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Role of social factors on cell death, cerebral plasticity and recovery after stroke

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Abstract

Stroke is a serious global health care problem. It is now the fourth leading cause of death and the primary cause of adult disability in the United States. Substantial evidence from both experimental and clinical studies has demonstrated that social isolation (SI) can increase stroke incidence and impair recovery. Epidemiological studies demonstrate that an increasing number of patients are living alone, and as the aging population increases, loneliness will only increase in prevalence. SI is increasingly identified as an independent risk factor for all-cause mortality. In contrast, individuals with high levels of social support exhibit more rapid and extensive functional and cognitive recovery after a wide variety of pathological insults, including stroke. Clinical data suggests that SI is an important risk factor for increased mortality and delayed functional recovery following ischemic stroke. Attesting to the importance of mortality and behavioral factors in stroke outcome is that these same effects can be reproduced in animal models of experimental stroke. This has allowed researchers to identify several mechanistic changes that occur with affiliative interactions. These include decreased systemic inflammation, elaboration of growth factors including brain derived neurotrophic factor (BDNF), enhanced neurogenesis, and improved neuroimmune responsiveness in group housed animals. These may mediate the beneficial effects of social interaction on improving stroke recovery and reducing neuronal death. In this review we provide an overview of the effects of SI on ischemic injury and recovery and discuss their clinical and therapeutic implications.

Keywords

Social isolation; social interaction; brain plasticity; stroke; behavior

Introduction

For social species, social interaction is vital for brain development and overall health (Cacioppo & Hawkley, 2009). Overwhelming evidence suggests that brain cells can rewire

to maintain brain vitality depending on social experiences (Yevchak *et al.*, 2008). Social isolation (SI) is not only an independent risk factor for mortality, but also shortens the lifespan and predicts morbidity from a multitude of health conditions including cancer, and stroke (House *et al.*, 1988; Boden-Albala *et al.*, 2005; Kroenke *et al.*, 2006; Holt-Lunstad *et al.*, 2010). The detrimental effects of SI are independent of race, ethnicity, age and gender (Mechakra-Tahiri *et al.*, 2010). In contrast, supportive social relationships are associated with improved health and healthy aging and an overall decrease in mortality (House *et al.*, 1988; Holt-Lunstad *et al.*, 2010). The influence of environmental factors on the phenotypic expression of vascular disease is becoming increasingly recognized (Schrijver *et al.*, 2002). It is hypothesized that many of the markers of increased vascular risk, such as elevated C-reactive protein, reflect the underlying immune status of the individual, which in turn can be influenced by psychosocial stress such as loneliness (Craft *et al.*, 2005; Hafner *et al.*, 2011; Heffner *et al.*, 2011; Shankar *et al.*, 2011). As SI and loneliness are associated with increased mortality, efforts to reduce isolation appear to be a viable therapeutic option and have been shown to significantly reduce mortality risk (House *et al.*, 1988; Cheng & Vickrey, 2006; Karelina *et al.*, 2009b; Cacioppo *et al.*, 2011; Heffner *et al.*, 2011; Venna *et al.*, 2014). Despite extensive studies that have attempted to understand the genetic and molecular factors involved in brain functioning and dysfunction over recent decades, the effects of housing have received far less attention.

Each year, 15 million people worldwide are affected by stroke, resulting in 5 million deaths and 5 million cases of long-term disability. In the United States, stroke is the fourth leading cause of death and the major cause of adult disability (Go *et al.*, 2013; Bushnell *et al.*, 2014; Go *et al.*, 2014; Roy-O'Reilly & McCullough, 2014). The American Heart Association predicts that by 2030, the direct cost of caring for stroke patients will triple from \$61.55 billion to \$183.13 billion, due in large part to increasing life expectancy and declining stroke-related mortality (Go *et al.*, 2013; Bushnell *et al.*, 2014; Go *et al.*, 2014). Ischemic stroke accounts for ~87% of all stroke, but tissue plasminogen activator remains the only FDA approved treatment (Roy-O'Reilly & McCullough, 2014). However due to its short therapeutic window and numerous exclusions for its use, currently less than 5% of acute stroke patients receive thrombolytic therapy (Leys & Deplanque, 2006; Bodenant *et al.*, 2010; Roy-O'Reilly & McCullough, 2014). Although several neuroprotective agents and non-interventional approaches have been proposed from animal research they showed little or no promising results in stroke survivors (Venna & McCullough, 2011). Therefore, there remains an urgent need to explore alternative potential approaches to improve stroke outcome.

