frontiers in
AGING NEUROSCIENCE

HYPOTHESIS AND THEORY ARTICLE
published: 29 November 2010
doi: 10.3389/fnagi.2010.00150

Neuronal and cognitive plasticity: a neurocognitive framework for ameliorating cognitive aging

Pamela M. Greenwood* and Raja Parasuraman

Arch Laboratory, Psychology Department, George Mason University, Fairfax, VA, USA

Edited by:
Arthur F. Kramer, University of Illinois at Urbana-Champaign, USA

Reviewed by:
Fernando Gomez-Pinilla, University of California at Los Angeles, USA

****Correspondence:***
Pamela M. Greenwood, George Mason University, David King Hall 2060, MSN 3F5, 4400 University Drive, Fairfax, VA 22030-4444, USA.
e-mail: pgreenw1@gmu.edu

What is the neurocognitive basis for the considerable individual differences observed in functioning of the adult mind and brain late in life? We review the evidence that in healthy old age the brain remains capable of both neuronal and cognitive plasticity, including in response to environmental and experiential factors. Neuronal plasticity (e.g., neurogenesis, synaptogenesis, cortical re-organization) refers to neuron-level changes that can be stimulated by experience. Cognitive plasticity (e.g., increased dependence on executive function) refers to adaptive changes in patterns of cognition related to brain activity. We hypothesize that successful cognitive aging requires interactions between these two forms of plasticity. Mechanisms of neural plasticity underpin cognitive plasticity and in turn, neural plasticity is stimulated by cognitive plasticity. We examine support for this hypothesis by considering evidence that neural plasticity is stimulated by learning and novelty and enhanced by both dietary manipulations (low-fat, dietary restriction) and aerobic exercise. We also examine evidence that cognitive plasticity is affected by education and training. This is a testable hypothesis which could be assessed in humans in randomized trials comparing separate and combined effects of cognitive training, exercise, and diet on measures of cognitive and brain integrity. Greater understanding of the factors influencing the course of cognitive aging and of the mechanisms underlying those factors could provide information on which people could base choices that improve their ability to age successfully.

Keywords: aging, cognition, adaptation, plasticity, diet, exercise, cortex

INTRODUCTION

There has recently been something of a sea change in research on cognitive aging. Following decades of work that focused relentlessly and narrowly on age-related cognitive decline, there is now increasing interest in behaviors and factors that can ameliorate the course of cognitive and brain aging. It is well recognized that on average older individuals perform more poorly than younger individuals on selected cognitive functions. However, such decline is not universal. Across a range of species – rats, monkeys, and humans – a sizeable subset of older individuals do not succumb to cognitive or brain decline (Willis and Schaie, 1986; Rapp and Amaral, 1991; Gallagher et al., 1993; Lee et al., 1994; Glisky et al., 2001). Moreover, even in old age the brain remains capable of plasticity – ability to change neurons and networks in response to experience (Kleim et al., 2003). The apparent persistence of plasticity late in life may provide some protection against age-related cognitive decline. If the mechanisms of plasticity were better understood, they could be exploited to guide interventions aimed at limiting or reversing age-related cognitive decline.

The neural substrate of cognitive aging is not understood. Although cortical shrinkage occurs with age, such shrinkage is unrelated to cognitive change. Several research groups have attempted to relate regional cortical shrinkage to longitudinal cognitive change and found either an inverse relation or no relation (Rodrigue and Raz, 2004; Van Petten, 2004; Van Petten et al., 2004). Looking longitudinally over 5 years, shrinkage in neither hippocampus nor prefrontal cortex was related to cognitive change over the same period. Only shrinkage in entorhinal cortex, known to be the initial site of pathology of AD, was related to memory change (Rodrigue and Raz, 2004). Similarly, neuron loss in aging is minimal. Although for many years, age-related neuron loss was reported, the use of newer, unbiased, stereological techniques for counting neurons revealed no significant neuron loss in old age (reviewed in (Morrison and Hof, 1997). Although cross-sectional studies show near linear decline in many cognitive functions from young to old adulthood (Park et al., 2002), white matter actually increases over the same age range (Bartzokis, 2004). Synapse loss occurs only late in life after age 65 or so (reviewed in Masliah et al., 2006) and is reversible (reviewed in Greenwood, 2007). Effects of aging on biophysical properties of neurons are selective and subtle, seen only in specific brain regions and cell types (Burke and Barnes, 2006). Dopamine neurotransmission has been found to influence working memory performance, in a way that varies with age but also varies with cognitive performance regardless of age (Volkow et al., 1998; Backman et al., 2000). Thus, the substrate of cognitive aging is not known. One source of the difficulty in relating brain structure to cognitive change in old age may be the brain's ability to adapt. In light of evidence that plastic changes leading to improved function after training can occur even following stroke (Taub et al., 2002; Ro et al., 2006), plastic changes may be ongoing, even in the face of cortical shrinkage and white matter damage. As reviewed below, there is evidence for such adaptation in old age in the heightened activation of cortical regions supporting executive resources, claimed to occur as compensation (Grady, 1996; Grady et al., 2005; Wingfield and Grossman, 2006).

Understanding the plasticity mechanisms that may contribute to individual differences in cognitive aging is critical if we are to develop ways and means of ameliorating it.

NEURONAL AND COGNITIVE PLASTICITY: A NEUROCOGNITIVE HYPOTHESIS FOR AMELIORATION OF COGNITIVE AGING

We hypothesize that successful cognitive aging requires interactions between *neuronal* and *cognitive* plasticity, with the interactions being stimulated by environmental demands and supported by factors which enhance brain integrity. Neuronal plasticity refers to changes at the neuronal level known to be stimulated by experience, e.g., neurogenesis, synaptogenesis, dendritic arborization, and network re-organization. Cognitive plasticity refers to changed patterns of cognitive behavior, e.g., greater susceptibility to distractors, and dependence on executive control, both known to be increased in aging. Manifestations of cognitive plasticity depend upon neural plasticity mechanisms. We further argue that in the absence of disease, factors that enhance this interactive process can promote both cognitive integrity (preserved cognitive ability) and brain integrity (preserved brain structure) in healthy old age. An important factor is exposure to novel experiences. There is substantial evidence that novelty detection is an important trigger in memory formation (Straube et al., 2003). Consistent with our claim that novelty can trigger plastic changes is evidence that environmental enrichment – associated with both improved cognitive performance and increased brain weight and cortical plasticity (reviewed in Grossman et al., 2003) – has no additional brain or cognitive effects 6 months after initiation (Kempermann and Gage, 1999). This indicates that the novelty of the new environment was the factor that induced the resultant brain and cognitive changes. Also consistent is evidence that new learning must occur for newborn neurons to survive (Mouret et al., 2008; Waddell and Shors, 2008). Like neuronal plasticity, cognitive plasticity may similarly thrive on novelty, although this remains a speculative hypothesis at present. To the extent that cognitive plasticity requires changed cognitive strategies and new learning, it may also be subject to individual motivation and circumstances. If so, to age successfully, the individual may need to be exposed to novel cognitive demands (e.g., voluntarily learn new material and skill and experience new challenges) in order to fully benefit from mechanisms of neural and cognitive plasticity. In sum, we propose that if an adult brain (a) retains normal mechanisms of neuronal plasticity, (b) is stimulated by novelty (new experiences, including learning), (c) has sustained neural integrity supported by diet and exercise and other factors, then it will be able to adapt cognitively and age successfully.

We next consider the empirical support for our hypothesis. First, we consider the evidence that the capability for neuronal plasticity continues late in life. Next, we consider the evidence that cognitive plasticity occurs late in life. We then evaluate our hypothesis in light of evidence that education and training experiences are associated with increased neural plasticity, improved cognitive performance, and brain changes. We also evaluate our hypothesis in light of evidence that certain voluntary behaviors and experiential factors appear to stimulate and sustain neural plasticity (types of diet, and exercise) and are associated with improved cognitive functioning. Finally, we consider testable predictions of the hypothesis and directions for future research.

NEURONAL PLASTICITY IN OLD AGE

Mattson has argued that neurons and glia respond to environmental stressors in aging by either adapting or succumbing, with adaptation associated with successful aging (Mattson et al., 2002). The aging brain can adapt through cellular defense mechanisms – DNA repair, release of neurotrophins, and promotion of neurogenesis (Anderson et al., 2001) – but also through the capability of dendrites and synapses to change in response to environmental demands (Chklovskii et al., 2004). Recent animal work suggests that certain plastic changes (expanding and contracting of dendrites) can occur over weeks (Lee et al., 2006). Moreover, such changes have been seen following forelimb training, during which spines form rapidly on dendrites of pyramidal neurons in contralateral motor cortex (Xu et al., 2009). Also important to our hypothesis, synaptogenesis is promoted by novelty. Compared to control animals, rats that learned a maze but also those that only swam in the maze for the same amount of time showed larger neuronal responses to stimulation and greater dendritic tree complexity. The authors concluded that the novelty of having to swim and explore on a daily basis affected synaptogenesis in adult-generated neurons (Ambrogini et al., 2007).

Another potential mediator of neuronal plasticity could be change in neural networks. Reorganization of cortical circuits is seen following sensory loss (Florence et al., 1998) and following frank brain damage when neurons near the lesion take over function (Engelien et al., 1995; Taub et al., 2002; Ro et al., 2006). In monkeys, axon sprouting has been seen from near an ischemic injury to a distant target (Dancause et al., 2005). There is imaging evidence that this occurs in humans as well (Voss et al., 2006). Moreover, new projections have also been observed in response to training, in the absence of damage. Novel cortico-cortical projections with functionally active synapses have been seen to arise when monkeys are trained in tool-use, but not in naive monkeys (Hihara et al., 2006).

