REVIEW

Aging gracefully: social engagement joins exercise and enrichment as a key lifestyle factor in resistance to age-related cognitive decline

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Abstract

Cognitive impairment is a consequence of the normal aging process that effects many species, including humans and rodent models. Decline in hippocampal memory function is especially prominent with age and often reduces quality of life. As the aging population expands, the need for interventional strategies to prevent cognitive decline has become more pressing. Fortunately, several major lifestyle factors have proven effective at combating hippocampal aging, the most well-known of which are environmental enrichment and exercise. While the evidence supporting the beneficial nature of these factors is substantial, a less well-understood factor may also contribute to healthy cognitive aging: social engagement. We review the evidence supporting the role of social engagement in preserving hippocampal function in old age. In elderly humans, high levels of social engagement correlate with better hippocampal function, yet there is a dearth of work to indicate a causative role. Existing rodent literature is also limited but has begun to provide causative evidence and establish candidate mechanisms. Summed together, while many unanswered questions remain, it is clear that social engagement is a viable lifestyle factor for preserving cognitive function in old age. Social integration across the lifespan warrants more investigation and more appreciation when designing living circumstances for the elderly.

Key Words: *aging; age-related cognitive decline; social engagement; hippocampus; cognitive enrichment; exercise; memory; neurogenesis*

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The recent global increase in life expectancy has resulted in an expansion of the population experiencing age-related cognitive impairment. Cognitive decline is a part of normal aging and occurs even in the absence of overt neurodegenerative disease such as Alzheimer's or Parkinson's diseases (Bettio et al., 2017). The memory functions of the hippocampus are particularly vulnerable to decline with age. The aged hippocampus is marked by atrophy, aberrant connectivity, inflammation, and reduced plasticity, resulting in progressive impairment of key functions such as declarative and spatial memory formation (Bartsch and Wulff, 2015). The diminished quality of life due to age-related hippocampal decline is a prominent health concern for the expanding elderly population. Despite a pressing need for strategies to preserve hippocampal function, pharmacological approaches have yet to yield an effective treatment. In contrast, a number of lifestyle factors such as cognitive enrichment and exercise are well-established to preserve hippocampal function in old age. This review examines the role of these major lifestyle factors in hippocampal aging and provides more in-depth discussion of the often-underappreciated role of social engagement. Together, these three factors provide viable intervention strategies for preventing age-related memory decline as well as experimental models that can help uncover the molecular mechanisms of altered memory function. We performed a PubMed literature search with no date restrictions in June 2018 of articles on aging and age-related cognitive decline as well as exercise, cognitive enrichment, and social engagement in relation to aging and cognition.

Humans that engage in cognitive enrichment throughout adulthood, by playing musical instruments, reading books, or having a higher level of education, show resistance to age-related hippocampal memory decline (Fratiglioni et al., 2004; Bettio et al., 2017). Prospective, interventional studies further suggest that engaging in enriching activities can yield benefit, even when started in old age as part of a clinical trial (Ballesteros et al., 2015; Train the Brain Consortium, 2017). The benefits of enriching activities have been successfully modeled in rodents, as well. In mice and rats, environmental enrichment protocols that expose animals to larger environments with a rotating collection of toys improve hippocampal-dependent spatial memory in young animals and slow the progression of age-related memory decline compared to standard housing (van Praag et al., 2000). A leading theory for the mechanism of enrichment-derived hippocampal protection is that exposure to a variety of stimuli drives neural activity, resulting in formation of a cognitive reserve. An adept cognitive reserve provides the brain with alternative cognitive strategies that can compensate for age-related impairments and thereby preserve function (Fratiglioni et al., 2004). Candidate cellular and molecular mediators of cognitive reserve include enhanced synaptic plasticity and

reduced cellular atrophy, both of which can be found in humans and rodents exposed to enrichment (Eckert and Abraham, 2013; Park and Bischof, 2013). Rodent studies additionally suggest that increased neurogenesis in the dentate gyrus subregion of the hippocampus may also contribute to preserved hippocampal function following enrichment (van Praag et al., 2000). Though aging is associated with a precipitous drop in the birth and survival of new neurons in this brain region, exposure to environmental enrichment can partially alleviate this loss, primarily by enhancing the survival of newly born neurons (Kempermann et al., 2002). In sum, research in humans and rodents suggest a strong, causative role of cognitive enrichment in preserving hippocampal health through aging.

