Published in final edited form as:

Acta Neuropathol. 2015 April ; 129(4): 493–509. doi:10.1007/s00401-014-1377-9.

One is the Deadliest Number: The Detrimental Effects of Social Isolation on Cerebrovascular Diseases and Cognition

Brett Friedler, M.S.^{1,*}, Joshua Crapser, B.S.^{1,*}, and Louise McCullough, M.D., PhD^{1,2}

¹University of Connecticut Health Center Department of Neuroscience- 263 Farmington Ave., Farmington, CT 06030

²The Stroke Center at Hartford Hospital- 85 Jefferson St., 6th floor, Hartford, CT 06106

Abstract

The deleterious effects of chronic social isolation (SI) have been recognized for several decades. Isolation is a major source of psychosocial stress and is associated with an increased prevalence of vascular and neurological diseases. In addition, isolation exacerbates morbidity and mortality following acute injuries such as stroke or myocardial infarction. In contrast, affiliative social interactions can improve organismal function and health. The molecular mechanisms underlying these effects are unknown. Recently, results from large epidemiological trials and pre-clinical studies have revealed several potential mediators of the detrimental effects of isolation. At least three major biological systems have been implicated; the neuroendocrine (HPA) axis, the immune system, and the autonomic nervous system.

This review summarizes studies examining the relationship between isolation and mortality and the pathophysiological mechanisms underlying SI. Cardiovascular, cerebrovascular, and neurological diseases including atherosclerosis, myocardial infarction, ischemic stroke and Alzheimer's disease are given special emphasis in the context of SI. Sex differences are highlighted and studies are separated into clinical and basic science for clarity.

Keywords

Social Isolation; HPA axis; SNS; Inflammation; Vascular disease; Neurological disease

Introduction

Over two decades ago a causal association between social relationships and health was established after a review of five large prospective studies concluded that social isolation predicted mortality [53]. Accumulating evidence from numerous epidemiological, clinical and experimental studies has shown that social factors can have a profound influence on physical and mental health. For example, people with high levels of social support or large social networks exhibit lower all-cause mortality and more rapid and extensive functional

Corresponding Author Information: Brett Friedler, Friedler@uchc.edu, Telephone: (203)-671-6770, Fax: (860)-679-1181.

*Both authors contributed equally to this work.

Conflict of Interest: The authors declare that they have no conflict of interest.

and cognitive recovery after a wide variety of pathological insults, including stroke [117, 7]. In contrast, social isolation (SI) is associated with increased morbidity and mortality in patients with established vascular disease and in animal models [7, 51, 127]. A recent meta-analysis of 148 studies that included over 300,000 participants found that people with strong social relationships had a 50% increased likelihood of survival compared to isolated individuals. This finding was consistent across age, sex, initial health status, cause of death, and follow-up period [51]. Data from the U.S. Census show an increase in the number of people living alone from 17.1% of households in 1970 to 27.4% in 2012 [131] and this trend is likely to increase, especially in the elderly. Taking the time to screen patients at risk for isolation has the potential to reduce medical complications. However, the development of efficacious socially based interventions is contingent on our understanding of the mechanism by which isolation impacts outcome. Attesting to the importance of social factors in disease is that these same detrimental effects can be reproducibly demonstrated in animals [129]. This allows for mechanistic investigations that are difficult to perform in humans.

The primary focus of this review is to highlight the potential mechanisms underlying the detrimental effects of SI. Data demonstrating a link between SI, the integrity of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic dysregulation, and changes in systemic inflammation are emerging. Each represents a plausible biological mechanism that potentially mediates the associated increased incidence, morbidity and mortality from common vascular and neurological diseases seen in isolated individuals. Particular attention is devoted to atherosclerosis and coronary heart disease, ischemic stroke, cognitive impairment, and Alzheimer's disease. Due to the considerable volume of literature available on psychosocial factors and disease, studies are separated into population-based epidemiological studies and experimental studies.

Part I: SI and its effects on all-cause mortality

1.1 Defining SI

The terms 'social isolation' and 'loneliness' are frequently used interchangeably, although they refer to different concepts [48, 24] and only demonstrate a moderate level of correlation [18, 13]. Objective social isolation and perceived social isolation (loneliness) are distinct biological stressors associated with unique downstream effects and susceptibility to disease, although they may have mechanistic overlap. Loneliness has been defined as "how individuals evaluate their level and quality of social contact and engagement" [132]. Absent from that definition is the quantity of relationships. Social isolation, by contrast, is an objective term that refers to the lack of social contacts (spouse, family, friends, colleagues etc.). These are related, though distinct concepts. Indeed, it is possible to feel lonely amongst a crowd and fulfillment in isolation. The focus of this review is primarily on objective isolation and the biological underpinnings linking it to disease risk and mortality. As such, a strong effort is made to reference studies explicitly examining the objective aspects of isolation rather than loneliness. However, studies on the physiological effects of loneliness in health and disease may offer insight into the biological mechanisms of objective social

isolation, and are occasionally examined throughout the review to supplement our understanding.

1.2 SI and mortality in humans

The impact of social relationships on health has been recognized for several decades. Two physician-epidemiologists Cassel [14] and Cobb [16] pioneered the concept that social relationships can reduce the deleterious health effects of psychosocial stress. They suggested that having social support promotes adaptive behaviors and favorable neuroendocrine responses to biological stressors. However, these early studies were retrospective or cross-sectional, limiting their reliability.

It was not until the late 1970's that empirical data from long-term prospective cohorts began to emerge [53]. Several of these studies showed that poor social support is linked to higher mortality rates (Table 1). Interestingly, some studies found that isolation [140] increased mortality only in older men, suggesting that the association between isolation and mortality is sex-specific, and may be missed if sex-specific analysis is not performed. These conflicting results exemplify the importance of standardizing our measures of objective and subjective isolation in clinical populations, and highlight the need for biological models in which confounders and sex differences can be controlled.

1.3 SI, comorbid depression, and mortality in rodents

SI in rodents is independently associated with increased mortality in a variety of disease models including cancer [80] and vascular disease. For example, the median survival time was significantly reduced in isolated atherogenic mice compared to animals pair housed (PH) 4-5/cage; animals PH 2-3/cage demonstrated a median survival time between these two groups [89]. 2 weeks of SI prior to experimental stroke decreased survival and enhanced stroke-induced behavioral deficits [65, 21].

Short term SI induces depressive symptoms in male mice [122] and this appears to be exacerbated in animals subjected to injury. In an experimental stroke model, Verma et al [130] showed that SI was associated with post-stroke development of several distinct phenotypes associated with depression: avolition, anhedonia, and sociability. Importantly, these deficits in sociability worsened over time in SI mice, suggesting that isolation induces progressive social withdrawal after brain injury. Pair housing reversed this depressive phenotype and was associated with increased brain derived neurotrophic factor (BDNF) levels and neurogenesis [127, 93]. Therefore, SI appears to contribute to a depressive phenotype in rodents. Given that depression is shown to be independently associated with mortality in animals with stroke [20] and humans [144], specifically men [62], SI-induced depression may partially mediate risks of mortality associated with isolation. Future experimental studies assessing the efficacy of antidepressants to treat these behaviors and potentially enhance survival are needed. However, designing appropriate and effective treatments to reverse the detrimental effects of isolation and other social stressors requires a better mechanistic understanding of how these factors influence mortality. Current evidence has implicated inflammatory signaling, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, and the autonomic nervous system (ANS).

Part II: SI, the HPA axis, the ANS, and systemic inflammation

2.1 Background

Chronic SI is a potent psychological stressor [15] that confers an increased susceptibility to inflammatory disease. This section will review the literature concerning how SI may impart neuroendocrine dysregulation via the well-defined HPA axis and the autonomic nervous system (ANS), and their downstream effects on the systemic immune response. All of the diseases considered later in this review have systemic inflammatory components; a comprehensive assessment of what is currently known on this topic is therefore both essential and warranted for a later discussion of the impact of SI on vascular and neurological disease.

The HPA axis serves dual roles as both the physiological responder to stress [26] as well as an immune system regulator. Downstream endogenous glucocorticoids synthesized in the adrenal cortex fulfill these roles, binding to the nuclear glucocorticoid receptor (GR) to inhibit the translocation of pro-inflammatory transcription factors (i.e. NF- κ B) while simultaneously transactivating anti-inflammatory gene expression [87, 103]. Therefore, glucocorticoid output helps the organism handle stressful situations in part by actively inhibiting pro-inflammatory processes and promoting an anti-inflammatory environment. The active glucocorticoid in humans is cortisol, whereas in rodents it is corticosterone.

Glucocorticoids play a critical role in determining the leukocyte subset composition in the blood. The GR is very sensitive to changes in serum glucocorticoid concentration, reliably producing a response in leukocyte subsets within 4–6 hours of receptor activation in healthy young adults [23]. The GR-mediated change in circulating leukocyte composition is accomplished by altering the rate of immune cell trafficking between the blood and surrounding perivascular parenchymal tissue in a cell-type specific manner [23, 18]. This pathway is regulated via a negative feedback mechanism operating on the HPA axis whereby secreted glucocorticoids inhibit upstream corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) secretion from the hypothalamus and pituitary, respectively [111, 125]. As CRH and ACTH are necessary to signal the adrenal cortex to produce glucocorticoids, inhibiting their secretion effectively suppresses glucocorticoid synthesis.

Chronic stressors contribute to persistent increases in plasma glucocorticoids in both humans and animals, and the body ultimately adapts through various pathological processes. An elevated serum glucocorticoid level globally overstimulates the GR, reducing the receptor's sensitivity- particularly in murine splenic macrophages [101] and human leukocytes [84]. One potential mechanism of GR desensitization involves p38 (a mitogen activated protein kinase) phosphorylation of the GR, inhibiting its nuclear translocation [134]. The GR normally functions as a transcriptional repressor of the pro-inflammatory transcription factor NF κ -B. Given the diverse functions of the HPA axis, it follows logically that its disruption would invoke multi-system pathology.

Neural activity in the brain is subject to modification in the presence or absence of social support, and displays robust differences in cortisol reactivity when presented with acute

social stressors (see Figure 1) [31]. Short-term positive social interaction has the capacity to alter HPA axis sensitivity, as well as alter the neuronal firing patterns of certain brain regions.