Neurogenesis is another important mechanism of neural plasticity. Mammals produce thousands of new hippocampal granule cells each day throughout life (van Praag et al., 1999). This is seen even in aged animals (van Praag et al., 2005), and aged humans (Eriksson et al., 1998; Curtis et al., 2003, 2007). Despite initial skepticism about the existence of neurogenesis (Rakic, 1985) in adult animals (Das and Altman, 1971), there is now a consensus that adult neurogenesis occurs in all mammalian species studied. Established "neurogenic" regions are the dentate gyrus of the hippocampus, the subventricular zone (the source of neocortical neurons in development), and the olfactory lobe. There is still debate on whether neurogenesis takes place in adult mammalian neocortex (Gould and Gross, 2002; Rakic, 2002; Bhardwaj et al., 2006). Importantly, it appears that newborn neurons can create functional connections. Several experimental approaches, including microscopic imaging and electrophysiology have clearly demonstrated that these newly formed neurons not only exhibit all the characteristics of functional neurons but that they are integrated into existing networks in which they actively participate, expressing postysnaptic potentials and spontaneous action potentials (Englund et al., 2002; Song et al., 2002; Kokoeva et al., 2005) and receiving excitatory and inhibitory inputs from the established neuronal network (Toni et al., 2008).

Summary

There are a number of mechanisms in the adult brain that allow plastic change. Even late in life, human brains are capable of both neurogenesis and functional recruitment of neurons adjacent to a lesion. Thus the older human brain retains the means to be re-wired, a capability that may be exploited to help limit age-related cognitive decline.

COGNITIVE PLASTICITY IN OLD AGE

There is evidence from several sources that, late in life, individuals either consciously or unconsciously adopt different cognitive approaches compared to the young. These changes could be considered compensatory or strategic or both. First, it has long been acknowledged that older people are more susceptible to distractors, and this observation is the basis for the well-known "Inhibition" theory of cognitive aging that has been used to explain age-related deficits in performance on different cognitive tasks (Hasher et al., 1991). More recently, however, Hasher and colleagues found evidence that reduced inhibitory processes can confer a *benefit* to older adults. They observed a relation between the ability to ignore apparently irrelevant distractors and the use of those distractors in a subsequent task (Healey et al., 2008). During the reading of passages during which participants were instructed to ignore imbedded italicized words, older people were more slowed than the young by the presence of those irrelevant words. However, in a subsequent task in which the irrelevant words were the solution to a problem (3 weakly related words could be linked if a fourth word was supplied), older people performed better than young (Kim et al., 2007). It has long been considered a deficit that older people are less able to ignore distractors then the young. However, when viewed in the context of other tasks and demands, such increased distractibility could confer a benefit. Are old people less able to ignore apparently irrelevant information or have they "learned" over the course of a long life that sometimes apparently irrelevant information may be relevant at a different time and/or context? We speculate that the latter explanation suggests a degree of cognitive plasticity associated with aging.

Secondly, there is evidence that those who age successfully process information differently from young people. Neuroimaging studies in older adults fairly consistently find bilateral activation of prefrontal cortex (PFC) on a range of tasks on which young people activate PFC unilaterally (Reuter-Lorenz et al., 2000; Cabeza, 2002; Cabeza et al., 2002; Rugg et al., 2002; Morcom et al., 2003; Gutchess et al., 2005). This was also seen in studies finding weaker activity of posterior regions but greater activation of anterior regions, notably PFC, across a range of tasks (Grady et al., 1994; Davis et al., 2008). Reuter-Lorenz interpreted their finding as revealing a compensatory process in older people, such that both hemispheres are needed by older people to carry out a task that one hemisphere can do in young people (Reuter-Lorenz et al., 2000). Others have reported that the bilateral brain activations seen in older people are linked to processing effectiveness. In an incidental memory paradigm, Rugg and colleagues found that although young people activated left PFC and left BA-20 during word classifications, old people activated PFC bilaterally. Bilateral activation during word classification was also related to the success of encoding in an old group (Morcom et al., 2003). Moreover, bilateral PFC activity was associated with faster RT (Reuter-Lorenz et al., 2000), also suggesting a benefit from the additional right PFC recruitment. Older people who were good at comprehending complex sentences showed reduced left temporal-parietal activation but greater left dorsal inferior frontal and right temporo-parietal activation during the task relative to young people. These regions have been associated with rehearsal of verbal information in working memory (Chein and Fiez, 2001). In contrast, those older people who were poorer at comprehension showed greater activation of dorsolateral PFC (Cooke et al., 2002), a region linked with general problem solving (e.g., Paulus et al., 2002).

Also reporting age-related differences in activation during memory retrieval (but not during encoding), Rypma and D'Esposito (2000) found no accuracy differences between the groups. However, they did find that, among the young, faster participants showed less dorsolateral PFC activation during retrieval than slower participants. By contrast, older adults showed the opposite pattern, interpreted as indicating that higher PFC activation is necessary for older adults to maintain the same level of performance as young people.

Grady and colleagues have argued that a more accurate characterization of the differences is that older adults recruited anterior regions to compensate for sensory processing deficits in occipito-temporal regions (Grady et al., 2003). Consistent with that view, young people with high-IQs compared to those with average IQs showed greater activity in prefrontal and parietal areas on difficult trials of a working memory task (Gray et al., 2003). The same investigators also found that the well-established association between self-control and higher IQ is mediated by activity in anterior prefrontal cortex (Shamosh et al., 2008). We have argued that a gradual shift from a bottom-up, stimulus-driven strategy in the young to a more top-down, controlled strategy directed from prefrontal areas in the old is the normal developmental course (Greenwood, 2007). This represents a second aspect of cognitive plasticity in aging.

Summary

There is human evidence that: (a) Activation of PFC is associated with higher IQ; (b) On average, older adults who activate PFC more extensively appear to benefit cognitively from that strategy. This suggests that, with age, there is increasing reliance on the executive functions associated with PFC and, further, that a cognitive benefit is associated with that increased reliance.

NOVEL COGNITIVE EXPERIENCES IN YOUTH STIMULATE NEURAL PLASTICITY MECHANISMS AND EXERT BROAD BENEFITS ON COGNITION

We have reviewed studies that provide compelling evidence that neuronal plasticity mechanisms are retained in aged human brains, as well as studies that indicate the existence of cognitive plasticity in older adults. What are the conditions that stimulate mechanisms of cognitive and neural plasticity? The neurocognitive framework advanced in this paper states that neural and cognitive plasticity mechanisms interact to produce successful aging. Two sources of evidence support the hypothesis: (1) Novel cognitive experiences both stimulate mechanisms of neural plasticity and lead to broad cognitive benefits, even late in life. (2) Factors that stimulate mechanisms of neural plasticity promote cognitive integrity, even late in life.

"EDUCATION" IN YOUNG ANIMALS EFFECTS COGNITIVE AND BRAIN INTEGRITY

Our hypothesis predicts that experiences that stimulate brain plasticity mechanisms confer benefits on cognition in general, but such experiences are of greatest importance late in life. There is a large animal literature documenting the brain and cognitive benefits of "environmental enrichment" (Rosenzweig and Bennett, 1972). This refers to a manipulation in which standard laboratory housing (one animal per cage with food, water, and bedding) is replaced with large cages containing cage mates along with toys, tunnels, and hidden food. Such "enriched" housing has been well-documented to yield changed cortical structure and superior cognitive performance relative to animals without those housing experiences. The cortical brain changes are macroscopic, such as increased cortical thickness and weight, and microscopic, such as increased dendritic extent and synaptic size (Greenough et al., 1985; Faherty et al., 2003). Thus experience can change brains both structurally and functionally. That the effects of environmental enrichment do not endure beyond about 6 months (Kempermann and Gage, 1999) suggests that it is the novelty of the experience that stimulates the brain changes.

Benefits of environmental enrichment are conferred even in old age (Kempermann et al., 1998; Frick and Fernandez, 2003; Arendash et al., 2004). For example, Kempermann and colleagues randomly assigned mice to standard or enriched housing at middle age (6 months) or old age (18 months out of a 24-month average lifespan). In the 18-month-old animals, after only 4 weeks of enrichment there was both a three-fold increase in new neurons and better performance on a spatial working memory task (Morris water maze) compared to the same aged animals kept in standard housing. A confound between exercise and cognitive stimulation is common to most studies of environmental enrichment. A few studies that attempted to separate effects of cognitive stimulation from effects of exercise reported that exercise alone has an effect on neurogenesis equal to that of enriched housing (van Praag et al., 1999).