Interestingly, patients with high levels of social support or large social networks exhibit more rapid and extensive functional recovery after stroke compared to socially isolated (SI) individuals (Boden-Albala *et al.*, 2005). Perceived SI predicts morbidity and mortality from both stroke and other vascular diseases (Boden-Albala *et al.*, 2005; Cheng & Vickrey, 2006; Karelina *et al.*, 2009b; Venna & McCullough, 2011; Venna *et al.*, 2012; Venna *et al.*, 2014). Individuals who report lack of social support or isolation have an increased incidence of recurrent stroke, poorer recovery, and greater functional decline following a stroke compared to individuals with social support (Friedman, 1993; Trigg *et al.*, 1999; Boden-

Albala *et al.*, 2005). Low social support is associated with increased vascular risk even after controlling for common risk factors such as age, education, obesity, exercise, smoking, and drinking (Morris *et al.*, 1993; Boden-Albala *et al.*, 2005). Loss of a spouse negatively affects overall health and decreases opportunities for functional recovery and return to the community after stroke and further contributes to SI in the elderly (Avendano *et al.*, 2006). Greater social support and higher neighborhood-level social cohesion were independently associated with reduced risk of mortality in stroke patients compared to stroke survivors exposed to pre-stroke isolation; however isolation also increased the risk of depression, anxiety and stress, which could have their own independent effects on health (Glass *et al.*, 2000; Ouimet *et al.*, 2001; Boden-Albala *et al.*, 2005; Cacioppo & Hawkey, 2009; Clark *et al.*, 2011; Kimet *et al.*, 2013; O'Keefe *et al.*, 2014). The mechanisms involved in the beneficial effects of social support remain unclear, but increasing attention has been given to inflammatory signaling (Craft *et al.*, 2005; Karelina *et al.*, 2009b; Olson *et al.*, 2010; Hafner *et al.*, 2011; Stuller *et al.*, 2012). Epidemiological data shows higher levels of Interleukin-6 (IL-6) and hs-CRP in socially isolated individuals, although this relationship was more notable in men. However in large epidemiological trials, numerous confounders such as compliance with medication, activity levels, and even differences in genetic polymorphisms that influence activation of inflammatory gene expression, are difficult to control for when attributing the risk of SI (Hafner *et al.*, 2011). Because of these difficulties, developing animal models and exploring endogenous mechanisms by which social support improves stroke outcome in a more controlled experimental environment are needed to develop successful future therapeutic approaches.

What is social isolation and why is it important?

Although, SI and social support is defined in a myriad of ways in epidemiological and clinical studies (Venna & McCullough, 2011), isolation in animal studies refers to the housing condition, i.e. housed individually or socially housed in pairs (either with the same or opposite sex), that facilitate interaction with a potential for enhanced grooming, increased whisker stimulation and providing an enriched social environment (Craft *et al.*, 2005; DeVries *et al.*, 2007; Karelina *et al.*, 2009a; Karelina *et al.*, 2011; Stuller *et al.*, 2012; Venna *et al.*, 2012; O'Keefe *et al.*, 2014; Venna *et al.*, 2014). However in some experimental paradigms, the effects of isolation are compared against a larger group of animals per cage (Gordon *et al.*, 1998; Bartolomucci *et al.*, 2003; Arndt *et al.*, 2009). Several factors need to be considered to ensure consistency in one's research findings especially when using paired housing of same sex animals (O'Keefe *et al.*, 2014; Venna *et al.*, 2014). One vital factor is compatibility, if the partner is aggressive the animal undergoes stress and this can worsen stroke outcomes (DeVries *et al.*, 2001; Bondar & Kudriavtseva, 2005). In this review, we mostly emphasize stroke studies, with a focus on rodents, which most studies have utilized.

Standard housing conditions often vary between laboratories. The most common housing condition constitute cages with bedding, providing ad libitum access to water and food pellets and nesting material (Nithianantharajah & Hannan, 2006; Febinger *et al.*, 2014). It is generally assumed that standard housing constitutes group housing of same sex animals (group size varies between 2-10/cage), while some define isolation (single) housing as the standard condition (Engesser-Cesar *et al.*, 2005). The exact nature of the housing conditions

and manipulation of housing conditions during the experiments is often not fully described in the experimental methods. Evidence that isolation is detrimental or paired housing is beneficial should be taken into account in the experimental design (**Figure.1**). Therefore “standard housing conditions” are important to report and it is important that these be maintained uniformly throughout the experiment when attempting to interpret any study on pharmacological or genetic outcomes after stroke.