The brain also communicates with the immune system through the ANS, via both the sympathetic (SNS) and the parasympathetic (PSNS) branches. Within the PSNS, stimulation of the vagus nerve is anti-inflammatory, inhibiting TNF- α release by macrophages [8]. While the PSNS dampens the immune response, the SNS mediates the ‘fight or flight’ reaction to stress, and its activation can stimulate immune cell mobilization [1]. The SNS appears to play a specific role in the detrimental effects of social stressors, and possibly isolation, via hematopoietic alterations (see Figure 3). The SNS therefore complements the HPA axis in the response to chronic stress insofar as that the former drives the production of pro-inflammatory immune cells in the bone marrow while the latter both alters trafficking patterns and desensitizes the switch that regulates the overall inflammatory state of existing leukocytes. Consequently, perturbations of these systems by chronic stress, such as social isolation, may impart extensive, long lasting, and damaging inflammatory processes upon the organism.

2.2 Comparison of SI versus loneliness, and their associated stress mechanisms in humans

Immunological changes are prevalent in socially isolated individuals. In large nationwide samples, serum fibrinogen levels were significantly increased in SI men of all ages, with older men displaying an elevated overall inflammation burden index [140]. Moreover, SI has been associated with elevated circulating levels of C-reactive protein (CRP), but again, only in men [81]. Greater serum IL-6 concentrations were reported in both sexes scoring low on a social network index compared to those with higher scores [82]. This isolation-dependent pro-inflammatory environment, often referred to as the ‘Conserved Transcriptional Response to Adversity’ (CTRA), is expected in the context of HPA axis dysfunction and GR desensitization. Providing further evidence that this mechanism is relevant, higher cortisol levels are observed in healthy middle-aged adults that are isolated [39].

Data gleaned from studies examining loneliness may provide clues as to how objective SI serves as a psychosocial stressor to further impart immunological changes. Cole et al. [19] analyzed differences in the adult leukocyte gene profile attributable to loneliness and found significant increases in leukocyte pro-inflammatory gene expression and significant decreases in antiviral gene expression in chronically lonely individuals. This pattern increases the risk of infections and exacerbates diseases with inflammatory components, such as atherosclerosis. Cole [18] later retrospectively analyzed a large population-based sample of relatively healthy Taiwanese adults to assess the effect of loneliness on GR sensitivity to endogenous glucocorticoids. For non-lonely participants, there was a positive correlation between urinary glucocorticoid concentration and blood leukocyte ratios. Among self-reported lonely participants this correlation was lost, suggesting GR desensitization and consequent dysfunction in the GR-mediated cellular trafficking system in the presence of loneliness. This process is illustrated in Figure 2.

The findings of these studies in lonely individuals closely mirror the downstream effects seen with SI. In both cases GR desensitization contributes to a pro-inflammatory CTRA in leukocytes. Collectively, this data suggests partial mechanistic overlap between objective SI and its more subjective counterpart, loneliness. Loneliness may exacerbate the deleterious health effects of SI in patients afflicted with both. However, the presence of either SI or loneliness is presumably sufficient to observe an effect on inflammatory disease. In fact, each independently increases coronary heart disease incidence and mortality [44, 45]. More research is needed to determine the extent of immunological changes downstream of HPA axis dysregulation following SI in humans. Emerging data has linked objective SI to deleterious chronic low-grade systemic inflammation that appears to be both sex- and age-dependent.

2.3 SI and stress mechanisms in rodents

Similar to what occurs in humans, SI alters the rodent HPA axis. Elevated levels of corticotropin-releasing hormone, adrenocorticotrophic hormone, and corticosterone were observed in rats subjected to SI. Isolation has also been shown to increase pituitary sensitivity to corticotropin-releasing hormone leading to impairments in HPA axis negative feedback mechanisms in rats [111, 12]. Interestingly, HPA axis deficits were ameliorated with antioxidant treatment, suggesting a role of oxidative stress in the effect of isolation on neuroendocrine function [17].

Rodent studies have identified another important contributory mechanism at work following social stress. Repeated social disruption, a model of psychosocial stress, results in a significant increase in pro-inflammatory myelopoietic cell egress from the bone marrow of mice, indicating that chronic social stress may alter hematopoiesis [99]. What is driving this process? Norepinephrine (as well as other circulating catecholamines) secreted from sympathetic nerves act on hematopoietic stem cell β -adrenergic receptors located in the bone marrow to initiate hematopoiesis [32]. Pharmacological antagonists targeting the β -adrenergic receptor, as well as the myelopoietic autocrine growth factor GM-CSF, independently ameliorated pro-inflammatory monocyte production in socially stressed murine bone marrow [99]. GM-CSF and β -adrenergic receptors may therefore represent viable therapeutic targets to reduce the damaging pro-inflammatory response associated with social stressors. By extension, it is feasible that other psychosocial stressors such as SI may similarly invoke SNS-mediated myelopoietic changes. Figure 3 illustrates this pathological response.

Future studies should examine whether the SNS constitutes a contributory, targetable pathway underlying the detrimental effects of SI as well. The contribution of SI to vascular disease pathogenesis and outcome may therefore involve multiple systems including the neuroendocrine (HPA) axis as well as the ANS, particularly the sympathetic branch. Indeed, the effects of social isolation on vascular disorders are wide-ranging, and merit in-depth analysis.

Part III: Isolation as a factor in Cardiovascular Disease and Ischemic Stroke

3.1 SI and CVD in humans

Social isolation has been identified as a risk factor for incident CVD [43]. Furthermore, SI [126] in CVD patients has been associated with increased recurrent cardiac morbidity and mortality, and accelerated development of carotid atherosclerosis is seen in isolated CVD patients [104]. Chronically elevated heart rate and blood pressure in response to psychological stress may generate a ‘hyperresponsive’ SNS in some individuals; these patients are more susceptible to plaque deposition than their socially integrated counterparts [104]. The risk ratios in these studies are quite substantial, suggesting that it will be critical for clinicians and caretakers to monitor discharged cardiac patients for signs and symptoms of isolation. Living alone after a MI is a significant predictor of poor prognosis [71] and a low social support network predicts 1-year mortality as well as other classical risk factors such as high cholesterol, tobacco use, and hypertension [85]. Post-discharge SI increased all-cause mortality rate, hospital readmission, and re-infarction, even after controlling for other risk factors [109, 11].

3.2 SI, sex differences and CVD in humans

Interestingly, sex differences exist in the amount of risk attributable to SI in coronary artery disease (CAD) incidence, post-CAD cardiac morbidity and mortality [9], and all-cause mortality [54]. Men living alone have higher overall mortality rates than women living alone after MI [109]. However, the risk of a fatal CVD event was twice as likely in women devoid of social ties within 9 years after adjustment for other coronary risk factors [137]. Interestingly in stroke studies, women have higher rates of disability, recurrence, and death after stroke [102]. This data implies that the pathophysiological processes underlying the link between isolation and CVD may be subject to sex hormone regulation or more subtle differences in sex chromosome complement and may differ based on the disease phenotype. As vascular disease affects older, post-menopausal women, these sex differences likely go beyond the acute systemic effects of testosterone and estrogen on the neuroendocrine and immune systems. Research efforts should be directed toward investigating sex-specific factors such as sex chromosome complement and organizational effects of gonadal hormones in vascular disease.

3.3 Prior SI and ischemic stroke in humans

SI has been associated with increased risk of incident stroke in both males [70] and females with established CVD including suspected MI [106]. The Atherosclerosis Risk in Communities (ARIC) study reports a 44% increased risk of incident stroke in both males and females with a small social network [88]. Low-grade chronic systemic inflammation, previously shown to be associated with SI, is an established risk factor for stroke incidence and mortality in humans [86, 114]. Specifically, neuroendocrine (HPA) axis dysregulation [25], chronic systemic inflammation [117], and maladaptive behavioral changes [37] contribute to this pro-inflammatory environment.

There are currently no studies linking pre-stroke isolation to prognostic biomarker profiles and stroke outcomes. SI has been linked to elevated CRP [81] and serum IL-6

concentrations [82]. Indeed, the pro-inflammatory profile induced by SI is long lasting and may be established early in childhood, as isolated children had higher levels of CRP when measured at middle age [74]. As these inflammatory markers have been shown to increase stroke risk, are correlated with initial stroke severity, and in some studies, correlate with clinical outcome [75, 136], exploring the relationship between these biomarkers, SI and stroke seems prudent. High levels could be used to identify “at risk populations” so that targeted therapies could be provided. Plasma levels of B-type Natriuretic Peptide (BNP), its N-terminal peptide (NT-proBNP), cortisol, and copeptin taken at the time of acute stroke hospital admission are highly discriminative prognostic indicators of both stroke severity and short-term functional outcome [124]. These molecules are neuroendocrine biomarkers released with SNS and HPA axis activation [35, 68]. Given the evidence for SNS and HPA axis dysregulation associated with chronic SI, it is possible that pre-stroke isolation may exacerbate histological damage through a neuroimmune pro-inflammatory priming effect [117]. Future prospective studies evaluating isolation as a risk factor for acute ischemic stroke should examine serum biomarkers at enrollment to assess their predictive value for either stroke incidence or severity.

3.4 Ischemic stroke and subsequent SI in humans

Considerable evidence has shown that patient outcomes after stroke are strongly influenced by psychosocial factors. Patients with high levels of social support or large social networks exhibit more rapid and extensive functional recovery after stroke than SI individuals [38]. Moreover, an increase in recurrent stroke and death was seen in the 5-year period following an initial stroke in isolated individuals [7]. This suggests that there is still an opportunity for interventions to reduce risk, even after the index event has occurred. A variety of factors likely contribute to poor outcomes after stroke in isolated patients, including an exacerbated and prolonged neuroinflammatory phase [117], or even something as simple as reduced access to treatment with thrombolytics.