Learning can affect synapse numbers in adults. Chen et al. (2010) assessed synapse numbers in hippocampal sections after young adult rats were allowed 30 min of unsupervised learning by being placed in a novel, complex environment. Learning more than doubled the number of synapses in the hippocampal CA1b field. Learning also appears to rescue newborn neurons from programmed cell death. Although adult neurogenesis occurs even in older adult humans (Eriksson et al., 1998; Bhardwaj et al., 2006), many newborn neurons do not survive long (e.g., Takasawa et al., 2002). Learning of a new skill (eyeblink conditioning) appears to rescue new neurons from programmed cell death (Leuner et al., 2004). Consistent with that, induction of long term potentiation (LTP) – believed to be the neural basis for memory formation – improves the survival rate of newborn neurons in dentate gyrus (Bruel-Jungerman et al., 2006). Moreover, several studies have reported a positive correlation between neurogenesis and learning a new skill, e.g., the water maze task (Kempermann et al., 1997; Kempermann and Gage, 2002) (Bruel-Jungerman et al., 2005). Also, learning can benefit from neurogenesis (Gould et al., 1999; Shors et al., 2001). Not all studies have observed a relation between new learning and neurogenesis (Dobrossy et al., 2003) and one study found an inverse effect (Saxe et al., 2007), suggesting that the relation may be complex and variable. Nevertheless, there is a growing literature documenting the importance of adult hippocampal neurogenesis to learning – including learning pattern separation (Clelland et al., 2009), a hidden spatial goal (Garthe et al., 2009), and eyeblink trace conditioning (Dalla et al., 2009).

EDUCATION IN YOUNG HUMANS EFFECTS COGNITIVE AND BRAIN INTEGRITY

Environmental enrichment in animals translates roughly to formal education in humans, and those with better educations in childhood decline less cognitively in old age (Colsher and Wallace, 1991) and have lower risk of AD (Yu et al., 1989). Although it would be difficult to randomly assign humans to an "enriched" or "impoverished" environment long enough to see brain effects (and it would not be ethical to do so in children), there have been efforts to compare brains of people who differ in their level of cognitive functioning. The brains of high-IQ children, undergo episodes of cortical thickening and thinning during childhood while cortical change is more linear in average-IQ children (Shaw et al., 2006). Consistent with that finding, the brains of high-functioning, but not average-functioning, older people appear to undergo cortical thickening in midlife (Fjell et al., 2006). Likewise, a recent study found that older people who exhibit good retention for new memories over months showed stable cortical thickness while those with poorer retention showed cortical thinning (Walhovd et al., 2006). Brain differences have been seen in functional neuroimaging studies as well. As reviewed above, there is evidence that increased reliance on PFC is associated in the young with better working memory performance (Gray et al., 2003) and higher IQ (Shamosh et al., 2008).

Formal education also alters brain activity patterns during task performance. In young adults, more education is associated with less frontal activation during encoding and recognition memory tasks while in older adults, more education is associated with greater bilateral frontal activity (Springer et al., 2005). This suggests that cognitive strategies change with age and change differentially according to early life experience (education). Evidence that more education is associated with greater reliance on prefrontal regions and better maintenance of cognitive performance late in life is consistent with our hypothesis that exposure to complexity and novelty stimulates neural plasticity mechanisms.

EDUCATION (COGNITIVE TRAINING) IN ADULTHOOD CAN CHANGE COGNITIVE AND BRAIN INTEGRITY

Consistent with our claim that exposure to novelty stimulates neuronal plasticity, learning can change the human brain morphologically. Human cortical organization changes in response to different types of perceptual-motor motor training. Novice Braille readers read with one finger and retain separate representation of each digit in the appropriately mapped region of somatosensory cortex. Skilled Braille readers, on the other hand, read with three fingers held together and have a "smeared" representation of those digits in their somatosensory cortical map (Sterr et al., 1998). Stringed instrument players (e.g., violin) who use their left hand on the strings have an enlarged hand area in the right hemisphere compared to the left (Elbert et al., 1995).

These findings provide evidence that learning can stimulate cortical reorganization. However these investigations were observational studies in which the participants self-selected to be Braille readers or stringed instrument players. More convincing is a report of brain changes as a consequence of random assignment to a motor activity (Draganski et al., 2004). College students were randomly selected and taught to juggle for 3 months. Their brains were scanned before training, 3 months after initiation of training, and 3 months after juggling practice had ceased. Several regions (intraparietal sulcus and area MT) were found to increase in volume 3 months after beginning juggling and to have decreased in volume (though not to pre-training levels) 3 months after ceasing to practice (Draganski et al., 2004). Nor are such changes in brain structure limited to motor training. Structural brain change in parietal cortex and hippocampus is detectable during and after 3 months of the extensive knowledge acquisition required of medical students preparing for their board exams (Draganski et al., 2006).

Formal cognitive training has been employed as a means of heightening cognitive functioning in old age. In the context of the hypothesis, cognitive training would be predicted to exert effects similar to formal education. In older people, nearly all studies have found that cognitive training benefits the specific cognitive functions that are trained (e.g., Ball et al., 2002; Willis et al., 2006). It has been harder to show that the benefits of cognitive training transfer to untrained tasks or to real-world functioning. Willis and colleagues (Willis and Schaie, 1986; Ball et al., 2002) have been pioneers in conducting longitudinal cognitive training and assessment of older individuals. After 5 years of annual cognitive training, compared with the control group, participants who received reasoning training (though not those receiving memory or processing speed training), showed less functional decline in "instrumental activities of daily living," with a small effect size (0.29). Formal cognitive training has also been associated with functional brain changes. In humans, there is evidence that training is associated with changed patterns of regional brain activation, particularly of prefrontal cortex. Kramer's group have been in the forefront of this research. They trained older participants on a "useful field of view" task (requires detection of peripheral events during a demanding foveal task) and observed training-related increased activation in right precentral gyrus and right inferior frontal gyrus. Moreover, the increased activation correlated positively with increased accuracy over training sessions (Scalf et al., 2007). In another study, the same group looked at brain activation patterns before and after training in a dual-task paradigm. A region in dorsolateral prefrontal cortex showed increased activation after training and in a manner correlated with improved performance (Erickson et al., 2007). Also reporting brain change associated with cognitive training is a recent study aimed at reducing distractibility. After 8 weeks of either distractibility or control training, older individuals undergoing distractibility training showed relatively greater increases in cerebral blood flow in prefrontal cortex. Moreover, the increase in blood flow showed a modest association with decreased distractibility on a cross-modal task (Mozolic et al., 2010).

What are the mechanisms underlying these experience-related morphological and activation changes? An array of plasticity mechanisms have been found to be enhanced by experience, including axon sprouting, dendritic branching, spine growth, and associated synapses (for a review see Chklovskii et al., 2004). Neurogenesis may not contribute to cortical change as it appears to occur only in certain subcortical areas. Non-neural cells could also contribute to cortical volume changes as exposure to challenging experiences and learning alters existing glial cells and also up-regulates gliogenesis in cerebral cortex at the same time and place as neuronal remodeling (Dong and Greenough, 2004). White matter changes may contribute to the functional changes observed with cognitive and motor training. Functional anistrophy (FA) is a measure of the integrity of white matter microstructure measured in a diffusion tensor imaging (DTI) scan. Training on a working memory task was found to be correlated with increased white-matter integrity (measured in fractional anistrophy, FA) both near the intraparietal sulcus and in the anterior body of the corpus callosum in young people (Takeuchi et al., 2010). Similarly, training on a visuo-motor skill (juggling) was associated with increased FA in white matter underlying the intraparietal sulcus (Scholz et al., 2009). This work was carried out in young people, so it is not known if older adults would show similar plasticity. Nevertheless, the increased integrity of white matter fibers tracts could be a substrate for altered functional changes by allowing faster transmission between brain regions. Additional work will be needed to determine if it is significant that the cognitive training produced more widespread effects on white matter than the sensorimotor training.

Summary

Evidence from a range of sources indicates that exposure to novelty is a key factor in promoting and maintaining mechanisms of brain plasticity and cognitive integrity. This is seen in environmental enrichment (complexity) effects even in old animals, and is also seen in the protective effects of education in childhood on adult human cognition. It can even be seen when the novel experiences – in the form of formal training – occur late in life. Novel experiences can change human brains, expanding cortex and increasing axonal integrity, whether they involve sensorimotor training or cognitive training.

BEHAVIORS THAT ENHANCE NEURAL PLASTICITY ALSO IMPROVE COGNITIVE INTEGRITY

Another prediction of our hypothesis is that factors that promote neural plasticity should result in improved cognitive function generally – particularly important late in life. In what follows, we consider the evidence pertaining to this prediction. A number of factors have been implicated in enhancing neuronal plasticity – e.g., physical exercise, diet, estrogen, cognitive–enhancing drugs. We limit our discussion to physical exercise and diet because there is good-quality human and animal evidence on these factors.

PHYSICAL EXERCISE

While the benefits of exercise on physical health are well known, a sizeable body of animal research points to the benefits of exercise on cognition and brain function. Rats given access to running wheels show improvement in various learning and memory tasks and neural changes (Cotman and Berchtold, 2002). Studies conducted in older humans have also pointed to beneficial effects of aerobic activity on cognitive and brain function (reviewed in Hillman et al., 2008).

Physical exercise is associated with improved cognitive performance in healthy animals, even in old age (van Praag et al., 2005). Rodents who exercise typically show superior learning on a range of learning and memory tasks compared to non-exercisers (Vaynman et al., 2004; van Praag et al., 2005; Nichol et al., 2007). Exercise also reduces the degree of impairment in spatial learning in rats associated with a high fat diet (Molteni et al., 2004). A related line of animal research indicates that cardiovascular exercise is generally neuroprotective (for a review, see Cotman et al., 2007). Animals who exercised on a running wheel before an experimental stroke showed reduced infarct volume and better function after the stroke (Ding et al., 2006; Hayes et al., 2008). These findings suggest that exercise confers broad benefits on neuronal integrity.