Social Isolation on neurological and psychiatric disorders

The effects of isolation in animals were initially reported over a half-century ago, with isolated animals being excessively sensitive to handling and demonstrating an anxiogenic phenotype, leading to the description of a ‘isolation-induced stress syndrome’ (Holson *et al.*, 1991; Fone & Porkess, 2008). House, *et al.*, 1988 reviewed findings from clinical studies (House *et al.*, 1988) which generated significant interest in understanding the physiological underpinnings of the detrimental effects of SI in the scientific community and encouraged researchers to develop animal models to study the effects of isolation. This has led to significant advancements in our understanding of SI effects in both disease and non-disease conditions over the past two decades (Liu & Wang, 2005; Stranahan *et al.*, 2006; Karelina *et al.*, 2009b; Cacioppo *et al.*, 2011; Karelina *et al.*, 2011; Liu *et al.*, 2012; Stuller *et al.*, 2012; Madden *et al.*, 2013). Animal studies using models of Alzheimer’s disease, schizophrenia, depression, stroke and epilepsy to note a few (**see Table. 1**) have ignited interest in the interaction between housing and disease. Consistent and impressive reports of the detrimental effects of SI have now been identified in many brain disorders (Drage & Heinrichs, 2005; Wang *et al.*, 2009; Nation *et al.*, 2010; Nakagawa-Toyama *et al.*, 2012). These findings might have immediate translational implications for clinical and rehabilitation therapies (Fone & Porkess, 2008; Marder *et al.*, 2011; Venna & McCullough, 2011). Moreover, these animal studies on housing manipulation provide powerful tools for dissecting cause and effect among molecular and cellular correlates of disease progression and recovery, and identify novel pharmacological targets for future therapeutic interventions (Nithianantharajah & Hannan, 2006; 2009; Venna & McCullough, 2011; Venna *et al.*, 2014). In the current review we not only attempt to update this rapidly advancing area of research but also attempt to provide the new insights from experimental paradigms that could be implicated in a wide range of brain pathologies.

Psychosocial Factors Influencing Stroke Outcome

Environmental and psychological factors are widely recognized as major contributors to stroke outcome, and predict outcome as well as, or better than, traditional risk factors. It is reported that pair-housed (PH) animals had significantly smaller infarcts than animals that were socially isolated prior to an induced stroke (**Figure 1**) (Craft *et al.*, 2005; Karelina *et al.*, 2009a; Karelina *et al.*, 2009b; Karelina *et al.*, 2011; Venna *et al.*, 2012; Venna *et al.*, 2014). Importantly, this was reflected in both histological and behavioral outcomes as PH animals had improved contralateral paw use relative to SI cohorts (DeVries *et al.*, 2001; Craft *et al.*, 2005; DeVries *et al.*, 2007; Karelina *et al.*, 2009a; Karelina *et al.*, 2009b; Karelina *et al.*, 2011; Venna *et al.*, 2012; O’Keefe *et al.*, 2014; Venna *et al.*, 2014) independent of significant changes in corticosterone levels. Similar findings have been