Like enrichment, exercise preserves hippocampal function in old age in humans and rodents. In humans, a life history of regular exercise correlates with resistance to hippocampal memory decline and assignment to exercise as an intervention, whether it be *via* aerobic exercise, dance, or martial arts, improves hippocampal function at any age (Ballesteros et al., 2015). In rodent models, physical activity, usually performed as voluntary wheel running, similarly enhances hippocampal function in old and young animals alike (van Praag et al., 1999, 2005). Rodent research further suggests a number of beneficial changes in hippocampal physiology that may underpin preserved memory function, including elevated brain-derived neurotrophic factor (BDNF) expression, increased birth of new neurons, and enhanced synaptic plasticity (Vivar et al., 2013). Human studies also show an increase in hippocampal volume with exercise, further suggesting structural enhancement of hippocampal networks (Erickson et al., 2011). How exercise stimulates these changes in the hippocampus is currently a matter of debate. While cognitive enrichment is primarily thought to improve hippocampal function by driving neural activity, exercise beneficially modulates many organ systems throughout the body (heart, muscles, endocrine organs, for example), all of which can impact the brain. Due to these wide-ranging effects, the mechanism by which increased physical movement translates in to improvements in hippocampal physiology and consequently memory function in old age remains a focus of current research (Stimpson et al., 2018). Regardless of the mechanism, though, the experimental evidence strongly supports a beneficial role for exercise in preserving hippocampal function in old age.

While cognitive enrichment and exercise both receive wide recognition for their roles in preserving memory throughout aging, the role of social engagement has received comparatively little attention. Yet existing research suggests that social engagement may play a substantial role in combating age-related cognitive decline (Haslam et al., 2014; Ballesteros et al., 2015). In general, social activity is thought to have positive benefits on health throughout life. Epidemiological studies, for example, show that risk of all-cause mortality is strongly and dose-dependently reduced with increasing numbers of social ties (Holt-Lunstad et al., 2010). Correlational studies focusing on cognitive aging similarly show strong relationships between high social engagement and preserved hippocampal health. Surveys of community-dwelling elderly adults show that those with mild cognitive impairment have less social engagement than those with more well-preserved cognition (Kotwal et al., 2016). Longitudinal studies further show that individuals with low levels of social engagement at younger ages experience greater memory decline over time in comparison to their more social counterparts (Ertel et al., 2008; Brown et al., 2016). Correlational studies like these have led to the hypothesis that the reduction in social engagement with age might drive cognitive decline. Candidate mechanisms for how social activity could stimulate resistance to hippocampal decline include an increased cognitive reserve secondary to the stimulation of social interaction, as well as buffering from the negative effects of stress due to socially-derived emotional support. However, there is a dearth of research investigating whether increased social engagement can directly cause improved memory function or whether changes in memory function dictate social engagement.

Several challenges have impeded the study of social engagement and cognitive function in aging. First, social engagement is closely associated with several confounding variables that also impact cognitive function. For instance, people who report high social activity also report higher rates of positive health-related behaviors, such as regular exercise, and show more participation in cognitively enriching activities (Watt et al., 2014). Conversely, individuals with low social engagement are more prone to unhealthy behaviors, notably smoking and drinking alcohol, and are more likely to be of low socioeconomic status (Watt et al., 2014). Nonetheless, when these factors are controlled for statistically, the relationship between social engagement and memory function in aging seems to persist (Ertel et al., 2008; Kotwal et al., 2016). Aside from confounding variables, studies of social engagement are also challenged by the unclear value of different kinds of social ties. In addition to the potential difference between supportive and unsupportive relationships, a recent study shows that group interactions correlate better with preserved cognitive function in old age than a similar number of individual interactions (Haslam et al., 2014). In other words, being part of a group of friends is potentially more beneficial than having the same number of isolated friendships. Metrics of social engagement are not currently standardized across studies to consistently capture these kinds of differences in social network quality. Of course, confounding factors and varying qualities of stimuli are also obstacles in correlational studies of exercise and enrichment. Yet the causative, therapeutic role of these two variables is firmly established, largely by interventional studies showing that random assignment to enrichment or exercise programs improves hippocampal function in humans and rodents. These types of prospective studies are currently lacking for social engagement.

To date, human intervention studies have rarely focused on enhancing social activity as an individual variable that can impact memory function. Interventions that feature increased social activity do improve social integration in the elderly (Dickens et al., 2011) and protect against age-related

cognitive decline, but they also typically incorporate exercise or enrichment as part of the intervention (for example, dance classes, exercise groups, and group learning programs for the elderly) (Ballesteros et al., 2015). The social interaction inherent in these interventions is often recognized as essential to encouraging continued adherence (Ballesteros et al., 2015), but its direct, independent role in preserving memory function is not well-resolved. Prospective, interventional studies of social engagement as an isolated variable are needed to better demonstrate the direct role of social interaction on memory preservation in aging. It is worth noting, however, that excluding participants from known beneficial activities such as exercise, cognitive enrichment, and social engagement is ethically problematic.

While social networks can be difficult to isolate as a variable in human studies, rodent studies provide a more controlled opportunity to investigate the effects of social interaction. Mice and rats are both spontaneously social, meaning that, like humans, they prefer the company of each other over isolation. Studies of environmental enrichment in aging rodents often include a social component where enriched groups have both more toys and more co-housed cage mates than standard-housed control rodents (Kempermann et al., 1998, 2002; Mora-Gallegos et al., 2015; Pérez-Martín et al., 2016). Like many interventional studies in humans, these studies show protection of hippocampal memory in aging, but do not allow evaluation of the separable role of social interaction in this effect. Complete isolation *via* long-term solitary housing is also well-established to be detrimental for hippocampal memory, but this kind of housing represents a severe stressor for mice of any age and may not have realistic human parallels.