3.5 SI and CVD in rodents: Potential role of Oxytocin

Interestingly, atherosclerotic lesion volumes are significantly reduced in rabbits and monkeys that engage in affiliative social interaction relative to SI and PH animals experiencing antagonistic/combative social interaction [64, 95]. One proposed mechanism that is gaining attention is abnormal regulation of oxytocin (OT), a hypophyseal-secreted peptide that increases with affiliative social interaction [121]. OT has antioxidative and anti-inflammatory properties in both vascular endothelial cells as well as macrophages [121]. In one study, oxytocin or vehicle was administered peripherally via osmotic minipumps in SI atherogenic ApoE^{-/-} young male mice over a period of 12 weeks [90]. OT significantly reduced aortic atherosclerotic lesion volume and significantly decreased pro-inflammatory IL-6 secretion from adipose tissue. These results indicate that long-term peripheral administration of OT is protective in mouse models primarily by combating inflammation. OT has been implicated in animal models of ischemic stroke as a neuroprotective agent capable of reversing the exacerbated histological damage associated with SI [67]. Future studies should test the hypothesis that reduced OT secretion represents an important underlying pathological mechanism for SI in general, and whether it is linked to HPA or SNS function.

SI predisposes animals to CVD and exacerbates atherosclerosis [6], and autonomic nervous system dysfunction may help explain this association as well [104]. In a study of the effects of pre-surgical SI on experimental cardiac arrest/cardiopulmonary resuscitation (CA/CPR) in mice, SI significantly increased SNS and decreased PSNS cardiac control after CA/CPR compared to pair-housed littermates, and these deficits lasted until at least day 7, indicating persistent autonomic dysfunction [92]. Female prairie voles similarly demonstrate various ANS functional parameter abnormalities including significantly increased heart rate [41], decreased heart rate variability [41], and diminished vagal regulation of the heart [42] following isolation. Two weeks of subcutaneous oxytocin (OT) administration reversed these ANS abnormalities and improved performance on behavioral tests of depression [42]. Taken together, this data suggests that isolation may impart ANS dysregulation via a mechanism involving OT deficiency, which may subsequently increase susceptibility to CVD through the development of cardiac arrhythmias as seen in humans.

3.6 SI and ischemic stroke in rodents

Similar to what happens in humans; pre-stroke SI increases histological damage, worsens behavioral deficits, delays functional recovery, and increases mortality after experimental stroke in mice [129, 66, 21]. See Figure 4 for a comparison of infarct volumes. Though isolation is clearly associated with increased infarct volume in both sexes, the effect may be more pronounced in females [128]. Affiliative interaction prior to stroke improved motor function a week after injury [21]. Intra-ischemic plasma CRP was also decreased in PH animals [21], suggesting that the presence of a partner prior to stroke attenuates susceptibility to inflammation. Interestingly, the use of a grid partition in the cage that prevented physical contact of PH mice increased infarct volume and decreased locomotor activity to levels observed in SI littermates [65]. This suggests that physical contact is necessary for the beneficial effects of affiliative interactions.

Do the detrimental effects of SI require pre-stroke isolation? As patients are often not identified as isolated or lonely prior to their event, there may only be opportunity for therapeutic intervention after an index event. Mice isolated immediately following stroke demonstrated increased infarct volumes and mortality [127], as well as decreased brain derived neurotrophic factor (BDNF) levels 2 months after stroke compared to mice that remained in pair housing [93]. See Figure 5 for a visual comparison of BDNF staining between groups in the mouse striatum after 49 days. BDNF is known to play critical roles in neuroplasticity [97], enhancing neuronal survival [79], and increasing hippocampal neurogenesis [120]. Recent evidence has shown that chronic glucocorticoid exposure alters BDNF expression and signaling patterns [113, 73], which may help explain stress-induced impairments in adult neurogenesis [110]. Taken together, this data suggests isolation may ultimately impair neurogenesis after ischemic insult via chronic HPA axis dysregulation.

Delaying isolation until 3 days after stroke ameliorated the detrimental effects of SI on infarct volume; however, isolated mice had persistent deficits in behavioral recovery, lower BDNF levels, and reduced neurogenesis 3 months after stroke compared to pair-housed littermates. Despite equivalent histological damage, isolated mice continued to die, even weeks after the stroke [127]. This data suggests that the molecular, cellular, and behavioral

changes observed in the ischemic brain due to SI are both long lasting and independent of infarct size.

SI also exacerbates the post-stroke neuroinflammatory response. Inhibition of NF- κ B and intracerebroventricular (ICV) injection of an IL-6 neutralizing antibody reversed SI-induced damage [129, 66]. The results of studies investigating the effect of isolation on post-stroke neuroinflammation are summarized in Table 2. GR signaling also appears to play a role in the ischemic response to social stress as mifepristone, a GR antagonist, reversed the detrimental effects of social stress on stroke outcome [119]. Chronic or peri-ischemic elevations in glucocorticoid levels have been associated with poorer stroke outcomes in both humans and rodents [117]. Therefore both stress and isolation contribute to enhanced inflammatory responses to stroke, prolonging inflammation, contributing to secondary injury [117].

Part IV: Isolation and Cognitive Function, Dementia, and Alzheimer's Disease

4.1 SI and cognitive decline in humans

Social isolation has the potential to impact the brain beyond cardiovascular diseases. Indeed, cognition in both health and disease is susceptible to the influence of social stressors. SI increases the risk of future cognitive impairment in old age [4]. Individuals with larger social networks and more social engagement demonstrate greater global cognitive function and a reduced rate of cognitive decline with aging [3]. The rate of memory decline effectively doubles in SI individuals in comparison to socially integrated participants [34].

Elevated cortisol levels have been associated with impairments in cognition [76]. Furthermore, heightened inflammation as detected by elevated circulating IL-6 levels and intracellular production of pro-inflammatory cytokines by monocytes have been linked to cognitive decline [83, 112]. The latter finding is reminiscent of studies in rodents that show SNS-mediated pro-inflammatory monocyte egress from the bone marrow. Taken together, it is feasible to attribute the link between isolation and cognitive decline to the downstream pro-inflammatory outputs of HPA axis and ANS perturbation. Further support for this mechanism is evidenced by analysis of hippocampal atrophy, which has been associated with cognitive decline [60]. As expected, hippocampal atrophy has been linked with HPA axis alterations, such as cortisol elevation [72, 139], and increased levels of pro-inflammatory cytokines such as IL-6 [118]. It is possible the pathological mechanisms underlying the association between isolation and impaired cognition may similarly contribute to more devastating forms of cognitive decline including dementia and Alzheimer's disease.

4.2 SI, dementia and Alzheimer's Disease in humans

Dementia involves cognitive deterioration and decline beyond what is seen with normal aging or mild cognitive impairment. It has been estimated that dementia afflicts 24.3 million people worldwide as of 2001, and that this number will double by 2020, with Alzheimer's disease (AD) being the primary cause of the disorder [36]. In an early study, SI, measured

only by marital status, was a risk factor for AD after adjustments for confounders [46]. Furthermore, a low level of social engagement has repeatedly been identified as a risk factor for dementia [107, 133].

Individuals afflicted by AD have higher levels of cortisol [98] and heightened cortisol levels have been associated with more rapid cognitive decline and hippocampal atrophy among AD patients [22, 57]. This data suggests a role for HPA axis dysregulation in moderating the rate of disease progression. Cortisol levels also positively correlate with amyloid-beta brain burden [123], potentially indicating a direct influence on disease pathogenesis, or at least providing a novel prognostic biomarker for AD patients. Furthermore, increased inflammatory markers associated with HPA axis alterations and isolation can be found in AD patients, such as IL-6 and CRP [47], can increase the risk of developing dementia and Alzheimer's [33], and can increase the rate of cognitive decline associated with AD [50]. Again reminiscent of SNS-driven myelopoeisis, circulating monocytes appear to shift to a more inflammatory state in the context of AD, favoring the production of IL-6 and CCR2, a monocyte chemoattractant [108]. Therefore it appears SI can induce both SNS and HPA axis alterations to influence the manifestation of dementia and AD.

It is known that the onset and severity of clinical symptoms in patients with neuropathological hallmarks of AD can vary dramatically, even among patients with a similar plaque burden [69]. Moreover, individuals with larger social networks demonstrate greater scores on tests of cognitive function compared to those with smaller networks even after controlling for the degree of global AD pathology [5]. To account for this, the concept of 'brain reserve' has been developed, which posits that larger brains have more neural matter that can be lost to normal aging or disease-related injury before clinical symptoms manifest [116, 115]. Indeed, social engagement has been linked to larger brain volumes as determined by MRI [61]. Presumably individuals who engage in affiliative interaction are more resistant to the development of dementia and AD by virtue of greater reserve. Yet, the question of how SI mechanistically reduces brain reserve warrants greater investigation.

Smaller brain volumes associated with SI may be mediated by inflammation-induced cell damage as the HPA axis and SNS shift towards a pro-inflammatory state. It is also possible that chronic stressors such as SI exacerbate the oxidative stress-mediated damage that is found in AD patients [100] as stress and HPA axis activity are associated with increased oxidative damage [2], and this damage may reduce available brain reserve. Increases in inflammation and oxidative stress likely reduce total neural substrate, and thus brain 'reserve', in isolated AD patients, allowing clinical symptoms to manifest at earlier stages of neuropathology. While cognitive reserve may partially account for the variable phenotypes of this disease, it is likely not the only factor. As in the case of ischemic stroke, sex differences can influence both disease pathology and clinical symptoms.

4.3 SI, sex differences and Alzheimer's Disease in humans

As differences in normal, healthy cognition between men and women are already well established, it is not surprising that sex differences in AD exist as well. Women have an increased risk for developing AD pathology, in addition to displaying a faster rate of cognitive decline [78]. This suggests that, similar to vascular disorders, sex hormones

modulate the relationship between SI and worsen AD prognosis. To further complicate the matter, meta-analysis shows that stroke increases the risk of AD [142], and so sex differences in stroke will also influence the subsequent risk of AD. Therefore, SI and its link to AD display regulation by sex hormones at multiple levels, underscoring the need for critical examination of sex factors in future clinical and animal AD studies.

4.4 SI and Alzheimer's Disease in rodents

In transgenic mice, SI attenuates cell proliferation in the hippocampus, impairs contextual memory, and increases the rate of amyloid-beta plaque formation [28]. Furthermore, SI impairs spatial working memory, increases hippocampal A β and decreases the number of cholinergic, serotonergic and noradrenergic neurons in the brain [58]. The effects of SI in transgenic models of AD are summarized in Table 3.