found by others in both global and focal rodent models of ischemia (Craft *et al.*, 2005). SI mice also have increased edema formation and higher mortality compared to PH mice (Craft *et al.*, 2005). Such effects are seen in both males and females (Craft *et al.*, 2005; Venna *et al.*, 2012). The mechanism by which social interaction influences ischemic outcomes is complex and involves altered neuroendocrine (Ros-Simo & Valverde, 2012; Stuller *et al.*, 2012; Liu *et al.*, 2013), inflammatory (Karelina *et al.*, 2009a; Karelina *et al.*, 2009b; Venna *et al.*, 2012), pro-survival growth factors (Berton *et al.*, 2006; Zhu *et al.*, 2006; O'Keefe *et al.*, 2014; Venna *et al.*, 2014), cell proliferation, neurogenesis (Stranahan *et al.*, 2006; Kannangara *et al.*, 2011; Venna *et al.*, 2014) and synaptic plasticity (Fone & Porkess, 2008). In addition, social stress can also affect stroke outcome. In models of chronic social intimidation, stressed male mice had significantly lower ischemia-induced bcl-2 levels, an important anti-apoptotic protein, and earlier neuronal cell loss than unstressed mice (DeVries *et al.*, 2001). Additionally, social stress exacerbated infarct in wild-type mice, but not in transgenic mice that constitutively express increased neuronal bcl-2, despite the fact that the two mice show equivalent post-ischemic concentrations of corticosterone (Craft *et al.*, 2005; DeVries *et al.*, 2007), suggesting that not all the deleterious effects of SI and psychosocial stress can be attributed to glucocorticoids. It has been thus hypothesized that social stress compromises an endogenous molecular neuroprotective mechanism that may include the enhancement of antioxidants and the expression of pro-survival genes (Craft *et al.*, 2005; DeVries *et al.*, 2007).

Social isolation in stroke survivors

Social relationships perceived as being supportive are associated with improved health and healthy aging (Gerretsen *et al.*, 2010; Krause *et al.*, 2011) and an overall decrease in mortality (House *et al.*, 1988; Holt-Lunstad *et al.*, 2010; Umberson & Montez, 2010; Heffner *et al.*, 2011). Patients with high levels of social support or large social networks exhibit more rapid and extensive functional recovery after stroke than socially isolated individuals (Burton, 2000; Boden-Albala *et al.*, 2005). In contrast, perceived SI predicts morbidity and mortality, including death from stroke and cerebrovascular disease (Cheng & Vickrey, 2006; Clark *et al.*, 2011). Individuals who report lack of social support or isolation have an increased incidence of recurrent stroke, poorer recovery, and greater functional decline over the years following a stroke as well as reduced survival compared to individuals with social support (see **Table. 2**) (Clark *et al.*, 2011; Kim *et al.*, 2013). Low social support is associated with increased vascular risk even after controlling for common risk factors such as age, education, obesity, exercise, smoking, and drinking (Avendano *et al.*, 2006; Shankar *et al.*, 2011). There is some evidence that the role of social networks may be even more important in promoting recovery than in preventing disease (Christakis & Fowler, 2007; Cacioppo *et al.*, 2009; Clark *et al.*, 2011; Christakis & Fowler, 2013; Kim *et al.*, 2013). In a large data set of over 2,000 HMO members, social support was most strongly associated with 15-year mortality, more so than heart disease, cancer, and stroke (Leutz *et al.*, 2005).

One important social factor in predicting stroke outcome is marital status. Being married is inversely associated with mortality, particularly among men (Gardner & Oswald, 2004). Women are more likely to be widowed or unmarried and living alone which may partially

explain the alarming statistic that women are significantly more likely to be disabled after a stroke and 3.5 times more likely to be institutionalized (Petrea *et al.*, 2009; Petrea *et al.*, 2013). Loss of a spouse negatively affects overall health, and decreases opportunities for functional recovery and return to the community (Appelroset *et al.*, 2003). In the Enhancing Recovery In Coronary Heart Disease Trial, social support appeared to benefit coronary disease recurrence and mortality outcomes in men but not in women (Lett *et al.*, 2005) in agreement with several other large trials. In a recent large prospective analysis, the risk of mortality from stroke was 1.6-fold higher for men with the lowest levels of social support compared with men with the highest levels, but there was no association between low social support and stroke mortality in women (Ikeda *et al.*, 2008). In clinical populations social factors may have effects through a number of difficult to quantify factors such as enhanced depression, poorer control of risk factors, and lack of compliance with medications. However, effective interventions to deliver social support in clinical settings have yet to be devised. Several randomized clinical trials that have attempted to deliver social support through cognitive behavioral therapy via social support groups, or family systems interventions have not been successful (Berkman *et al.*, 2003). One possibility is that the duration, timing, or intensity (i.e., the “dose”) of social support provided in these trials to cardiovascular disease survivors was insufficient to affect clinical prognosis. It is imperative that we identify a preclinical model that successfully mirrors (in a relatively controlled environment) possible mechanisms of stress related exacerbations in stroke that will allow us to target new therapies and devise novel interventions with the highest likelihood of success.