Only a few studies have assessed the independent contribution of social interaction to hippocampal preservation in animal models beyond the extreme case of complete isolation. We recently demonstrated that housing aged mice in a larger social network for 3 months improves performance in hippocampus-dependent memory tasks and decreases hippocampal microgliosis (a sign of neuroinflammation) compared to housing in pairs (Smith et al., 2018). These findings suggest that a larger social network may preserve hippocampal function in the aged brain by minimizing neuroinflammation. A second study further suggests that the quality of the social network may also influence cognitive outcomes (Hsiao et al., 2014). Hsaio et al. (2014) found that pairing aged Alzheimer's disease-model mice with young wild-type controls improved hippocampal memory performance, increased BDNF levels and enhanced neurogenesis compared to housing two Alzheimer's disease mice together. These findings suggest that the quality of social interaction may play a role independent of quantity, though it only addresses pathological phenotypes in an Alzheimer's disease model. To determine how this finding would apply to physiological aging will require more research. While the limited data available support a causative role of social interaction in preserving hippocampal function in aging, more research is needed to support these findings and determine the mechanisms by which the social environment impacts the aging brain.

When considering social integration as an intervention to prevent cognitive decline, it is worth noting that societal and individual factors may present challenges to enhancing social engagement in the elderly. For instance, limited community accessibility can result in insufficient social engagement. While the elderly will go to great lengths, and even risk bodily harm, to participate in social activities, poor community accessibility for the mobility-impaired may still limit their ability to achieve social contact. It may therefore be necessary to redesign living communities to promote social engagement (Williams, 2005; Gardner, 2014). Digital social integration through social media may help circumvent community mobility problems in the future. However, some research indicates that digital social interaction may actually be detrimental (Utz and Breuer, 2017) and therefore of limited utility. Beyond accessibility issues, cognitive decline and social isolation may result in a feedback loop by which individuals become impaired and isolate themselves, leading to further cognitive decline and isolation. These issues will require consideration in attempts to boost social engagement in the elderly.

This review highlights the potency of lifestyle and environment in regulating cognitive aging, particularly the memory functions mediated by the mammalian hippocampus. The beneficial effects of cognitive enrichment and exercise on hippocampal health in aging are well-supported by studies in humans and rodent models, and are likely mediated by enhanced cellular plasticity, growth factor production and neurogenesis. The existing evidence also suggests a key role for social engagement in preventing age-related cognitive decline, but there are still many unanswered questions. Clinical trials targeting social interaction specifically are needed to determine how social integration can be used to prevent cognitive decline and how that integration can be effectively and practically achieved. More mechanistic studies, most likely in rodent models, are also needed to gain understanding of how increased social engagement stimulates hippocampal resistance to aging. Current evidence suggests that growth factor levels, neuroinflammation and neurogenesis may all play a role but further research is needed. Given the public health burden presented by cognitive decline in an expanding aging population, it is necessary to identify the most effective intervention(s) for combating age-related cognitive decline. Lifestyle interventions such as enrichment, exercise and social engagement present viable opportunities for improving cognitive and often physical health in aging humans (**Figure 1**). Long-term consideration of these factors in individual choices and in community designs has the potential to broadly improve and extend quality of life.

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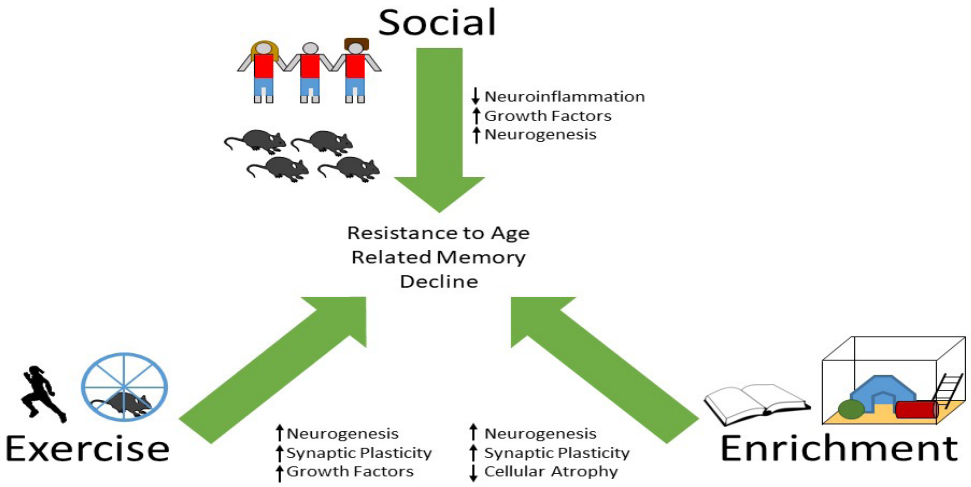

Figure 1 Cognitive enrichment, exercise, and social engagement are lifestyle interventions that can help to prevent age related memory decline.

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