Similar to what has been reported for CVD and stroke, SI increased plasma corticosterone, GR levels and corticotropin-releasing factor receptor-1 expression in a murine AD model [29]. This was associated with decreased hippocampal volume. Plasma corticosterone levels also positively correlated with amyloid plaque deposition and inversely correlated with hippocampal volume, mirroring findings in humans [123, 57]. Furthermore, increased HPA axis activity (via exogenous administration of glucocorticoids) in transgenic mice led to accelerated A β formation and tau accumulation, the primary component of neurofibrillary tangles seen in AD brains [40]. Interestingly, endogenous plasma corticosterone levels only increased after the development of AD pathology in transgenic mice. As a chronic stressor, SI may increase the risk of developing AD or worsen pathology in established AD by causing HPA axis hyperactivity and elevated glucocorticoid levels.

Hsiao et al. [56] found that SI also induced an increase in the activity of the enzymes that produce A β peptide, β - and γ -secretase. Mechanistically, oxidative stress induced by SI [143] increased the activity of β - and γ -secretases, increasing A β levels, further impairing cognitive function as neuropathology progresses. Chronic treatment with the antioxidant N-acetylcysteine helped reverse these SI-induced effects, lending support for the idea that SI influences AD pathology, at least in part, via oxidative stress [55]. As oxidative stress appears to mediate the effect of SI on HPA axis function [17], it is possible that neuroendocrine dysregulation is involved in this mechanism as well. Taken together, these results suggest an intricate pathway whereby isolation induces oxidative stress and subsequent HPA axis dysfunction, increasing the likelihood of developing AD pathology. After the development of plaques and/or neurofibrillary tangles, the HPA axis is further dysregulated, resulting in accelerated and uninhibited pathology development, cell death and cognitive deterioration.

The SNS may also play a mediating role in the influence of SI on AD development. Propranolol, the β -blocker found to ameliorate the stress-induced upregulation of pro-inflammatory myelopoiesis [99], attenuated cognitive deficits, amyloid accumulation, and tau phosphorylation in AD transgenic mice [27]. Genetic inhibition of β 2-adrenergic receptors in particular has been shown to reduce tau pathology [138]. Furthermore, stress-induced increases in amyloid beta peptide are mediated partly by β 2-adrenergic receptor activation, and are reduced after receptor antagonist treatment [141]. This pathway appears

to involve elevated γ -secretase activity downstream to β 2-adrenergic receptor activation [91]. Collectively, this data suggests SI may exacerbate progression of established AD in mice via β -adrenergic receptor activation, associated downstream enzymatic activities, and inflammatory myelopoiesis. Future studies should investigate the efficacy and mechanisms of β -blockers in the treatment of SI-induced worsening of AD pathology and symptoms. The mechanisms potentially involved in the detrimental effects of SI in AD are illustrated in Figure 6.

Conclusion

Psychosocial stressors, including SI, have been shown to exacerbate disease-related morbidity and mortality. Isolation influences both the risk of disease and enhances deleterious outcomes after acute events. The past several decades have provided a large body of epidemiological and experimental evidence that support various potential underlying mechanisms, though much remains to be discovered. Impaired HPA axis feedback mechanisms and SNS-driven myelopoiesis shift the cellular environment to a pro-inflammatory state, accounting for the observed increases in susceptibility to inflammatory disease following chronic social stress. Changes in leukocyte trafficking patterns as well as disinhibited pro-inflammatory gene expression increase disease incidence and exacerbate damage in both cardiovascular and cerebrovascular diseases. Alterations in HPA axis and SNS dynamics increase the risk of cognitive impairment and Alzheimer's disease, in addition to accelerating disease progression and cognitive decline. Moving forward, it will be important to develop standardized methods for measuring isolation, and to discriminate isolation-specific effects from those of the frequently experienced comorbid conditions of loneliness and depression. Sex differences have also been reported in numerous epidemiological studies investigating isolation, subjective loneliness, and disease outcomes. The organizational effects of sex hormones and their contribution to disease susceptibility cannot be ignored when developing novel drug targets. The overwhelming evidence regarding the deleterious health effects of isolation should warrant routine 'psychosocial' screening upon hospital admission or during regular check-ups so that these individuals are identified early and efficacious interventions can be swiftly implemented.

Acknowledgments

Financial support for B.F. and J.C. generously provided by NIH/NINDS grant Psychosocial Stress and Behavioral Response to Stroke (5R01NS077769) as well as NIH/NINDS grant Chromosomal and Hormonal Contributions to Sex Differences in Ischemic Stroke (5R01NS055215). Financial support was also received in the form of an American Heart Association undergraduate student summer fellowship awarded to J.C.

References

1. An C, Shi Y, Li P, Hu X, Gan Y, Stetler RA, Leak RK, Gao Y, Sun BL, Zheng P, Chen J. Molecular dialogs between the ischemic brain and the peripheral immune system: dualistic roles in injury and repair. *Prog Neurobiol.* 2014; 115:6–24.10.1016/j.pneurobio.2013.12.002 [PubMed: 24374228]
2. Aschbacher K, O'Donovan A, Wolkowitz OM, Dhabhar FS, Su Y, Epel E. Good stress, bad stress and oxidative stress: insights from anticipatory cortisol reactivity. *Psychoneuroendocrinology.* 2013; 38:1698–1708.10.1016/j.psyneuen.2013.02.004 [PubMed: 23490070]

3. Barnes LL, Mendes de Leon CF, Wilson RS, Bienias JL, Evans DA. Social resources and cognitive decline in a population of older African Americans and whites. *Neurology*. 2004; 63:2322–2326. 63/12/2322 [pii]. [PubMed: 15623694]
4. Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann Intern Med*. 1999; 131:165–173. 199908030-00002 [pii]. [PubMed: 10428732]
5. Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurol*. 2006; 5:406–412. S1474-4422(06)70417-3 [pii]. [PubMed: 16632311]
6. Bernberg E, Andersson IJ, Gan LM, Naylor AS, Johansson ME, Bergstrom G. Effects of social isolation and environmental enrichment on atherosclerosis in ApoE^{-/-} mice. *Stress*. 2008; 11:381–389. 10.1080/10253890701824051 [PubMed: 18609305]
7. Boden-Albala B, Litwak E, Elkind MS, Rundek T, Sacco RL. Social isolation and outcomes post stroke. *Neurology*. 2005; 64:1888–1892. 64/11/1888 [pii]. [PubMed: 15955939]
8. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000; 405:458–462. 10.1038/35013070 [PubMed: 10839541]
9. Brezinka V, Kittel F. Psychosocial factors of coronary heart disease in women: a review. *Soc Sci Med*. 1996; 42:1351–1365. 0277953695002847 [pii]. [PubMed: 8735892]
10. Brummett BH, Barefoot JC, Siegler IC, Clapp-Channing NE, Lytle BL, Bosworth HB, Williams RB Jr, Mark DB. Characteristics of socially isolated patients with coronary artery disease who are at elevated risk for mortality. *Psychosom Med*. 2001; 63:267–272. [PubMed: 11292274]
11. Bucholz EM, Rathore SS, Gosch K, Schoenfeld A, Jones PG, Buchanan DM, Spertus JA, Krumholz HM. Effect of living alone on patient outcomes after hospitalization for acute myocardial infarction. *Am J Cardiol*. 2011; 108:943–948. 10.1016/j.amjcard.2011.05.023 [PubMed: 21798499]
12. Butler TR, Ariwodola OJ, Weiner JL. The impact of social isolation on HPA axis function, anxiety-like behaviors, and ethanol drinking. *Front Integr Neurosci*. 2014; 7:102. 10.3389/fnint.2013.00102 [PubMed: 24427122]
13. Cacioppo JT, Hawkley LC. Social isolation and health, with an emphasis on underlying mechanisms. *Perspect Biol Med*. 2003; 46:S39–52. [PubMed: 14563073]
14. Cassel J. The contribution of the social environment to host resistance: the Fourth Wade Hampton Frost Lecture. *Am J Epidemiol*. 1976; 104:107–123. [PubMed: 782233]
15. Cene CW, Loehr L, Lin FC, Hammond WP, Foraker RE, Rose K, Mosley T, Corbie-Smith G. Social isolation, vital exhaustion, and incident heart failure: findings from the Atherosclerosis Risk in Communities Study. *Eur J Heart Fail*. 2012; 14:748–753. 10.1093/eurjhf/hfs064 [PubMed: 22588323]
16. Cobb S. Presidential Address-1976. Social support as a moderator of life stress. *Psychosom Med*. 1976; 38:300–314. [PubMed: 981490]
17. Colaïanna M, Schiavone S, Zotti M, Tucci P, Morgese MG, Backdahl L, Holmdahl R, Krause KH, Cuomo V, Trabace L. Neuroendocrine profile in a rat model of psychosocial stress: relation to oxidative stress. *Antioxid Redox Signal*. 2013; 18:1385–1399. 10.1089/ars.2012.4569 [PubMed: 23320850]
18. Cole SW. Social regulation of leukocyte homeostasis: the role of glucocorticoid sensitivity. *Brain Behav Immun*. 2008; 22:1049–1055. 10.1016/j.bbi.2008.02.006 [PubMed: 18394861]
19. Cole SW, Hawkley LC, Arevalo JM, Sung CY, Rose RM, Cacioppo JT. Social regulation of gene expression in human leukocytes. *Genome Biol*. 2007; 8:R189. gb-2007-8-9-r189 [pii]. [PubMed: 17854483]
20. Craft TK, DeVries AC. Role of IL-1 in poststroke depressive-like behavior in mice. *Biol Psychiatry*. 2006; 60:812–818. S0006-3223(06)00376-3 [pii]. [PubMed: 16730336]
21. Craft TK, Glasper ER, McCullough L, Zhang N, Sugo N, Otsuka T, Hurn PD, DeVries AC. Social interaction improves experimental stroke outcome. *Stroke*. 2005; 36:2006–2011. 01.STR.0000177538.17687.54 [pii]. [PubMed: 16100018]

