also support effects of isolation on neural processing of emotional information, as socially isolated individuals show stronger activation of visual cortex when in the presence of socially negative information, as well as reduced reward-related activation of ventral striatum in response to emotionally positive information [22•].

Social isolation can also be experimentally induced in humans to study its acute, proximal effects. One of the common approaches to inducing isolation involves the Cyberball game [23••], in which participants pass a digital ball back and forth with two ostensible other people that are connected online from a different location. The Cyberball program is designed to either pass the ball from the other participants to the real participant 33% of the time (equality condition), or once or twice at the beginning and then never again (exclusion condition). The exclusion condition has been shown to mirror the effects of social isolation, engendering feelings of isolation and exclusion [24], increasing social susceptibility [25] and financial risk-taking [26], and impairing self-regulation [27•], and social/emotional processing [28]. Neurologically, the exclusion condition leads to reduced recruitment of dorsomedial prefrontal cortex when processing negative social information [29]. Whereas these studies strongly support an association between isolation and complex cognitive/social processing, there has been little work using experimental induction paradigms such as these to explore basic cognitive functions like memory, decision making, and executive functioning. Future work in this domain will help elucidate the potential effects of induced social isolation on basic cognitive functions (see below).

Social isolation and cardiovascular disease risk

The connection between psychosocial factors and physical health is well established. In 1979, Berkman and Syme reported an inverse association between social and community ties and all-cause mortality in a cohort of 6928 adults [30•]. Since this landmark report, several studies have confirmed that socially isolated individuals have a higher risk of mortality [31•,32••,33], collectively determining that low social support is as potent a predictor of mortality as traditional risk factors routinely assessed in clinical practice such as high blood pressure, smoking, obesity, high cholesterol and diabetes [30•,31•,32••]. The association between social isolation and mortality may be arbitrated by cardiovascular disease (CVD). Lack of social support is an independent predictor of CVD morbidity [34], and as CVD remains the most prevalent killer in the United States in men and women alike, the implications of this are profound. Epidemiological studies note that low social support predicts the development of hypertension [35], coronary artery disease [34], and heart failure [36]. Further, in those already afflicted with hypertension and/or CVD, lack of social support is associated with accelerated progression of coronary atherosclerosis [37], higher rates CVD events such as myocardial infarction and stroke [38,39], and a two-threefold higher risk of CVD mortality [34,38].

Although not yet entirely understood, mediating mechanisms linking social support to CVD are hypothesized to involve both health behaviors and biological (i.e. neuroendocrine) pathways. Those who report more expansive social networks may have access to more tangible resources that help promote a healthier lifestyle. Individuals with more social support tend to be more physically active and engage in less risky health behaviors such as smoking, excessive consumption of alcohol and poor dietary practices [40•]. Conversely, those living alone may be at increased risk from death to CVD due to lack of social confidantes that may help prompt immediate medical attention when needed (i.e. chest pain prompting subsequent activation of emergency medical services) [41]. Additionally, social relationships may provide cardiovascular benefit via their roles as stress-buffers [42]. Individuals with adequate social support may perceive strenuous life events as less taxing, reducing physiological arousal and overall allostatic load.

Biologically, as well, there is evidence that social isolation impacts CVD risk. Experimental studies employing animal models of social isolation (described above) have established that caging animals alone increases risk for obesity and type 2 diabetes mellitus [43], important risk factors for CVD, while also affecting autonomic balance [44], inflammation [45], and augmenting stress reactivity [46]. Over time, exaggerated stress responsiveness may increase load on the vasculature and heart, contributing to