What mechanisms are involved in the benefits of exercise on cognition and brain function? Increased neurogenesis in the hippocampus has been consistently observed in exercise intervention studies in animals (van Praag et al., 1999; Trejo et al., 2001). Exercise-induced increased numbers of new neurons in the hippocampus can occur in young adulthood (van Praag et al., 1999). More importantly, the same exercise-driven increase can occur in old age (van Praag et al., 2005). Finally, continued voluntary exercise in rodents has been found to reduce the typical age-dependent decline in adult neurogenesis that occurs in sedentary animals (Kronenberg et al., 2006).

Most studies of the effects of physical exercise in humans are observational, comparing cognitive functioning between groups who self-select whether and how much to exercise. Despite this design limitation, similar to the well-controlled animal studies that use random assignment, human observational studies find exercise to be associated with cognitive benefits. This has been confirmed in several recent meta-analyses (Colcombe and Kramer, 2003; Heyn et al., 2004; Etnier et al., 2006). Colcombe and Kramer (2003) hypothesized that effects of aerobic exercise on cognition are specific to executive functioning – a somewhat loosely defined set of functions characterized by ability to form and carry out plans, resolve conflicts, etc. In a meta-analysis they found that the largest effects of exercise were seen for tasks dependent on executive processes, although significant effects were also observed for non-executive tasks such as spatial processing and perceptual speed.

Kramer and colleagues have also been in the vanguard of studying effects of exercise on cognition in previously sedentary older people. After 6 months of random assignment to either aerobic (walking) or non-aerobic (stretching and toning) supervised exercise sessions for 45 min 3 days a week, those assigned to aerobic exercise (a) performed better on an executive attention task and (b) showed greater activation of brain regions associated with working memory (Colcombe et al., 2004). Smiley-Oyen et al. (2008) conducted a randomized trial comparing aerobic training with strength training in old people and also found benefits of aerobic training on tasks dependent on executive functioning, although their battery was weighted toward such tasks. Working memory capacity appeared to play a role in the findings. A similar study found faster RT both immediately and 30 min after aerobic exercise, but not after resistance exercise or rest. Moreover, the strongest effect was seen on tasks that required greater working memory capacity (Pontifex et al., 2009). This study is important as it shows effects of acute exercise on cognition, suggesting some overlap in mechanisms with effects of chronic exercise.

Another study in non-demented older people at increased risk of dementia based on self-assessment of memory problems also found cognitive benefits of exercise. People randomly assigned to an aerobic exercise intervention (increase in number of steps (measured by a pedometer) taken per week over the 24-week intervention period, showed a significant increase in a standardized test of global cognitive function (ADAS-Cog). Another group who were randomized to "usual care" showed a slight decline in the ADAS-Cog over the same period of time (Lautenschlager et al., 2008). Although Alzheimer's Disease (AD) is not the primary focus of our review, it is relevant to note that cognitive decline has been found to be slowed in AD patients who exercised (Teri et al., 2003; Rolland et al., 2007) and incidence of AD was lower in people who chose to exercise (Larson et al., 2006).

Summary

When considered together, evidence from both animal and human studies supports the view that aerobic exercise (walking, strength-training), but not non-aerobic exercise (stretching/toning) has a robust effect on cognitive performance in both healthy and demented older adults. There is some support for the view that executive functions benefit selectively from aerobic exercise. However, that is not a consistent finding. One possible mechanism of such selectivity could be the claim by a number of investigators that PFC is selectively vulnerable to negative effects of aging (e.g., West, 1996; Raz et al., 1997). If so, then that selective vulnerability of prefrontal cortex to age-related loss (broadly defined) might lead to a particular benefit from improved vascular health due to exercise. However, as there is only weak and conflicting evidence for the claim that PFC is somehow more subject to age-related white or gray-matter shrinkage or hypometabolism (Greenwood, 2000; Piguet et al., 2009), no conclusion can be drawn at present.

Neural mechanisms underlying exercise effects

What factors underlie the effects of physical activity on brain and cognitive functioning? Several mechanisms have been identified: neurogenesis; synaptic plasticity; neurotrophins; cerebral blood flow.

Neurogenesis and exercise. Animal work has consistently shown that physical exercise increases proliferation and survival of new neurons in the dentate gyrus of the hippocampus of adults (Gould et al., 1999; van Praag et al., 1999; Lou et al., 2008; Naylor et al., 2008). Rodents given access to a running wheel typically voluntarily run as much as 3–8 km per night and this is associated with a doubling or tripling of the number of newborn cells in the subventricular zone of the dentate gyrus where neurogenesis occurs. Voluntary wheel running over long periods of time is also associated with an increase in survival of later-stage progenitor cells and newly-formed (early post-mitotic) neurons in mouse dentate gyrus (Kronenberg et al., 2006). After experimental stroke, voluntary running enhanced progenitor cell survival in dentate gyrus in mice (Luo et al., 2007). This effect may extend beyond the hippocampus, as running rats also showed significantly higher number of cholinergic neurons in the diagonal band of Broca (Ang et al., 2003).

Synaptic plasticity. Some of the benefits of exercise on learning may be attributable to its effects on mechanisms of synaptic plasticity. LTP, which is a durable increase in the strength of a synapse after being repeatedly stimulated, appears to be the basis for memory formation, in that it can be induced by learning alone (Whitlock et al., 2006). In the dentate gyrus of the hippocampus, benefits of exercise have been observed on both neurogenesis (Pereira et al., 2007) and LTP (Farmer et al., 2004). Finally, exercise also alters the length and complexity of dendrites and of the density of the spines found on dendrites (Eadie et al., 2005). These exercise-induced dendritic changes can improve the efficiency of communication between neurons.

Neurotrophins. Neurotrophins are naturally occurring growth factors long known to pay a major role in neuronal development, but more recently found to act as synaptic modulators. There is emerging evidence that neurotrophins may mediate effects of exercise on cognition. The effects of exercise on new neuron formation (neurogenesis) and new capillary blood vessel formation (angiogenesis) are associated with upregulation of several neurotrophic agents (brain-derived neurotrophic factor, BDNF (Berchtold et al., 2001), insulin-like growth factor, IGF-1 (Trejo et al., 2001), vascular endothelial growth factor, VEGF (Fabel et al., 2003; Lou et al., 2008), and nerve growth factor, NGF (Ang et al., 2003). BDNF specifically plays an important role in modulating LTP (reviewed in Poo, 2001). BDNF concentration in CSF was found to decrease with age among older cognitively normal people, and lower CSF BDNF concentration was associated with both poorer immediate recall and delayed recall at baseline and after 3 years (Li et al., 2009). Also in humans, serum BDNF was recently found to be related to hippocampal shrinkage and memory decline late in adulthood (Erickson et al., 2010).

Cerebral blood flow. Exercise can increase neurogenesis and affect BDNF gene expression in the brains of adult rats. One week of low- or moderate-intensity exercise in a treadmill running task enhanced neurogenesis in the dentate gyrus of hippocampus. Gene expression levels in the low-intensity exercise group were greater than the high-intensity group for BDNF (Lou et al., 2008). Exercise can also increase cerebral blood flow with consequences for cognition. A recent human neuroimaging study observed that blood flow increased selectively in the dentate gyrus following a 3-month aerobic exercise program. Moreover, that increase was related to both improved cardiopulmonary and cognitive function. Reported in the same paper, a similar exercise manipulation in mice also resulted in increased blood flow in dentate gyrus that was correlated with neurogenesis in the same structure (Pereira et al., 2007). This finding is consistent with a recent report that blood glucose levels in older people were related to both blood flow in dentate gyrus and memory performance (Wu et al., 2008b). This indicates that aerobic exercise has the potential to counteract the apparent negative influence of blood glucose levels on the integrity of the dentate gyrus and memory formation dependent on it.

DIET AND NUTRITION

There is increasing evidence that diet can have direct effects on brain function apart from simple nutrition. Stimulation of vagal afferents from the gastrointestinal tract has become a standard treatment for a type of epilepsy (reviewed in Gomez-Pinilla, 2008). Omega-3 fatty acids, available through cold water fish, influence the ionic permeability of plasma membranes at synaptic regions thereby affecting synaptic and cognitive function (Bourre et al., 1989; Adams et al., 1996; Freeman et al., 2006). Diets that are high in saturated fat appear to negatively affect cognitive processing and increase the risk of neurological dysfunction (Molteni et al., 2002; Greenwood and Winocur, 2005). We focus on two aspects of diet – restriction of calories and resveratrol – which may act through the same mechanisms. Restriction of calories in an otherwise balanced diet – "calorie restriction" or "dietary restriction" (DR) – exerts positive effects on insulin and blood glucose levels in rodents and primates, including humans. It should be noted that DR must be implemented carefully to avoid dangerous deficiencies. Poor glucose regulation is linked to hippocampal atrophy and poor memory performance even in non-diabetics (Convit et al., 2003). Resveratrol, a polyphenol found abundantly in red grapes and red wine, appears to exert its effects via some of the same mechanisms as DR and has been found to protect the hippocampus from insults such as stroke (reviewed in Baur and Sinclair, 2006). Thus, both DR and resveratrol have a role in hippocampal neuroprotection. Both can influence neural plasticity, as the dentate gyrus of the hippocampus is the source of new neurons in all species examined, including humans. Likewise, a high fat diet exerts negative effects on cognition. A high-fat diet has been shown to increase insulin resistance (Tschop and Thomas, 2006), and insulin resistance has been linked to hippocampal dysfunction (Convit et al., 2003). We describe the experimental evidence from studies examining the effects on cognition and brain function of DR and high-fat diet.