22. Csernansky JG, Dong H, Fagan AM, Wang L, Xiong C, Holtzman DM, Morris JC. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. *Am J Psychiatry*. 2006; 163:2164–2169. 163/12/2164 [pii]. [PubMed: 17151169]
23. Dale DC, Fauci AS, Guerry DIV, Wolff SM. Comparison of agents producing a neutrophilic leukocytosis in man. Hydrocortisone, prednisone, endotoxin, and etiocholanolone. *J Clin Invest*. 1975; 56:808–813.10.1172/JCI108159 [PubMed: 1159089]
24. de Jong-Gierveld J, Kamphuis F, Dykstra P. Old and lonely? *Compr Gerontol B*. 1987; 1:13–17. [PubMed: 3453277]
25. DeVries AC, Craft TK, Glasper ER, Neigh GN, Alexander JK. 2006 Curt P. Richter award winner: Social influences on stress responses and health. *Psychoneuroendocrinology*. 2007; 32:587–603. S0306-4530(07)00084-4 [pii]. [PubMed: 17590276]
26. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull*. 2004; 130:355–391.10.1037/0033-2909.130.3.355 [PubMed: 15122924]
27. Dobarro M, Gerenu G, Ramirez MJ. Propranolol reduces cognitive deficits, amyloid and tau pathology in Alzheimer's transgenic mice. *Int J Neuropsychopharmacol*. 2013; 16:2245–2257.10.1017/S1461145713000631 [PubMed: 23768694]
28. Dong H, Goico B, Martin M, Csernansky CA, Bertchume A, Csernansky JG. Modulation of hippocampal cell proliferation, memory, and amyloid plaque deposition in APPsw (Tg2576) mutant mice by isolation stress. *Neuroscience*. 2004; 127:601–609.10.1016/j.neuroscience.2004.05.040 [PubMed: 15283960]
29. Dong H, Yuede CM, Yoo HS, Martin MV, Deal C, Mace AG, Csernansky JG. Corticosterone and related receptor expression are associated with increased beta-amyloid plaques in isolated Tg2576 mice. *Neuroscience*. 2008; 155:154–163.10.1016/j.neuroscience.2008.05.017 [PubMed: 18571864]
30. Drageset J, Eide GE, Kirkevold M, Ranhoff AH. Emotional loneliness is associated with mortality among mentally intact nursing home residents with and without cancer: a five-year follow-up study. *J Clin Nurs*. 2013; 22:106–114.10.1111/j.1365-2702.2012.04209.x [PubMed: 22882807]
31. Eisenberger NI, Taylor SE, Gable SL, Hilmert CJ, Lieberman MD. Neural pathways link social support to attenuated neuroendocrine stress responses. *Neuroimage*. 2007; 35:1601–1612. S1053-8119(07)00085-7 [pii]. [PubMed: 17395493]
32. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev*. 2000; 52:595–638. [PubMed: 11121511]
33. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, Stijnen T, Hofman A, Witteman JC, Breteler MM. Inflammatory proteins in plasma and the risk of dementia: the rotterdam study. *Arch Neurol*. 2004; 61:668–672.10.1001/archneur.61.5.668 [PubMed: 15148142]
34. Ertel KA, Glymour MM, Berkman LF. Effects of social integration on preserving memory function in a nationally representative US elderly population. *Am J Public Health*. 2008; 98:1215–1220.10.2105/AJPH.2007.113654 [PubMed: 18511736]
35. Feibel JH, Hardy PM, Campbell RG, Goldstein MN, Joynt RJ. Prognostic value of the stress response following stroke. *JAMA*. 1977; 238:1374–1376. [PubMed: 578192]
36. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. Alzheimer's Disease International . Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005; 366:2112–2117. S0140-6736(05)67889-0 [pii]. [PubMed: 16360788]
37. Gafarov VV, Panov DO, Gromova EA, Gagulin IV, Gafarova AV. The influence of social support on risk of acute cardiovascular diseases in female population aged 25–64 in Russia. *Int J Circumpolar Health*. 2013; 72 eCollection 2013. 10.3402/ijch.v72i0.21210
38. Glass TA, Maddox GL. The quality and quantity of social support: stroke recovery as psychosocial transition. *Soc Sci Med*. 1992; 34:1249–1261. [PubMed: 1641684]
39. Grant N, Hamer M, Steptoe A. Social isolation and stress-related cardiovascular, lipid, and cortisol responses. *Ann Behav Med*. 2009; 37:29–37.10.1007/s12160-009-9081-z [PubMed: 19194770]

40. Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J Neurosci.* 2006; 26:9047–9056. 26/35/9047 [pii]. [PubMed: 16943563]
41. Grippo AJ, Lamb DG, Carter CS, Porges SW. Social isolation disrupts autonomic regulation of the heart and influences negative affective behaviors. *Biol Psychiatry.* 2007; 62:1162–1170. S0006-3223(07)00366-6 [pii]. [PubMed: 17658486]
42. Grippo AJ, Trahanas DM, Zimmerman RR 2nd, Porges SW, Carter CS. Oxytocin protects against negative behavioral and autonomic consequences of long-term social isolation. *Psychoneuroendocrinology.* 2009; 34:1542–1553.10.1016/j.psyneuen.2009.05.017 [PubMed: 19553027]
43. Hatmi ZN, Nasiri LF, Sadegianmehr Z, Mirkia S, Darbooy S. Association of myocardial infarction with stressful life events and psychiatric symptoms: a population-based survey. *East Mediterr Health J.* 2011; 17:398–403. [PubMed: 21796952]
44. Hawkley LC, Cacioppo JT. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. *Ann Behav Med.* 2010; 40:218–227.10.1007/s12160-010-9210-8 [PubMed: 20652462]
45. Heffner KL, Waring ME, Roberts MB, Eaton CB, Gramling R. Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults. *Soc Sci Med.* 2011; 72:1482–1488.10.1016/j.socscimed.2011.03.016 [PubMed: 21492978]
46. Helmer C, Damon D, Letenneur L, Fabrigoule C, Barberger-Gateau P, Lafont S, Fuhrer R, Antonucci T, Commenges D, Orgogozo JM, Dartigues JF. Marital status and risk of Alzheimer's disease: a French population-based cohort study. *Neurology.* 1999; 53:1953–1958. [PubMed: 10599764]
47. Helmy AA, Naseer MM, Shafie SE, Nada MA. Role of interleukin 6 and alpha-globulins in differentiating Alzheimer and vascular dementias. *Neurodegener Dis.* 2012; 9:81–86.10.1159/000329568 [PubMed: 22133543]
48. Henderson AS, Scott R, Kay DW. The elderly who live alone: their mental health and social relationships. *Aust N Z J Psychiatry.* 1986; 20:202–209. [PubMed: 3464264]
49. Henderson KM, Clark CJ, Lewis TT, Aggarwal NT, Beck T, Guo H, Lunos S, Brearley A, Mendes de Leon CF, Evans DA, Everson-Rose SA. Psychosocial distress and stroke risk in older adults. *Stroke.* 2013; 44:367–372.10.1161/STROKEAHA.112.679159 [PubMed: 23238864]
50. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, Culliford D, Perry VH. Systemic inflammation and disease progression in Alzheimer disease. *Neurology.* 2009; 73:768–774.10.1212/WNL.0b013e3181b6bb95 [PubMed: 19738171]
51. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. *PLoS Med.* 2010; 7:e1000316.10.1371/journal.pmed.1000316 [PubMed: 20668659]
52. House JS. Social isolation kills, but how and why? *Psychosom Med.* 2001; 63:273–274. [PubMed: 11292275]
53. House JS, Landis KR, Umberson D. Social relationships and health. *Science.* 1988; 241:540–545. [PubMed: 3399889]
54. House JS, Robbins C, Metzner HL. The association of social relationships and activities with mortality: prospective evidence from the Tecumseh Community Health Study. *Am J Epidemiol.* 1982; 116:123–140. [PubMed: 7102648]
55. Hsiao YH, Kuo JR, Chen SH, Gean PW. Amelioration of social isolation-triggered onset of early Alzheimer's disease-related cognitive deficit by N-acetylcysteine in a transgenic mouse model. *Neurobiol Dis.* 2012; 45:1111–1120.10.1016/j.nbd.2011.12.031 [PubMed: 22227002]
56. Hsiao YH, Chen PS, Chen SH, Gean PW. The involvement of Cdk5 activator p35 in social isolation-triggered onset of early Alzheimer's disease-related cognitive deficit in the transgenic mice. *Neuropsychopharmacology.* 2011; 36:1848–1858.10.1038/npp.2011.69 [PubMed: 21544067]
57. Huang CW, Lui CC, Chang WN, Lu CH, Wang YL, Chang CC. Elevated basal cortisol level predicts lower hippocampal volume and cognitive decline in Alzheimer's disease. *J Clin Neurosci.* 2009; 16:1283–1286.10.1016/j.jocn.2008.12.026 [PubMed: 19570680]