Social isolation in animal stroke models and involved mechanisms

The detrimental effects of isolation were first reported by Horie using spontaneously hypertensive rats that are stroke-prone (SHRSP) (Horie *et al.*, 1991). SHRSP rats that were exposed to isolation had increased hypertension and higher stroke incidence than non-isolated rats (Horie *et al.*, 1991). Later animal models of isolation were developed and the first extensive findings on stroke outcomes were reported by Craft *et al.* (Craft *et al.*, 2005). This study showed that even a brief (two weeks) period of SI prior to a 90-minute middle cerebral artery occlusion led to a significant increase in infarct size and poorer contralateral paw use in both males and females compared with pair-housed cohorts (Craft *et al.*, 2005). These findings of increased infarct along with increased edema in SI mice have been consistently reported in number of later studies (**Table. 2**) (Karelina *et al.*, 2009b; Venna *et al.*, 2012; O'Keefe *et al.*, 2014; Venna *et al.*, 2014). Isolated cohorts have higher mortality rates after stroke (Karelina *et al.*, 2009a; Karelina *et al.*, 2009b; Venna *et al.*, 2014), increased cerebral edema (Karelina *et al.*, 2009b), and an elevated neuroimmune response (Stuller *et al.*, 2012) compared to pair housed control animals, providing a much-needed platform to investigate the possible mechanisms that mediate the effects of SI. Socially isolated mice have significantly higher levels of serum IL-6 (Karelina *et al.*, 2009b), increased transcriptional activity of nuclear factor kappa-B (Venna *et al.*, 2012), and reduced oxytocin gene expression (Karelina *et al.*, 2011) compared to pair housed mice.

From a translational perspective it is important to recognize that patients at elevated risk for SI might not be identified until after a stroke has occurred (Venna & McCullough, 2011). SI

has numerous detrimental effects on brain that include impaired neurogenesis and increased demyelination that are important in brain rewiring after injury. Therefore several recent studies have investigated the effect of SI on functional recovery that is initiated after the initial stroke (O'Keefe *et al.*, 2014; Venna *et al.*, 2014). Emerging evidence suggests that even delayed social interaction can improve post-stroke functional recovery and behavioral outcomes (Venna *et al.*, 2014). This improvement in behavior occurred in parallel with changes in cell proliferation and increased brain derived neurotrophic factor (BDNF) levels (O'Keefe *et al.*, 2014; Venna *et al.*, 2014). Furthermore, the health of the interacting partner appears to be an important factor in recovery, as stroke mice paired with a healthy partner recovered faster than those paired with a partner that also had a stroke. These factors need to be investigated in future studies.

Social isolation reduces myelination that impairs brain plasticity

Isolation resulted in the down-regulation of BDNF and reduced post-stroke neurogenesis (O'Keefe *et al.*, 2014; Venna *et al.*, 2014), leading to impaired recovery and enhanced mortality. SI is known to alter brain plasticity. Studies have shown that rats raised in isolation had decreased myelination of the corpus callosum (Juraska & Kopcik, 1988). Myelination is vital for synaptic function and plasticity. A recent study demonstrated that only a few weeks of isolation led to reduced levels of heterochromatin in oligodendrocytes, leading to reduced myelination in isolated mice (Liu *et al.*, 2012). SI is known to impair long term potentiation and synaptic transmission, an important functional index of brain plasticity (Quan *et al.*, 2010). Plasticity may be a very important mechanism by which the brain recovers after an injury. New evidence suggests that even delayed interaction can enhance stroke recovery, even when the infarct size is controlled (O'Keefe *et al.*, 2014; Venna *et al.*, 2014). Recent work in our laboratory suggests that animals isolated after stroke have progressive deficits in sociability that worsen over time (Verma *et al.*, submitted). This suggests that SI compounds the behavioral deficits that occur with stroke, and progressive isolation occurs, even when the animal is later given the opportunity to interact with others. These mice have several phenotypic features consistent with depression such as enhanced anhedonia and defeat behavior, further exacerbating stroke-induced behavioral deficits. Future work will evaluate if these deficits can be reversed with pharmacological agents such as serotonin reuptake inhibitors. Understanding the critical time window to reverse the detrimental effects of isolation on brain plasticity will be important as we advance these studies to clinical setting.