Dietary restriction

In a large range of species, DR has been observed to extend the lifespan by 20–40% (reviewed in Weindruch and Sohal, 1997). Effects of DR can be seen even when initiated in old age in animals (Ingram et al., 1987) and in midlife in humans (Walford et al., 1999). In addition to lifespan, it has been known for some time that DR reduces the incidence of age-related disease, maintains youthful physiological measures, increases resistance to stress, and protects neurons against toxic insults (for reviews, see Mattson, 2000; Heilbronn and Ravussin, 2003). In a primate model, Roth and colleagues randomly assigned monkeys for 6 months to a DR or *ad libitum* diet then exposed them to a neurotoxin to produce a hemiparkinson condition. Compared to *ad libitum* monkeys, DR monkeys showed significantly higher levels of locomotor activity, dopamine (DA), and glial cell line-derived neurotrophic factor (Maswood et al., 2004). Even when initiated in old monkeys, DR improves some markers of health (fasting and peak insulin, triglycerides; Lane, 2000). Random assignment of DR in adult primates (aged 7–14 years out of a 27-year average lifespan) lowered the incidence of aging-related deaths, but not of deaths overall. DR monkeys showed other benefits, including preservation of lean muscle mass, prevention of diabetes, cancer, cardiovascular disease, and preservation of subcortical gray matter volume (Colman et al., 2009).

Perhaps related to the above-mentioned benefits on physiology and cellular defense, DR also has benefits for cognition. In rodents, DR maintains cognitive functioning in old age (Ingram et al., 1987)

and prevents deficits in LTP (Eckles-Smith et al., 2000). One underlying mechanism may be the effects of DR on glucose regulation. Poor glucose regulation has been linked to lower memory performance and hippocampal atrophy in non-diabetic older people (Convit et al., 2003). Another mechanism that may be supported by DR is increased plasticity in rodent hippocampal NMDA circuits (Fontan-Lozano et al., 2007). DR also eliminated the previously observed age-related loss in numbers of subunits of types of the glutamate receptor (Shi et al., 2007).

What about effects of DR in humans? As might be expected, controlled, random assignment studies of DR are not possible with humans, and even observational studies are rare, but the limited available evidence is nevertheless illuminating. Observational studies of people voluntarily restricting their diets suggest effects similar to those seen in rodents (Walford et al., 1999; Fontana and Klein, 2007), but such designs are limited because participants self-select. Probably the best observational data comes from the Biosphere 2 project. The participants in that experiment in self sufficiency inadvertently experienced about a 30% reduction in calories for about 3 months due to crop problems. Nevertheless, during that time they showed a decline in metabolic rate, body temperature, blood pressure, blood glucose, and insulin (Walford et al., 1999). Only a few empirical human studies have been conducted using random assignment to DR. Six months of randomly assigned DR in healthy, sedentary adults has been found to improve fasting insulin levels and body temperature – both considered to be markers of longevity. DNA damage was also reduced in the DR group (Heilbronn et al., 2006). They also assessed properties of cultured cells collected from humans who had undergone 6 months of DR. These cells showed greater resistance to stress (increased heat resistance) and also up-regulation of the sirtuin 1 (SIRT1) gene, linked to longevity.

Only a few studies have assessed cognition in the context of DR. In a small randomized clinical trial of 12 over-weight adults aged 25–50 years, there was no effect on cognition after 6 months of DR (Martin et al., 2007). A larger randomized study did see improved memory following 3 months of DR in 50 post-menopausal women. Normal to overweight older women were assigned to 3 months of either: DR (instructed to achieve 30% reduction of calories), "UFA" (instructed to achieve 20% enhancement of unsaturated fatty acid consumption), or Control (instructed to not change eating habits). Verbal memory increased by 20% in the DR group, in a manner correlated with resting plasma fasting insulin. There were no memory changes in the other groups (Witte et al., 2009).

In summary, animal work with DR shows robust effects on lifespan, resistance to neuropathology, and age-related declines in health and cognition in a range of species, including infra-human primates. While human work to date is limited, initial results suggest beneficial effects of DR on health, markers of longevity, and – in one study – cognition.

Resveratrol

Resveratrol is a natural polyphenol notably abundant in grapes, grape skins, and red wine. Resveratrol has been found to have broad beneficial effects on health. A recent review has summarized effects of resveratrol on cancer, angiogenesis, drug metabolism, heart disease, platelet aggregation, antioxidant activity, stress, and aging (Baur and Sinclair, 2006). Interestingly, there is increasing evidence that resveratrol acts by mimicking the beneficial effects of DR. Resveratrol has been hypothesized to activate the SIRT1 gene which has a role in longevity across a large range of species (Browner et al., 2004). In a direct test of that hypothesis, Barger and colleagues compared gene expression changes in middle aged and old mice on a control diet, a DR diet, or resveratrol-supplemented diet. Both the DR and the resveratrol-supplemented diets inhibited expression of genes associated with brain, cardiac, and skeletal muscle aging, and prevented age-related cardiac dysfunction (Barger et al., 2008). In a separate study they also directly compared transcriptional changes associated with (a) resveratrol (b) standard diet, (c) alternate day fasting, and (d) high-calorie diet. They found resveratrol induced gene expression patterns that paralleled those induced by DR. Moreover, on resveratrol, the animals had less heart disease, fewer cataracts, and greater mobility, although lifespan was not extended (Pearson et al., 2008). Sinclair and colleagues also observed that resveratrol counteracts the negative effects of a high-calorie diet on the liver (Baur and Sinclair, 2006).

Overall, therefore, does the evidence on resveratrol indicate that the benefits of DR be obtained without the rigors of restricting calories? Baur and Sinclair have estimated that drinking about two glasses of red wine a day provides a pharmacologically relevant dose of resveratrol (Baur and Sinclair, 2006). The resveratrol literature is consistent with the "French Paradox," in which there is low risk of cardiovascular disease with a diet high in saturated fat that includes regular consumption of red wine (Renaud and de Lorgeril, 1992).

Dietary fat

There is increasing evidence that a high-fat diet can impair cognition. Both experimental studies in rodents and epidemiological studies in humans observe similar cognitive deficits from such a diet (for a review, see Greenwood and Winocur, 2005). A high-fat diet reduces both neuronal plasticity and the capacity of the rodent brain for learning (Greenwood and Winocur, 1996). Such a diet is associated with greater deficits after experimental injury and reduced hippocampal plasticity (Wu et al., 2003). One source of the negative effect of a high fat diet on cognition may be the development of insulin resistance and its effect on the hippocampus (Greenwood and Winocur, 2005). This is consistent with recent findings by Small and colleagues that high levels of blood glucose are associated in humans with hippocampal pathogenesis (Wu et al., 2008b). Cognitive deficits in spatial working memory associated with a high fat diet were avoided in animals allowed access to wheel running but were not avoided in animals that were sedentary (Molteni et al., 2004). Because BDNF levels increased in the running animals but decreased in the sedentary animals, the authors concluded that both the high-fat diet and the exercise influenced the same mechanisms of synaptic plasticity but in opposite directions. As reviewed above, another mechanism may involve the Sirt1 enzyme. Resveratrol is a Sirt1 ligand. Mice with overexpression of SIRT1 showed fewer consequences of a high fat diet – lower lipid-induced inflammation and better glucose tolerance (Pfluger et al., 2008). Considered together, these findings suggest a common mechanism underlying effects of resveratrol, dietary fat, DR, and even exercise on cognition.

Summary. Specific forms of exercise (aerobic) and diet (low-fat, DR) promote brain integrity with consequences for cognitive integrity. There are a number of mechanisms of plasticity that are affected, including neurogenesis, synaptic plasticity, neurotrophin release, and there is some evidence that there is an overlap in the mechanisms underlying the benefits of aerobic exercise and a low-fat diet.

COMBINATIONS OF FACTORS

Because each of the factors that appear to slow or reverse age-related cognitive decline has typically been investigated by a separate research group, few studies have considered the influence of combinations of factors. Gomez-Pinilla and colleagues examined synergistic effects of omega-3 fatty acids (DHA) and exercise in rats. The omega-3 enriched diet was associated with improvements in spatial learning and this effect was heightened in rats assigned to exercise. Moreover, animal assigned to both diet and exercise manipulations showed the greatest reductions in levels of oxidized proteins in hippocampus (Wu et al., 2008a). A combined investigation of two factors with a putative influence on cognitive aging has been carried out in dogs (Milgram et al., 2002). Young and old dogs were randomly assigned to either (a) fortified (anti-oxidant enriched) vs standard diet; (b) standard housing vs enriched housing (housing with kennel-mates and toys and outdoor walks; or (c) both fortified diet and enriched housing. Because the animals assigned to the "enriched" condition were also walked more, exercise, and cognitive stimulation were confounded. While both manipulations improved performance of the older dogs on a size discrimination and reversal learning task compared to the controls, performance of the old dogs was best in the group who experienced both manipulations. Older people were randomly assigned to aerobic training, cognitive training, or both ($n = 8$ in each group). The aerobic training was two supervised 45 min sessions per week of interval training (brisk walking and/or jogging) and the cognitive training was 90 min per week of broad-based memory and attention training aimed at strategies. The memory quotient from the Wechsler Memory Scale showed improvement from pre- to post-training in all three experimental groups (aerobic, cognitive, and combined groups) while the controls showed no improvement. Improvement was greatest in the combined groups (Fabre et al., 2002). A similar combined effect has been observed in humans in an observational study. In a large study of community-dwelling older people, (a) adherence to a Mediterranean-type diet (low in red meat and saturated fat, high in fruits, vegetables, cereals, and fish) and (b) amount of physical exercise were examined for effects on risk of AD. Both higher Mediterranean diet adherence and higher levels of exercise were independently associated with lower risk of developing AD over 15 years (Scarmeas et al., 2009).