58. Huang HJ, Liang KC, Ke HC, Chang YY, Hsieh-Li HM. Long-term social isolation exacerbates the impairment of spatial working memory in APP/PS1 transgenic mice. *Brain Res.* 2011; 1371:150–160.10.1016/j.brainres.2010.11.043 [PubMed: 21114967]
59. Ikeda A, Kawachi I, Iso H, Iwasaki M, Inoue M, Tsugane S. Social support and cancer incidence and mortality: the JPHC study cohort II. *Cancer Causes Control.* 2013; 24:847–860.10.1007/s10552-013-0147-7 [PubMed: 23549959]
60. Ikram MA, Vrooman HA, Vernooij MW, den Heijer T, Hofman A, Niessen WJ, van der Lugt A, Koudstaal PJ, Breteler MM. Brain tissue volumes in relation to cognitive function and risk of dementia. *Neurobiol Aging.* 2010; 31:378–386.10.1016/j.neurobiolaging.2008.04.008 [PubMed: 18501994]
61. James BD, Glass TA, Caffo B, Bobb JF, Davatzikos C, Yousem D, Schwartz BS. Association of social engagement with brain volumes assessed by structural MRI. *J Aging Res.* 2012; 2012:512714.10.1155/2012/512714 [PubMed: 22997582]
62. Jeong HG, Lee JJ, Lee SB, Park JH, Huh Y, Han JW, Kim TH, Chin HJ, Kim KW. Role of severity and gender in the association between late-life depression and all-cause mortality. *Int Psychogeriatr.* 2013; 25:677–684.10.1017/S1041610212002190 [PubMed: 23256908]
63. Kaplan GA, Salonen JT, Cohen RD, Brand RJ, Syme SL, Puska P. Social connections and mortality from all causes and from cardiovascular disease: prospective evidence from eastern Finland. *Am J Epidemiol.* 1988; 128:370–380. [PubMed: 3394703]
64. Kaplan JR, Manuck SB, Clarkson TB, Lusso FM, Taub DM. Social status, environment, and atherosclerosis in cynomolgus monkeys. *Arteriosclerosis.* 1982; 2:359–368. [PubMed: 6889852]
65. Karelina K, Norman GJ, Zhang N, DeVries AC. Social contact influences histological and behavioral outcomes following cerebral ischemia. *Exp Neurol.* 2009; 220:276–282.10.1016/j.expneurol.2009.08.022 [PubMed: 19733169]
66. Karelina K, Norman GJ, Zhang N, Morris JS, Peng H, DeVries AC. Social isolation alters neuroinflammatory response to stroke. *Proc Natl Acad Sci U S A.* 2009; 106:5895–5900.10.1073/pnas.0810737106 [PubMed: 19307557]
67. Karelina K, Stuller KA, Jarrett B, Zhang N, Wells J, Norman GJ, DeVries AC. Oxytocin mediates social neuroprotection after cerebral ischemia. *Stroke.* 2011; 42:3606–3611.10.1161/STROKEAHA.111.628008 [PubMed: 21960564]
68. Katan M, Elkind MS. Inflammatory and neuroendocrine biomarkers of prognosis after ischemic stroke. *Expert Rev Neurother.* 2011; 11:225–239.10.1586/ern.10.200 [PubMed: 21306210]
69. Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Renbing X, Peck A. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol.* 1988; 23:138–144.10.1002/ana.410230206 [PubMed: 2897823]
70. Kawachi I, Colditz GA, Ascherio A, Rimm EB, Giovannucci E, Stampfer MJ, Willett WC. A prospective study of social networks in relation to total mortality and cardiovascular disease in men in the USA. *J Epidemiol Community Health.* 1996; 50:245–251. [PubMed: 8935453]
71. Kitamura T, Sakata Y, Nakatani D, Suna S, Usami M, Matsumoto S, Hara M, Hamasaki T, Nanto S, Sato H, Hori M, Iso H, Komuro I. Living alone and risk of cardiovascular events following discharge after acute myocardial infarction in Japan. *J Cardiol.* 2013; 62:257–262.10.1016/j.jjcc.2013.04.009 [PubMed: 23778005]
72. Knoop AJ, Gerritsen L, van der Graaf Y, Mali WP, Geerlings MI. Basal hypothalamic-pituitary-adrenal axis activity and hippocampal volumes: the SMART-Medea study. *Biol Psychiatry.* 2010; 67:1191–1198.10.1016/j.biopsych.2010.01.025 [PubMed: 20299006]
73. Kunugi H, Hori H, Adachi N, Numakawa T. Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression. *Psychiatry Clin Neurosci.* 2010; 64:447–459.10.1111/j.1440-1819.2010.02135.x [PubMed: 20923424]
74. Lacey RE, Kumari M, Bartley M. Social isolation in childhood and adult inflammation: Evidence from the National Child Development Study. *Psychoneuroendocrinology.* 2014; 50C:85–94. S0306-4530(14)00312-6 [pii]. [PubMed: 25197797]
75. Lambertsen KL, Biber K, Finsen B. Inflammatory cytokines in experimental and human stroke. *J Cereb Blood Flow Metab.* 2012; 32:1677–1698.10.1038/jcbfm.2012.88 [PubMed: 22739623]

76. Lara VP, Caramelli P, Teixeira AL, Barbosa MT, Carmona KC, Carvalho MG, Fernandes AP, Gomes KB. High cortisol levels are associated with cognitive impairment no-dementia (CIND) and dementia. *Clin Chim Acta*. 2013; 423:18–22.10.1016/j.cca.2013.04.013 [PubMed: 23611893]
77. Lee M, Rotheram-Borus MJ. Challenges associated with increased survival among parents living with HIV. *Am J Public Health*. 2001; 91:1303–1309. [PubMed: 11499123]
78. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol*. 2014; 35:385–403.10.1016/j.yfrne.2014.01.002 [PubMed: 24434111]
79. Lipsky RH, Marini AM. Brain-derived neurotrophic factor in neuronal survival and behavior-related plasticity. *Ann N Y Acad Sci*. 2007; 1122:130–143. 1122/1/130 [pii]. [PubMed: 18077569]
80. Liu H, Wang Z. Effects of social isolation stress on immune response and survival time of mouse with liver cancer. *World J Gastroenterol*. 2005; 11:5902–5904. [PubMed: 16270407]
81. Loucks EB, Berkman LF, Gruenewald TL, Seeman TE. Relation of social integration to inflammatory marker concentrations in men and women 70 to 79 years. *Am J Cardiol*. 2006; 97:1010–1016. S0002-9149(05)02221-6 [pii]. [PubMed: 16563907]
82. Loucks EB, Sullivan LM, D'Agostino RBS, Larson MG, Berkman LF, Benjamin EJ. Social networks and inflammatory markers in the Framingham Heart Study. *J Biosoc Sci*. 2006; 38:835–842. S0021932005001203 [pii]. [PubMed: 16441967]
83. Marsland AL, Petersen KL, Sathanoori R, Muldoon MF, Neumann SA, Ryan C, Flory JD, Manuck SB. Interleukin-6 covaries inversely with cognitive performance among middle-aged community volunteers. *Psychosom Med*. 2006; 68:895–903. 68/6/895 [pii]. [PubMed: 17132839]
84. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol*. 2002; 21:531–541. [PubMed: 12433005]
85. Mookadam F, Arthur HM. Social support and its relationship to morbidity and mortality after acute myocardial infarction: systematic overview. *Arch Intern Med*. 2004; 164:1514–1518.10.1001/archinte.164.14.1514 [PubMed: 15277281]
86. Muir KW, Tyrrell P, Sattar N, Warburton E. Inflammation and ischaemic stroke. *Curr Opin Neurol*. 2007; 20:334–342.10.1097/WCO.0b013e32813ba151 [PubMed: 17495630]
87. Munck A, Guyre PM. Glucocorticoid physiology, pharmacology and stress. *Adv Exp Med Biol*. 1986; 196:81–96. [PubMed: 3012985]
88. Nagayoshi M, Everson-Rose SA, Iso H, Mosley TH Jr, Rose KM, Lutsey PL. Social Network, Social Support, and Risk of Incident Stroke: Atherosclerosis Risk in Communities Study. *Stroke*. 2014 STROKEAHA.114.005815 [pii].
89. Nakagawa-Toyama Y, Zhang S, Krieger M. Dietary manipulation and social isolation alter disease progression in a murine model of coronary heart disease. *PLoS One*. 2012; 7:e47965.10.1371/journal.pone.0047965 [PubMed: 23112879]
90. Nation DA, Szeto A, Mendez AJ, Brooks LG, Zaias J, Herderick EE, Gonzales J, Noller CM, Schneiderman N, McCabe PM. Oxytocin attenuates atherosclerosis and adipose tissue inflammation in socially isolated ApoE^{-/-} mice. *Psychosom Med*. 2010; 72:376–382.10.1097/PSY.0b013e3181d74c48 [PubMed: 20368478]
91. Ni Y, Zhao X, Bao G, Zou L, Teng L, Wang Z, Song M, Xiong J, Bai Y, Pei G. Activation of beta2-adrenergic receptor stimulates gamma-secretase activity and accelerates amyloid plaque formation. *Nat Med*. 2006; 12:1390–1396. nm1485 [pii]. [PubMed: 17115048]
92. Norman GJ, Zhang N, Morris JS, Karelina K, Berntson GG, DeVries AC. Social interaction modulates autonomic, inflammatory, and depressive-like responses to cardiac arrest and cardiopulmonary resuscitation. *Proc Natl Acad Sci U S A*. 2010; 107:16342–16347.10.1073/pnas.1007583107 [PubMed: 20805484]
93. O'Keefe LM, Doran SJ, Mwilambwe-Tshilobo L, Conti LH, Venna VR, McCullough LD. Social isolation after stroke leads to depressive-like behavior and decreased BDNF levels in mice. *Behav Brain Res*. 2014; 260:162–170.10.1016/j.bbr.2013.10.047 [PubMed: 24211537]
94. Orrell M, Butler R, Bebbington P. Social factors and the outcome of dementia. *Int J Geriatr Psychiatry*. 2000; 15:515–520. [pii]. 10.1002/1099-1166(200006)15:6<515::AID-GPS147>3.0.CO;2-U [PubMed: 10861917]