Social interaction as a novel therapeutic intervention and rehabilitative strategy

With the increasing number of stroke survivors in our communities, many of which experience isolation, elucidating the functional and molecular changes associated with social interaction might not only provide mechanistic insights into the pathogenesis of post-stroke behavioral and functional impairments but could also offer a possibility of development of a new class of therapeutic interventions. From the clinical perspective, these findings could have an important translational relevance as we attempt to optimize post-stroke environments for our patients. Encouraging social interactions in aged and isolated populations could be cost-effective and a feasible approach for improving post-stroke outcome to minimize the substantial economic burden of stroke (Berkman *et al.*, 2003).

More recent findings that delayed social interaction may still be an important modulator that can improve functional and behavioral outcomes in stroke mice suggests a wider therapeutic window for social interaction in improving stroke outcomes.

Conclusions and future directions

Despite the rapid advancement in our understanding of the detrimental mechanisms that mediate the histological, functional and molecular effects of SI, the translation of this research into clinical populations must still overcome several hurdles. How the effects of perceived loneliness (feeling lonely despite being in group) differs from the effects of isolation (living independently, with no social contact), needs to be understood. Are these two separate entities or does loneliness represent the emotional pathway through which SI impairs health? Does SI increase the susceptibility to brain pathology? Can this be minimized by early interventions? Does increasing use of social interaction using electronic media (such as Facebook and Twitter) offer the same benefits as social support offered by a physical interaction? Are there critical periods in life when social interventions have the greatest impact on minimizing the vulnerability to late-life CNS diseases? How do parameters such as partner compatibility, sex, age and genetics alter the effects of social interaction? Most importantly we must determine how to efficiently translate the finding from epidemiological data and experimental studies to therapeutic and rehabilitative settings. Other intriguing questions are how age and sex interact with isolation. Stroke is a disease of aging and is sexually dimorphic; the molecular changes identified in male mice models could be very different in females. None of the studies have directly compared males and females or young and aged mice under identical experimental conditions. Some studies have reported that pair-housing is beneficial for young females. However, the mechanisms identified in male only cohorts such as enhanced oxytocin signaling may differ, due to more prominent effects on lactation and parturition in females (Karelina *et al.*, 2011; Venna & McCullough, 2011). Similarly, it still remains to be elucidated whether social interaction in aged animals offers similar benefits, as previous reports indicate that the beneficial effects of social housing in young are mediated by regulation of factors like Bcl-2 (DeVries *et al.*, 2001), and the brain levels of Bcl-2 naturally decrease with age (Kaufmann *et al.*, 2001).

We have numerous challenges ahead in the translation of animal findings to humans, as individual preferences vary widely as humans differ in their level of comfort in the presence and absence of social cohesion and people differ in the degree of desired social interaction. The perception of loneliness or perceived social stress may differ among individuals (Stewart *et al.*, 2006; Cacioppo *et al.*, 2009; Cacioppo & Hawkley, 2009; Cacioppo *et al.*, 2011). Moreover, clinical studies are complicated by a number of factors including poor control of risk factors and lack of compliance with medications, which are therefore expensive and often difficult to quantify and control. Nevertheless, the findings from animal research, combined with epidemiological data and follow-up studies on stroke survivors, paves the way for a new understanding of beneficial effects of social interaction on stroke recovery, which could eventually lead to a range of therapeutic advances. Attempts to enhance social networks in patients after myocardial ischemia have not been able to successfully mimic the beneficial effects of social interaction (Berkman *et al.*, 2003) and we must further delineate the mechanisms underlying the detrimental effects of isolation if we

hope to design efficacious future clinical trials in stroke patients. Finally, before translating these important findings from animal studies to the clinical setting additional studies are needed to replicate these results in females; aged animals; and in models that study animals with comorbid illnesses, such as diabetes and hypertension.

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Figure 1. Pathway implied in stroke outcomes influenced by social isolation and paired housing
 Schematic of postulated pathway and possible mechanisms by which pair housing regulates stroke outcome. Blue shading represents factors associated in cell death or survival. Green shaded factors are associated with recovery. The yellow shaded area indicates processes on which social interaction have beneficial effects during stroke onset and recovery.