DIRECTIONS FOR FUTURE RESEARCH

It is important for the wellbeing of everyone – those who are old and those who will one day be old – that we improve our understanding of the factors that influence cognitive and brain integrity late in life. Enhanced understanding of these factors and their mechanisms could allow people to adopt a lifestyle that increases their ability to age successfully. We have summarized evidence that the minds and brains of older individuals retain the capability for both neural plasticity and cognitive plasticity ("Neuronal and Cognitive Plasticity: A Neurocognitive Hypothesis for Amelioration of Cognitive Aging"). We hypothesized that these capabilities can be stimulated and sustained in the aging brain by exposure to novel experiences, including education and training ("Novel Cognitive Experiences in Youth Stimulate Neural Plasticity Mechanisms and Exert Broad Benefits on Cognition"). Moreover, lifestyle factors of diet and exercise ("Behaviors that Enhance Neural Plasticity Also Improve Cognitive Integrity") can play a role in that they support the underlying neural plasticity mechanisms. As noted above, some of the behaviors affecting cognitive aging – low dietary fat, DR, resveratrol consumption, exercise – appear to share a mechanism or mechanisms. This suggest that combined factors would have the strongest effect on cognition, as has been seen in a few studies ("Combinations of Factors"). However, very few combined studies have been conducted.

An important next step would be a comprehensive human study with random assignment to compare separate and combined "treatment" effects. Older people could be randomly assigned to diet, exercise, and cognitive manipulations (separately and combined) for some extended period of time (probably months). All manipulations would have to be supervised or monitored in some way. Predictions could be made for outcome measures on (a) a range of cognitive tasks, (b) patterns of brain activation, (c) measures of brain integrity such as FA measured in DTI, (d) fitness measures like VO_{2max}, and (e) activities of daily living. The most powerful dietary manipulation would involve restriction of calories, which would limit the duration of the study. A likely less potent but easier manipulation would involve random assignment to either a Mediterranean or more typical diet. The cognitive manipulation could compare effects of training on novel vs non-novel tasks. Selection of the cognitive training tasks would require careful consideration and also pilot work. The exercise manipulation would compare aerobic with non-aerobic exercise, using exercise parameters established in previous research (Hillman et al., 2008). Based on findings of Fabre et al., Milgram et al., and Scarmeas et al., and on evidence (reviewed above) that exercise and DR share mechanisms in common, it can be predicted that stronger effects on cognitive performance would come from combinations of effects – e.g., novel training plus DR plus aerobic exercise. However, more complex interactions could be observed. In addition, measures of brain integrity such as FA (measured in DTI) and recently shown to increase after sensorimotor and working memory training can also be predicted to increase differentially after novel relative to non-novel training.

CONCLUSIONS

Given that the population of older adults is rapidly increasing throughout the world, it is imperative that we gain a better understanding of the neurocognitive bases of individual differences in functioning of the older brain and mind. Many nations are now faced with the prospect of large numbers of their workers retiring in the next few years and a number of countries are consequently raising the retirement age. In the US, the full retirement age is 66 for people about to retire and 67 for people born after 1960. In 2008 Italy changed the retirement age from 57 to 60 for women and to 65 for men. Britain plans to raise the retirement age from 65 to 68 by 2044. Germany is increasing the retirement age to 67

by 2029. As a result of such policies, there will be greater numbers of older adults in the workforce. Even workers who do retire will have economic incentives to continue working. In a recent report, McKinsey & Company determined that 85% of US baby boomers plan to work in retirement (Farrell, 2008) – in part because they have not saved sufficiently. In order for older workers to continue to earn money to support themselves late in life, they need to avoid the decline in cognitive functioning that accompanies aging on average.

These demographic trends indicate that there are economic as well as personal reasons for older adults to enjoy cognitive vitality for a longer period of time as they age. Although the neural substrate of cognitive and brain aging is still unknown, the factors influencing that substrate are beginning to be increasingly well understood. Our hypothesis predicts that manifestations of cognitive plasticity depend upon neural plasticity mechanisms, which are enhanced by exposure to novelty and cognitive challenge and supported by factors with broad effects on health – notably diet and exercise. To date there have been no randomized trials in humans of the multiple factors influencing cognition in old age. As the first wave of baby boomers reaches retirement age, there is an urgent need to acquire knowledge about the optimal way to age successfully so that our older citizens can remain vital and productive as long as possible.

ACKNOWLEDGMENTS

This work was supported in part by National Institute on Aging Grant AG19653 to Raja Parasuraman.

REFERENCES

Adams, P. B., Lawson, S., Sanigorski, A., and Sinclair, A. J. (1996). Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 31(Suppl), S157–S161.

Ambrogini, P., Cuppini, R., Lattanzi, D., Ciuffoli, S., Frontini, A., and Fanelli, M. (2007). Synaptogenesis in adult-generated hippocampal granule cells is affected by behavioral experiences. *Hippocampus* 20, 799–810.

Anderson, I., Adinolfi, C., Doctrow, S., Huffman, K., Joy, K. A., Malfroy, B., Soden, P., Rupniak, H. T., and Barnes, J. C. (2001). Oxidative signalling and inflammatory pathways in Alzheimer's disease. *Biochem. Soc. Symp.* 67, 141–149.

Ang, E. T., Wong, P. T., Moochhala, S., and Ng, Y. K. (2003). Neuroprotection associated with running: is it a result of increased endogenous neurotrophic factors? *Neuroscience* 118, 335–345.

Arendash, G. W., Garcia, M. F., Costa, D. A., Cracchiolo, J. R., Wefes, I. M., and Potter, H. (2004). Environmental enrichment improves cognition in aged Alzheimer's transgenic mice despite stable beta-amyloid deposition. *Neuroreport* 15, 1751–1754.

Backman, L., Ginovart, N., Dixon, R. A., Wahlin, T. B., Wahlin, A., Halldin, C., and Farde, L. (2000). Age-related cognitive deficits mediated by changes in the striatal dopamine system. *Am. J. Psychiatry* 157, 635–637.

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., Morris, J. N., Rebok, G. W., Smith, D. M., Tennstedt, S. L., Unverzagt, F. W., and Willis, S. L. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA* 288, 2271–2281.

Barger, J. L., Kayo, T., Vann, J. M., Arias, E. B., Wang, J., Hacker, T. A., Wang, Y., Raederstorff, D., Morrow, J. D., Leeuwenburgh, C., Allison, D. B., Saupe, K. W., Cartee, G. D., Weindruch, R., and Prolla, T. A. (2008). A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. *PLoS ONE* 3, e2264. doi: 10.1371/journal.pone.0002264.

Bartzokis, G. (2004). Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiol. Aging* 25, 5–18; author reply 49–62.

Baur, J. A., and Sinclair, D. A. (2006). Therapeutic potential of resveratrol: the in vivo evidence. *Nat. Rev. Drug Discov.* 5, 493–506.

Berchtold, N. C., Kesslak, J. P., Pike, C. J., Adlard, P. A., and Cotman, C. W. (2001). Estrogen and exercise interact to regulate brain-derived neurotrophic factor mRNA and protein expression in the hippocampus. *Eur. J. Neurosci.* 14, 1992–2002.

Bhardwaj, R. D., Curtis, M. A., Spalding, K. L., Buchholz, B. A., Fink, D., Bjork-Eriksson, T., Nordborg, C., Gage, F. H., Druid, H., Eriksson, P. S., and Frisen, J. (2006). Neocortical neurogenesis in humans is restricted to development. *Proc. Natl. Acad. Sci. U.S.A.* 103, 12564–12568.

Bourre, J. M., Francois, M., Youyou, A., Dumont, O., Piciotti, M., Pascal, G., and Durand, G. (1989). The effects of dietary alpha-linolenic acid on the composition of nerve membranes, enzymatic activity, amplitude of electrophysiological parameters, resistance to poisons and performance of learning tasks in rats. *J. Nutr.* 119, 1880–1892.

Browner, W. S., Kahn, A. J., Ziv, E., Reiner, A. P., Oshima, J., Cawthon, R. M., Hsueh, W. C., and Cummings, S. R. (2004). The genetics of human longevity. *Am. J. Med.* 117, 851–860.

Bruel-Jungerman, E., Davis, S., Rampon, C., and Laroche, S. (2006). Long-term potentiation enhances neurogenesis in the adult dentate gyrus. *J. Neurosci.* 26, 5888–5893.

Bruel-Jungerman, E., Laroche, S., and Rampon, C. (2005). New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. *Eur. J. Neurosci.* 21, 513–521.

Burke, S. N., and Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nat. Rev. Neurosci.* 7, 30–40.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol. Aging* 17, 85–100.

Cabeza, R., Anderson, N. D., Locantore, J. K., and McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* 17, 1394–1402.