95. Paredes J, Szeto A, Levine JE, Zaias J, Gonzales JA, Mendez AJ, Llabre MM, Schneiderman N, McCabe PM. Social experience influences hypothalamic oxytocin in the WHHL rabbit. *Psychoneuroendocrinology*. 2006; 31:1062–1075. S0306-4530(06)00130-2 [pii]. [PubMed: 16963189]
96. Patterson TL, Shaw WS, Semple SJ, Cherner M, McCutchan JA, Atkinson JH, Grant I, Nannis E. HIV Neurobehavioral Research Center (HNRC) Group . Relationship of psychosocial factors to HIV disease progression. *Ann Behav Med*. 1996; 18:30–39.10.1007/BF02903937 [PubMed: 24203641]
97. Poo MM. Neurotrophins as synaptic modulators. *Nat Rev Neurosci*. 2001; 2:24–32.10.1038/35049004 [PubMed: 11253356]
98. Popp J, Schaper K, Kolsch H, Cvetanovska G, Rommel F, Klingmuller D, Dodel R, Wullner U, Jessen F. CSF cortisol in Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging*. 2009; 30:498–500. S0197-4580(07)00261-8 [pii]. [PubMed: 17716786]
99. Powell ND, Sloan EK, Bailey MT, Arevalo JM, Miller GE, Chen E, Kobor MS, Reader BF, Sheridan JF, Cole SW. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via beta-adrenergic induction of myelopoiesis. *Proc Natl Acad Sci U S A*. 2013; 110:16574–16579.10.1073/pnas.1310655110 [PubMed: 24062448]
100. Pratico D. Oxidative stress hypothesis in Alzheimer's disease: a reappraisal. *Trends Pharmacol Sci*. 2008; 29:609–615.10.1016/j.tips.2008.09.001 [PubMed: 18838179]
101. Quan N, Avitsur R, Stark JL, He L, Lai W, Dhabhar F, Sheridan JF. Molecular mechanisms of glucocorticoid resistance in splenocytes of socially stressed male mice. *J Neuroimmunol*. 2003; 137:51–58. S0165572803000420 [pii]. [PubMed: 12667647]
102. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A, Lisabeth L. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008; 7:915–926.10.1016/S1474-4422(08)70193-5 [PubMed: 18722812]
103. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med*. 2005; 353:1711–1723. 353/16/1711 [pii]. [PubMed: 16236742]
104. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation*. 1999; 99:2192–2217. [PubMed: 10217662]
105. Rutledge T, Reis SE, Olson M, Owens J, Kelsey SF, Pepine CJ, Mankad S, Rogers WJ, Bairey Merz CN, Sopko G, Cornell CE, Sharaf B, Matthews KA. National Heart Lung and Blood Institute . Social networks are associated with lower mortality rates among women with suspected coronary disease: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation study. *Psychosom Med*. 2004; 66:882–888. 66/6/882 [pii]. [PubMed: 15564353]
106. Rutledge T, Linke SE, Olson MB, Francis J, Johnson BD, Bittner V, York K, McClure C, Kelsey SF, Reis SE, Cornell CE, Vaccarino V, Sheps DS, Shaw LJ, Krantz DS, Parashar S, Merz CN. Social networks and incident stroke among women with suspected myocardial ischemia. *Psychosom Med*. 2008; 70:282–287.10.1097/PSY.0b013e3181656e09 [PubMed: 18378868]
107. Saczynski JS, Pfeifer LA, Masaki K, Korf ES, Laurin D, White L, Launer LJ. The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study. *Am J Epidemiol*. 2006; 163:433–440. kwj061 [pii]. [PubMed: 16410348]
108. Saresella M, Marventano I, Calabrese E, Piancone F, Rainone V, Gatti A, Alberoni M, Nemni R, Clerici M. A complex proinflammatory role for peripheral monocytes in Alzheimer's disease. *J Alzheimers Dis*. 2014; 38:403–413.10.3233/JAD-131160 [PubMed: 23979026]
109. Schmaltz HN, Southern D, Ghali WA, Jelinski SE, Parsons GA, King KM, Maxwell CJ. Living alone, patient sex and mortality after acute myocardial infarction. *J Gen Intern Med*. 2007; 22:572–578.10.1007/s11606-007-0106-7 [PubMed: 17443363]
110. Schoenfeld TJ, Gould E. Stress, stress hormones, and adult neurogenesis. *Exp Neurol*. 2012; 233:12–21.10.1016/j.expneurol.2011.01.008 [PubMed: 21281629]

111. Serra M, Pisu MG, Floris I, Biggio G. Social isolation-induced changes in the hypothalamic-pituitary-adrenal axis in the rat. *Stress*. 2005; 8:259–264. P0R2346T77643492 [pii]. [PubMed: 16423714]
112. Simpson EE, Hodkinson CF, Maylor EA, McCormack JM, Rae G, Strain S, Alexander HD, Wallace JM. Intracellular cytokine production and cognition in healthy older adults. *Psychoneuroendocrinology*. 2013; 38:2196–2208.10.1016/j.psyneuen.2013.04.007 [PubMed: 23664267]
113. Smith MA. Hippocampal vulnerability to stress and aging: possible role of neurotrophic factors. *Behav Brain Res*. 1996; 78:25–36. 0166432895002200 [pii]. [PubMed: 8793034]
114. Spencer SJ, Mouihate A, Pittman QJ. Peripheral inflammation exacerbates damage after global ischemia independently of temperature and acute brain inflammation. *Stroke*. 2007; 38:1570–1577. STROKEAHA.106.476507 [pii]. [PubMed: 17395866]
115. Steffener J, Stern Y. Exploring the neural basis of cognitive reserve in aging. *Biochim Biophys Acta*. 2012; 1822:467–473.10.1016/j.bbdis.2011.09.012 [PubMed: 21982946]
116. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012; 11:1006–1012.10.1016/S1474-4422(12)70191-6 [PubMed: 23079557]
117. Stuller KA, Jarrett B, DeVries AC. Stress and social isolation increase vulnerability to stroke. *Exp Neurol*. 2012; 233:33–39.10.1016/j.expneurol.2011.01.016 [PubMed: 21281636]
118. Sudheimer KD, O'Hara R, Spiegel D, Powers B, Kraemer HC, Neri E, Weiner M, Hardan A, Hallmayer J, Dhabhar FS. Cortisol, cytokines, and hippocampal volume interactions in the elderly. *Front Aging Neurosci*. 2014; 6:153.10.3389/fnagi.2014.00153 [PubMed: 25071562]
119. Sugo N, Hurn PD, Morahan MB, Hattori K, Traystman RJ, DeVries AC. Social stress exacerbates focal cerebral ischemia in mice. *Stroke*. 2002; 33:1660–1664. [PubMed: 12053008]
120. Suri D, Vaidya VA. Glucocorticoid regulation of brain-derived neurotrophic factor: relevance to hippocampal structural and functional plasticity. *Neuroscience*. 2013; 239:196–213.10.1016/j.neuroscience.2012.08.065 [PubMed: 22967840]
121. Szeto A, Nation DA, Mendez AJ, Dominguez-Bendala J, Brooks LG, Schneiderman N, McCabe PM. Oxytocin attenuates NADPH-dependent superoxide activity and IL-6 secretion in macrophages and vascular cells. *Am J Physiol Endocrinol Metab*. 2008; 295:E1495–501.10.1152/ajpendo.90718.2008 [PubMed: 18940936]
122. Takatsu-Coleman AL, Patti CL, Zanin KA, Zager A, Carvalho RC, Borcoi AR, Ceccon LM, Berro LF, Tufik S, Andersen ML, Frussa-Filho R. Short-term social isolation induces depressive-like behaviour and reinstates the retrieval of an aversive task: mood-congruent memory in male mice? *J Psychiatry Neurosci*. 2013; 38:259–268.10.1503/jpn.120050 [PubMed: 23182303]
123. Toledo JB, Toledo E, Weiner MW, Jack CR Jr, Jagust W, Lee VM, Shaw LM, Trojanowski JQ. Alzheimer's Disease Neuroimaging Initiative . Cardiovascular risk factors, cortisol, and amyloid-beta deposition in Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement*. 2012; 8:483–489.10.1016/j.jalz.2011.08.008 [PubMed: 23102118]
124. Tu WJ, Dong X, Zhao SJ, Yang DG, Chen H. Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischaemic stroke. *J Neuroendocrinol*. 2013; 25:771–778.10.1111/jne.12052 [PubMed: 23701638]
125. Uchoa ET, Aguilera G, Herman JP, Fiedler JL, Deak T, de Sousa MB. Novel aspects of glucocorticoid actions. *J Neuroendocrinol*. 2014; 26:557–572.10.1111/jne.12157 [PubMed: 24724595]
126. Udell JA, Steg PG, Scirica BM, Smith SC Jr, Ohman EM, Eagle KA, Goto S, Cho JI, Bhatt DL. REduction of Atherothrombosis for Continued Health (REACH) Registry Investigators . Living alone and cardiovascular risk in outpatients at risk of or with atherothrombosis. *Arch Intern Med*. 2012; 172:1086–1095. 1188041 [pii]. [PubMed: 22711020]
127. Venna VR, Xu Y, Doran SJ, Patrizzi A, McCullough LD. Social interaction plays a critical role in neurogenesis and recovery after stroke. *Transl Psychiatry*. 2014; 4:e351.10.1038/tp.2013.128 [PubMed: 24473442]
128. Venna VR, Verma R, O'Keefe LM, Xu Y, Crapser J, Friedler B, McCullough LD. Inhibition of Mitochondrial P53 Abolishes the Detrimental Effects of Social Isolation on Ischemic Brain Injury. *Stroke*. 2014 STROKEAHA.114.006553 [pii].

129. Venna VR, Weston G, Benashski SE, Tarabishy S, Liu F, Li J, Conti LH, McCullough LD. NF-kappaB contributes to the detrimental effects of social isolation after experimental stroke. *Acta Neuropathol.* 2012; 124:425–438.10.1007/s00401-012-0990-8 [PubMed: 22562356]
130. Verma R, Friedler BD, Harris NM, McCullough LD. Pair housing reverses post-stroke depressive behavior in mice. *Behav Brain Res.* 2014; 269:155–163.10.1016/j.bbr.2014.04.044 [PubMed: 24793492]
131. Vespa J, Lewis JM, Kreider RM. America's Families and Living Arrangements: 2012. *Current Population Reports* P20–570. 2013:1–34.
132. Victor, CR.; Bowling, A.; Bond, J.; Scambler, S. ESRC Growing Older Programme. Sheffield: 2003. Loneliness, social isolation and living alone in later life.
133. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. *Am J Epidemiol.* 2002; 155:1081–1087. [PubMed: 12048221]
134. Wang X, Wu H, Miller AH. Interleukin 1alpha (IL-1alpha) induced activation of p38 mitogen-activated protein kinase inhibits glucocorticoid receptor function. *Mol Psychiatry.* 2004; 9:65–75.10.1038/sj.mp.4001339 [PubMed: 14699442]
135. Weil ZM, Norman GJ, Barker JM, Su AJ, Nelson RJ, Devries AC. Social isolation potentiates cell death and inflammatory responses after global ischemia. *Mol Psychiatry.* 2008; 13:913–915.10.1038/mp.2008.70 [PubMed: 18800053]
136. Whiteley W, Jackson C, Lewis S, Lowe G, Rumley A, Sandercock P, Wardlaw J, Dennis M, Sudlow C. Association of circulating inflammatory markers with recurrent vascular events after stroke: a prospective cohort study. *Stroke.* 2011; 42:10–16.10.1161/STROKEAHA.110.588954 [PubMed: 21127302]
137. Wingard, DL.; Cohn, BA. Coronary Heart Disease Mortality Among Women in Alameda County, 1965 to 1973. In: Eaker, ED.; Packard, B.; Wenger, NK.; Clarkson, TB.; Tyroler, HA., editors. *Coronary Heart Disease in Women.* Haymarket Doyma; New York: 1987. p. 99-105.
138. Wisely EV, Xiang YK, Oddo S. Genetic suppression of beta2-adrenergic receptors ameliorates tau pathology in a mouse model of tauopathies. *Hum Mol Genet.* 2014; 23:4024–4034.10.1093/hmg/ddu116 [PubMed: 24626633]
139. Wolf OT, Convit A, de Leon MJ, Caraos C, Qadri SF. Basal hypothalamo-pituitary-adrenal axis activity and corticotropin feedback in young and older men: relationships to magnetic resonance imaging-derived hippocampus and cingulate gyrus volumes. *Neuroendocrinology.* 2002; 75:241–249. 54715 [pii]. [PubMed: 11979054]
140. Yang YC, McClintock MK, Kozloski M, Li T. Social isolation and adult mortality: the role of chronic inflammation and sex differences. *J Health Soc Behav.* 2013; 54:183–203.10.1177/0022146513485244 [PubMed: 23653312]
141. Yu NN, Wang XX, Yu JT, Wang ND, Lu RC, Miao D, Tian Y, Tan L. Blocking beta2-adrenergic receptor attenuates acute stress-induced amyloid beta peptides production. *Brain Res.* 2010; 1317:305–310.10.1016/j.brainres.2009.12.087 [PubMed: 20059989]
142. Zhou J, Yu JT, Wang HF, Meng XF, Tan CC, Wang J, Wang C, Tan L. Association between Stroke and Alzheimer's Disease: Systematic Review and Meta-Analysis. *J Alzheimers Dis.* 2014 96435J5720586417 [pii].
143. Zlatkovic J, Filipovic D. Chronic social isolation induces NF-kappaB activation and upregulation of iNOS protein expression in rat prefrontal cortex. *Neurochem Int.* 2013; 63:172–179.10.1016/j.neuint.2013.06.002 [PubMed: 23770205]
144. Zuidersma M, Conradi HJ, van Melle JP, Ormel J, de Jonge P. Self-reported depressive symptoms, diagnosed clinical depression and cardiac morbidity and mortality after myocardial infarction. *Int J Cardiol.* 2013; 167:2775–2780.10.1016/j.ijcard.2012.07.002 [PubMed: 22835990]