Table 1

Effects of social isolation on animal models of brain injury

Disorder	Functional & behavioral effects	Histological and molecular changes	References
Alzheimer's disease	SI exacerbates memory deficits, accelerates impairment of contextual fear memory, reduced hippocampal LTP.	SI increased hippocampal amyloid β peptide ($A\beta$) accumulation, γ -secretase activity, calpain activity and the p25/p35 ratio concomitant with decrease in membrane-associated p35 and p35/Cdk5 activity. Decrease in GluR1 Ser831 phosphorylation, surface expression of AMPARs and p35-GluR1-CaMKII interactions.	(Hsiao et al., 2011; Hsiao et al., 2012)
Schizophrenia	SI-induced an exacerbation of schizophrenia-like phenotypes. Reduced pre-pulse inhibition, novel object recognition discrimination.	Plasma tryptophan, kynurenine, anthranilic acid, 3-OHAA and quinolinic acid were elevated. Loss of neuronal plasticity. Involvement of NOX2-derived oxidative stress. Changes in the functional state of various cortical and hippocampal neurotransmitters, including glutamate and serotonin.	(Schiaivone et al., 2009; Marsden et al., 2011; Moller et al., 2012; Jiang et al., 2013; Moller et al., 2013)
Depression	Isolated animals displayed higher levels of anxiety-like behavior in the open field and elevated plus maze tests and depression-like behavior in forced swim test.	SI increase corticosterone levels, reduced cell proliferation, neurogenesis in hippocampus, decreased cAMP response element-binding protein activity in the nucleus accumbens.	(Wallace et al., 2009; Lieberwirth et al., 2012; Takatsu-Coleman et al., 2013)
Stroke	SI reduced locomotor activity, impaired functional recovery, induced post-stroke anxiety and depression like behavior.	Increased ischemic damage, elevated CRP concentration, IL-6, NF- κ B activity and protein levels. SI reduced Bcl-2 and BDNF levels compared to pair-housed controls. Isolation is also associated with reduced cell proliferation.	(Karelina et al., 2009a; Karelina et al., 2009b; Karelina et al., 2011; Stuller et al., 2012; Venna et al., 2012; O'Keefe et al., 2014; Venna et al., 2014)
Epilepsy	Increased the vulnerability to seizures in animals suffering from status epilepticus. Increase of seizure susceptibility to the GABA(A) receptor antagonist picrotoxin.	Isolated animals release higher corticosterone in response to status epilepticus. Critical role of N-methyl-D-aspartic acid receptor. Reduced GABA(A) receptor function caused by a decrease of endogenous allopregnanolone.	(Matsumoto et al., 2003; Lai et al., 2006; Lai et al., 2009).

Table 2

Studies of social isolation in stroke

Factor	Study type	Findings	References
Stroke incidence	Pre-clinical & human data	Increased the incidence of stroke in spontaneously hypertensive rats compared to controls. Pre-stroke SI is also identified as a risk factor for stroke in humans.	(Horie et al., 1991; Vogt et al., 1992; Boden-Albala et al., 2005)
Infarct size	Pre-clinical	Increases size of ischemic damage after stroke. Increases post-stroke edema.	(Craft et al., 2005; DeVries et al., 2007; Karelina et al., 2009b; Venna et al., 2012; Venna et al., 2014)
Physiological changes	Pre-clinical	Changes in the hypothalamic-pituitary-adrenal (HPA) axis and accelerated urinary epinephrine excretion, indicating emotional stress with SI. Important physiological variables such as blood pressure monitoring, heart rate, core body temperature, blood glucose and oxygen saturation need to be more thoroughly investigated.	(Horie et al., 1991; Craft et al., 2005; Karelina et al., 2009b)
Functional recovery	Pre-clinical & Human data	SI is a predictor of worse stroke outcomes in clinical populations. Animals studies have consistently shown that SI is associated with impaired recovery	(Boden-Albala et al., 2005; Craft et al., 2005; Venna et al., 2012; Venna et al., 2014)
Behavioral recovery	Pre-clinical & Human data	Both pre and post-stroke SI is an important risk factor for post-stroke depression in stroke survivors and may contribute to poor compliance, depression, and stress. Depression-like behavior is observed in animals subjected to SI and stroke.	(Whyte & Mulsant, 2002; Craft et al., 2005; Venna et al., 2012; Venna et al., 2014)
Mortality	Pre-clinical & Human data	In clinical populations, SI is associated with higher post stroke mortality through a number of underlying mechanisms including depression, decreased medication compliance and decreased physical activity. Animal studies also reported an increased stroke mortality with isolation.	(Boden-Albala et al., 2005; Karelina et al., 2009b; Venna et al., 2014)