Chein, J. M., and Fiez, J. A. (2001). Dissociation of verbal working memory system components using a delayed serial recall task. *Cereb. Cortex* 11, 1003–1014.

Chen, L. Y., Rex, C. S., Sanaiha, Y., Lynch, G., and Gall, C. M. (2010). Learning induces neurotrophin signaling at hippocampal synapses. *Proc. Natl. Acad. Sci. U.S.A.* 107, 7030–7035.

Chklovskii, D. B., Mel, B. W., and Svoboda, K. (2004). Cortical rewiring and information storage. *Nature* 431, 782–788.

Clelland, C. D., Choi, M., Romberg, C., Clemenson, G. D., Jr., Fragniere, A., Tyers, P., Jessberger, S., Saksida, L. M., Barker, R. A., Gage, F. H., and Bussey, T. J. (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science* 325, 210–213.

Colcombe, S., and Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol. Sci.* 14, 125–130.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., Webb, A., Jerome, G. J., Marquez, D. X., and Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proc. Natl. Acad. Sci. U.S.A.* 101, 3316–3321.

Colman, R. J., Anderson, R. M., Johnson, S. C., Kastman, E. K., Kosmatka, K. J., Beasley, T. M., Allison, D. B., Cruzen, C., Simmons, H. A., Kemnitz, J. W., and Weindruch, R. (2009). Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science* 325, 201–204.

Colsher, P. L., and Wallace, R. B. (1991). Longitudinal application of cognitive function measures in a defined population of community-dwelling elders. *Ann. Epidemiol.* 1, 215–230.

Convit, A., Wolf, O. T., Tarshish, C., and de Leon, M. J. (2003). Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. *Proc. Natl. Acad. Sci. U.S.A.* 100, 2019–2022.

Cooke, A., Zurif, E. B., DeVita, C., Alsop, D., Koenig, P., Detre, J., Gee, J., Pinango, M., Balogh, J., and Grossman, M. (2002). Neural basis for sentence comprehension: grammatical and short-term memory components. *Hum. Brain Mapp.* 15, 80–94.

Cotman, C. W., and Berchtold, N. C. (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 25, 295–301.

Cotman, C. W., Berchtold, N. C., and Christie, L. A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci.* 30, 464–472.

Curtis, M. A., Eriksson, P. S., and Faull, R. L. (2007). Progenitor cells and adult neurogenesis in neurodegenerative diseases and injuries of the basal ganglia. *Clin. Exp. Pharmacol. Physiol.* 34, 528–532.

Curtis, M. A., Penney, E. B., Pearson, A. G., van Roon-Mom, W. M., Butterworth, N. J., Dragunow, M., Connor, B., and Faull, R. L. (2003). Increased cell proliferation and neurogenesis in the

adult human Huntington's disease brain. *Proc. Natl. Acad. Sci. U.S.A.* 100, 9023–9027.

Dalla, C., Papachristos, E. B., Whetstone, A. S., and Shors, T. J. (2009). Female rats learn trace memories better than male rats and consequently retain a greater proportion of new neurons in their hippocampi. *Proc. Natl. Acad. Sci. U.S.A.* 106, 2927–2932.

Dancause, N., Barbay, S., Frost, S. B., Plautz, E. J., Chen, D., Zoubina, E. V., Stowe, A. M., and Nudo, R. J. (2005). Extensive cortical rewiring after brain injury. *J. Neurosci.* 25, 10167–10179.

Das, G. D., and Altman, J. (1971). Postnatal neurogenesis in the cerebellum of the cat and tritiated thymidine autoradiography. *Brain Res.* 30, 323–330.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cereb. Cortex* 18, 1201–1209.

Ding, Y. H., Ding, Y., Li, J., Bessert, D. A., and Rafols, J. A. (2006). Exercise preconditioning strengthens brain microvascular integrity in a rat stroke model. *Neurol. Res.* 28, 184–189.

Dobrossy, M. D., Drapeau, E., Aurousseau, C., Le Moal, M., Piazza, P. V., and Abrous, D. N. (2003). Differential effects of learning on neurogenesis: learning increases or decreases the number of newly born cells depending on their birth date. *Mol. Psychiatry* 8, 974–982.

Dong, W. K., and Greenough, W. T. (2004). Plasticity of nonneuronal brain tissue: roles in developmental disorders. *Ment. Retard Dev. Disabil. Res. Rev.* 10, 85–90.

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., and May, A. (2004). Neuroplasticity: changes in grey matter induced by training. *Nature* 427, 311–312.

Draganski, B., Gaser, C., Kempermann, G., Kuhn, H. G., Winkler, J., Buchel, C., and May, A. (2006). Temporal and spatial dynamics of brain structure changes during extensive learning. *J. Neurosci.* 26, 6314–6317.

Eadie, B. D., Redila, V. A., and Christie, B. R. (2005). Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J. Comp. Neurol.* 486, 39–47.

Eckles-Smith, K., Clayton, D., Bickford, P., and Browning, M. D. (2000). Caloric restriction prevents age-related deficits in LTP and in NMDA receptor expression. *Brain Res. Mol. Brain Res.* 78, 154–162.

Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., and Taub, E. (1995). Increased cortical representation of the fingers of the left hand in string players. *Science* 270, 305–307.

Engelien, A., Silbersweig, D., Stern, E., Huber, W., Doring, W., Frith, C., and Frackowiak, R. S. (1995). The functional anatomy of recovery from auditory agnosia. A PET study of sound categorization in a neurological patient and normal controls. *Brain* 118(Pt 6), 1395–1409.

Englund, U., Fricker-Gates, R. A., Lundberg, C., Bjorklund, A., and Wictorin, K. (2002). Transplantation of human neural progenitor cells into the neonatal rat brain: extensive migration and differentiation with long-distance axonal projections. *Exp. Neurol.* 173, 1–21.

Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., Scalf, P. E., Kim, J. S., Alvarado, M., and Kramer, A. F. (2007). Training-induced functional activation changes in dual-task processing: an FMRI study. *Cereb. Cortex* 17, 192–204.

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Heo, S., McLaren, M., Pence, B. D., Martin, S. A., Vieira, V. J., Woods, J. A., McAuley, E., and Kramer, A. F. (2010). Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. *J. Neurosci.* 30, 5368–5375.

Eriksson, P. S., Perfilieva, E., Bjork-Eriksson, T., Alborn, A. M., Nordborg, C., Peterson, D. A., and Gage, F. H. (1998). Neurogenesis in the adult human hippocampus. *Nat. Med.* 4, 1313–1317.

Etnier, J. L., Nowell, P. M., Landers, D. M., and Sibley, B. A. (2006). A meta-regression to examine the relationship between aerobic fitness and cognitive performance. *Brain Res. Rev.* 52, 119–130.

Fabel, K., Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., Kuo, C. J., and Palmer, T. D. (2003). VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur. J. Neurosci.* 18, 2803–2812.

Fabre, C., Chamari, K., Mucci, P., Masse-Biron, J., and Prefaut, C. (2002). Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. *Int. J. Sports Med.* 23, 415–421.

Faherty, C. J., Kerley, D., and Smeyne, R. J. (2003). A Golgi-Cox morphological analysis of neuronal changes induced by environmental enrichment. *Brain Res. Dev. Brain Res.* 141, 55–61.

Farmer, J., Zhao, X., van Praag, H., Wodtke, K., Gage, F. H., and Christie, B. R. (2004). Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* 124, 71–79.

Farrell, D. (2008). *Talkin' 'bout my Generation: The Economic Impact of Aging U.S. Baby Boomers*. San Francisco, CA: McKinsey Global Institute.

Fjell, A. M., Walhovd, K. B., Reinvang, I., Lundervold, A., Salat, D., Quinn, B. T., Fischl, B., and Dale, A. M. (2006). Selective increase of cortical thickness in high-performing elderly-structural indices of optimal cognitive aging. *Neuroimage* 29, 984–994.

Florence, S. L., Taub, H. B., and Kaas, J. H. (1998). Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. *Science* 282, 1117–1121.

Fontan-Lozano, A., Saez-Cassanelli, J. L., Inda, M. C., de los Santos-Arteaga, M., Sierra-Dominguez, S. A., Lopez-Lluch, G., Delgado-Garcia, J. M., and Carrion, A. M. (2007). Caloric restriction increases learning consolidation and facilitates synaptic plasticity through mechanisms dependent on NR2B subunits of the NMDA receptor. *J. Neurosci.* 27, 10185–10195.

Fontana, L., and Klein, S. (2007). Aging, adiposity, and calorie restriction. *JAMA* 297, 986–994.

Freeman, M. P., Hibbeln, J. R., Wisner, K. L., Davis, J. M., Mischoulon, D., Peet, M., Keck, P. E., Jr., Marangell, L. B., Richardson, A. J., Lake, J., and Stoll, A. L. (2006). Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J. Clin. Psychiatry* 67, 1954–1967.

Frick, K. M., and Fernandez, S. M. (2003). Enrichment enhances spatial memory and increases synaptophysin levels in aged female mice. *Neurobiol. Aging* 24, 615–626.

Gallagher, M., Burwell, R., and Burchinal, M. (1993). Severity of spatial learning impairment in aging: development of a learning index for performance in the Morris water maze. *Behav. Neurosci.* 107, 618–626.

Garthe, A., Behr, J., and Kempermann, G. (2009). Adult-generated hippocampal neurons allow the flexible use of spatially precise learning strategies. *PLoS One* 4, e5464. doi: 10.1371/journal.pone.0005464.