Fig. 1.

Lower levels of daily social support correlated with increased neural activity in both the dorsal anterior cingulate cortex (dACC) and Brodmann's area (BA) 8 of the dorsal superior frontal gyrus as well as increased cortisol reactivity to acute social stress tasks. Neurons of the dACC fire in animals experiencing distress associated social rejection, whereas BA 8 activity has been associated with maternal separation. By contrast, participants who interacted with more supportive individuals displayed attenuated neural activity and cortisol response to the acute stress task. Yellow indicate regions that correlate positively with social distress; green indicate regions that correlate negatively with social support; red indicates regions that correlate positively with cortisol responses. Reprinted from *NeuroImage*, Vol 35/Issue 4, Naomi I. Eisenberger, Shelley E. Taylor, Shelly L. Gable, Clayton J. Hilmert, Matthew D. Lieberman, Neural pathways link social support to attenuated neuroendocrine stress responses, pp. 1601–1612, Copyright (2007), with permission from Elsevier.

Fig. 2.

Effect of chronic loneliness on neuroendocrine and peripheral leukocyte response.

Loneliness stimulates the HPA axis by increasing ACTH and CRH secretion from the hypothalamus and pituitary, respectively. Consequently, the physiological concentrations of serum GC (cortisol in humans; corticosterone in rodents) will become chronically elevated. This contributes to excessive stimulation of the intracellular GR, particularly in peripheral leukocytes, leading to receptor desensitization and a reduction in GR expression. Leukocyte GR signaling normally regulates trafficking patterns as well as inflammatory gene expression. Alterations in these fundamental peripheral immune cell functions contribute to susceptibility to inflammatory diseases. This figure was generated using Servier Medical Arts

Fig. 3.

SNS-mediated leukocyte dysregulation with stress. Chronic stressors (such as repeated social disruption) exacerbate the activity of the sympathetic branch of the autonomic nervous system. These motor projections innervate bone marrow throughout the body, releasing norepinephrine (NE) into the synaptic space. NE binds to G-protein coupled β -adrenergic receptors present on the hematopoietic stem cell membrane to drive it toward a monocytic/granulocytic progenitor cell (via cAMP-PKA signaling). Pharmacological antagonists (propranolol) rescue the non-stressed phenotype, reducing the percentage of circulating immature pro-inflammatory monocytes to control levels. This figure was generated using Servier Medical Arts

Fig. 4.

Pre-stroke SI exacerbates histological damage in rodents. Comparison of tetrazolium chloride (TTC) staining of 2 mm coronal sections taken from young male and female mice assigned to their permanent housing conditions 7 days prior to surgery and analyzed at 72 hours post-reperfusion. With kind permission from Springer Science and Business Media and *Acta Neuropathologica*, Vol 124, 2012, pp. 425–438, NF κ B contributes to the detrimental effects of social isolation after experimental stroke, Venugopal R. Venna, Gillian Weston, Sharon E. Benashski, Sami Tarabishy, Fudong Liu, Jun Li, Lisa H. Conti, and Louise D. McCullough, Figure 1a and 1c, Copyright (2012).

Fig. 5.

Ipsilateral striatal brain sections in mouse 49 days after surgery showing increased BDNF immunohistochemical staining in PH animals. Green represents BDNF positive cells and blue represents cell nuclei. Animals were assigned to their permanent housing condition immediately following experimental stroke or sham (control) surgery. SH/SH displays a sham operated mouse brain that was PH with another healthy (sham) partner, ST/SH indicates a stroked mouse that was PH with a healthy (sham) partner, ST/ST shows a stroked mouse brain that was PH with an unhealthy (stroked) partner, and ST/ISO describes a stroked and isolated mouse. Post-stroke isolation was associated with significantly decreased BDNF signaling, suggesting that isolation decreased neuroplasticity and neurogenesis after ischemic injury. Reprinted from Behavioural Brain Research, Vol 260, Lena M. O’Keefe, Sarah J. Doran, Laetitia MwilambweTshilobo, Lisa H. Conti, Venugopal R. Venna, Louise D. McCullough, Social isolation after stroke leads to depressive-like behavior and decreased BDNF levels in mice, pp. 162–170, Copyright (2014), with permission from Elsevier.

Fig. 6.

Social isolation and other stressors may accelerate AD pathology by increasing the activity of both the SNS and the HPA axis. Isolation-induced HPA axis dysfunction increases the likelihood of developing AD pathology. Accumulation of plaques and/or neurofibrillary tangles further dysregulates HPA axis functioning and increases glucocorticoid secretion, which in turn accelerates pathology. This results in a cycle of increasing HPA axis disruption and pathology buildup. Stimulation of the SNS by social isolation increases β -adrenergic receptor activation, resulting in the upregulation of tau pathology, amyloid beta accumulation, and pro-inflammatory myelopoiesis. This figure was generated using Servier Medical Arts

Table 1

Clinical studies demonstrating a link between low social support indices and increased disease-related mortality

Cause of mortality	Reference (Year)
All-cause	House et al. 1988 [53] House, 2001 [52] Holt-Lunstad et al., 2010 [51]
Cardiovascular	Kaplan et al., 1988 [63] Brummett et al., 2001 [10] Rutledge et al., 2004 [105]
Cerebrovascular	Henderson et al., 2013 ^a [49]
Infectious disease	Patterson et al., 1996 [96] Lee & Rotheram-Borus, 2001 [77]
Dementia/Alzheimer's Disease Cancer	Orrell et al., 2000 [94] Ikeda et al., 2013 ^b [59] Drageset et al., 2013 [30]

^a Authors investigated psychosocial distress and stroke mortality

^b More pronounced in males

Table 2

Effects of SI on post-stroke neuroinflammation in mice

Effect of SI	Comments	Reference (Year)
Decreased striatal IL-6 gene expression	Relative to contralateral hemisphere	Karelina et al., 2009 [66]
Decreased cortical IL-6 protein expression	Relative to contralateral hemisphere	
Increased serum IL-6 cytokine expression	N/A	
No change in serum cortisol at 12/24 hr post-injury	N/A	
No change in microglial IL-1 β mRNA at 12/24 hr post-injury	N/A	
No change in microglial TNF- α mRNA at 12/24 hr post-injury	N/A	
No change in microglial TGF- β mRNA at 12/24 hr post-injury	N/A	
No change in microglial COX-2 mRNA at 12/24 hr post-injury	N/A	Craft et al., 2005 [21]
Increased plasma CRP during ischemia	Blood taken immediately following 60 minute MCAO	
No change in plasma CRP at 24 hr post-injury	N/A	
No change in plasma corticosterone at 24 hr post-injury	N/A	
No change in plasma corticosterone at 7 days post-injury	Both male and female 60 or 90 minute MCAO	Venna et al., 2012 [129]
Increased NF- κ B nuclear translocation and transcriptional activity	Pro-inflammatory transcription factor	
Increased striatal Mac-1 gene expression at 12 hours post-injury	N/A	Karelina et al., 2009 [66]
	Utilize the global cerebral ischemia model	Weil et al., 2008 [135]
Increased striatal GFAP gene expression at 12 hours post-injury	N/A	Karelina et al., 2009 [66]
	Utilize the global cerebral ischemia model	Weil et al., 2008 [135]

Table 3

The effect of SI in different models of AD neuropathology

Transgenic Mouse Model	Effect of SI	Reference (Year)
Tg2576	Decreased hippocampal cell proliferation, impaired contextual memory, increased A β plaques.	Dong et al., 2004 [28]
Tg2576	Increased A β brain levels and A β plaques, plasma corticosterone, glucocorticoid receptor and corticotropin-releasing factor receptor-1 expression, and hippocampal atrophy.	Dong et al., 2008 [29]
APP/PS1	Impaired spatial working memory, increased beta- amyloid levels in hippocampus, and, in certain brain regions, increased MnSOD levels, decreased cholinergic, serotonergic, and noradrenergic neurons, and decreased NMDA 2B receptor levels.	Huang et al., 2011 [58]
APP/PS1	Impaired contextual memory, decreased long-term potentiation magnitude in hippocampal CA1 neurons, increased A β levels in hippocampus, increased β - and γ -secretase activity, calpain activity and p25/p35 ratio, decreased membrane-associated p35, GluR1 Ser831 phosphorylation and surface expression of AMPA receptors, and decreased association of p35 and α -CaMKII.	Hsiao et al., 2011 [56]