Glisky, E. L., Rubin, S. R., and Davidson, P. S. (2001). Source memory in older adults: an encoding or retrieval problem? *J. Exp. Psychol. Learn. Mem. Cogn.* 27, 1131–1146.

Gomez-Pinilla, F. (2008). Brain foods: the effects of nutrients on brain function. *Nat. Rev. Neurosci.* 9, 568–578.

Gould, E., Beylin, A., Tanapat, P., Reeves, A., and Shors, T. J. (1999). Learning enhances adult neurogenesis in the hippocampal formation. *Nat. Neurosci.* 2, 260–265.

Gould, E., and Gross, C. G. (2002). Neurogenesis in adult mammals: some progress and problems. *J. Neurosci.* 22, 619–623.

Grady, C. L. (1996). Age-related changes in cortical blood flow activation during perception and memory. *Ann. N. Y. Acad. Sci.* 777, 14–21.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerna, J. A., Pietrini, P., Wagner, E., and Haxby, J. V. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. *J. Neurosci.* 14, 1450–1462.

Grady, C. L., McIntosh, A. R., and Craik, F. I. (2003). Age-related differences in the functional connectivity of the hippocampus during memory encoding. *Hippocampus* 13, 572–586.

Grady, C. L., McIntosh, A. R., and Craik, F. I. (2005). Task-related activity in prefrontal cortex and its relation to recognition memory performance in young and old adults. *Neuropsychologia* 43, 1466–1481.

Gray, J. R., Chabris, C. F., and Braver, T. S. (2003). Neural mechanisms of general fluid intelligence. *Nat. Neurosci.* 6, 316–322.

Greenough, W. T., Hwang, H. M., and Gorman, C. (1985). Evidence for active synapse formation or altered postsynaptic metabolism in visual cortex of rats reared in complex environments. *Proc. Natl. Acad. Sci. U.S.A.* 82, 4549–4552.

Greenwood, C. E., and Winocur, G. (1996). Cognitive impairment in rats fed high-fat diets: a specific effect of saturated fatty-acid intake. *Behav. Neurosci.* 110, 451–459.

Greenwood, C. E., and Winocur, G. (2005). High-fat diets, insulin resistance and declining cognitive function. *Neurobiol. Aging* 26(Suppl. 1), 42–45.

Greenwood, P. M. (2000). The frontal aging hypothesis evaluated. *J. Int. Neuropsychol. Soc.* 6, 705–726.

Greenwood, P. M. (2007). Functional plasticity in cognitive aging: review and hypothesis. *Neuropsychology* 21, 657–673.

Grossman, A. W., Churchill, J. D., McKinney, B. C., Kodish, I. M., Otte, S. L., and Greenough, W. T. (2003). Experience effects on brain development: possible contributions to psychopathology. *J. Child. Psychol. Psychiatry* 44, 33–63.

Gutchess, A. H., Welsh, R. C., Hedden, T., Bangert, A., Minear, M., Liu, L. L., and Park, D. C. (2005). Aging and the neural correlates of successful picture encoding: frontal activations compen-

sate for decreased medial-temporal activity. *J. Cogn. Neurosci.* 17, 84–96.
Hasher, L., Stoltzfus, E. R., Zacks, R. T., and Rypma, B. (1991). Age and inhibition. *J. Exp. Psychol. Learn Mem. Cogn.* 17, 163–169.
Hayes, K., Sprague, S., Guo, M., Davis, W., Friedman, A., Kumar, A., Jimenez, D. F., and Ding, Y. (2008). Forced, not voluntary, exercise effectively induces neuroprotection in stroke. *Acta Neuropathol.* 115, 289–296.
Healey, M. K., Campbell, K. L., and Hasher, L. (2008). Cognitive aging and increased distractibility: costs and potential benefits. *Prog. Brain Res.* 169, 353–363.
Heilbronn, L. K., de Jonge, L., Frisard, M. I., DeLany, J. P., Larson-Meyer, D. E., Rood, J., Nguyen, T., Martin, C. K., Volaufova, J., Most, M. M., Greenway, F. L., Smith, S. R., Deutsch, W. A., Williamson, D. A., and Ravussin, E. (2006). Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA* 295, 1539–1548.
Heilbronn, L. K., and Ravussin, E. (2003). Calorie restriction and aging: review of the literature and implications for studies in humans. *Am. J. Clin. Nutr.* 78, 361–369.
Heyn, P., Abreu, B. C., and Ottenbacher, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Arch. Phys. Med. Rehabil.* 85, 1694–1704.
Hihara, S., Notoya, T., Tanaka, M., Ichinose, S., Ojima, H., Obayashi, S., Fujii, N., and Iriki, A. (2006). Extension of corticocortical afferents into the anterior bank of the intraparietal sulcus by tool-use training in adult monkeys. *Neuropsychologia* 44, 2636–2646.
Hillman, C. H., Erickson, K. I., and Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nat. Rev. Neurosci.* 9, 58–65.
Ingram, D. K., Weindruch, R., Spangler, E. L., Freeman, J. R., and Walford, R. L. (1987). Dietary restriction benefits learning and motor performance of aged mice. *J. Gerontol.* 42, 78–81.
Kempermann, G., and Gage, F. H. (1999). Experience-dependent regulation of adult hippocampal neurogenesis: effects of long-term stimulation and stimulus withdrawal. *Hippocampus* 9, 321–332.
Kempermann, G., and Gage, F. H. (2002). Genetic determinants of adult hippocampal neurogenesis correlate with acquisition, but not probe trial performance, in the water maze task. *Eur. J. Neurosci.* 16, 129–136.
Kempermann, G., Kuhn, H. G., and Gage, F. H. (1997). More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386, 493–495.
Kempermann, G., Kuhn, H. G., and Gage, F. H. (1998). Experience-induced neurogenesis in the senescent dentate gyrus. *J. Neurosci.* 18, 3206–3212.
Kim, S., Hasher, L., and Zacks, R. T. (2007). Aging and a benefit of distractibility. *Psychon. Bull. Rev.* 14, 301–305.
Kleim, J. A., Jones, T. A., and Schallert, T. (2003). Motor enrichment and the induction of plasticity before or after brain injury. *Neurochem. Res.* 28, 1757–1769.
Kokoeva, M. V., Yin, H., and Flier, J. S. (2005). Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. *Science* 310, 679–683.
Kronenberg, G., Bick-Sander, A., Bunk, E., Wolf, C., Ehninger, D., and Kempermann, G. (2006). Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. *Neurobiol. Aging* 27, 1505–1513.
Lane, M. A. (2000). Nonhuman primate models in biogerontology. *Exp. Gerontol.* 35, 533–541.
Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L., Crane, P., and Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann. Intern. Med.* 144, 73–81.
Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J., Greenop, K. R., and Almeida, O. P. (2008). Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 300, 1027–1037.
Lee, J. M., Ross, E. R., Gower, A., Paris, J. M., Martensson, R., and Lorens, S. A. (1994). Spatial learning deficits in the aged rat: neuroanatomical and neurochemical correlates. *Brain Res. Bull.* 33, 489–500.
Lee, W. C., Huang, H., Feng, G., Sanes, J. R., Brown, E. N., So, P. T., and Nedivi, E. (2006). Dynamic remodeling of dendritic arbors in GABAergic interneurons of adult visual cortex. *PLoS Biol.* 4, e29. doi: 10.1371/journal.pbio.0040029.
Leuner, B., Mendolia-Loffredo, S., Kozorovitskiy, Y., Samburg, D., Gould, E., and Shors, T. J. (2004). Learning enhances the survival of new neurons beyond the time when the hippocampus is required for memory. *J. Neurosci.* 24, 7477–7481.
Li, G., Peskind, E. R., Millard, S. P., Chi, P., Sokal, I., Yu, C. E., Bekris, L. M., Raskind, M. A., Galasko, D. R., and Montine, T. J. (2009). Cerebrospinal fluid concentration of brain-derived neurotrophic factor and cognitive function in non-demented subjects. *PLoS ONE* 4, e5424. doi: 10.1371/journal.pone.0005424.
Lou, S. J., Liu, J. Y., Chang, H., and Chen, P. J. (2008). Hippocampal neurogenesis and gene expression depend on exercise intensity in juvenile rats. *Brain Res.* 1210, 48–55.
Luo, C. X., Jiang, J., Zhou, Q. G., Zhu, X. J., Wang, W., Zhang, Z. J., Han, X., and Zhu, D. Y. (2007). Voluntary exercise-induced neurogenesis in the postischemic dentate gyrus is associated with spatial memory recovery from stroke. *J. Neurosci. Res.* 85, 1637–1646.
Martin, C. K., Anton, S. D., Han, H., York-Crowe, E., Redman, L. M., Ravussin, E., and Williamson, D. A. (2007). Examination of cognitive function during six months of calorie restriction: results of a randomized controlled trial. *Rejuvenation Res.* 10, 179–190.
Masliah, E., Crews, L., and Hansen, L. (2006). Synaptic remodeling during aging and in Alzheimer's disease. *J. Alzheimers Dis.* 9(3 Suppl.), 91–99.
Maswood, N., Young, J., Tilmont, E., Zhang, Z., Gash, D. M., Gerhardt, G. A., Grondin, R., Roth, G. S., Mattison, J., Lane, M. A., Carson, R. E., Cohen, R. M., Mouton, P. R., Quigley, C., Mattson, M. P., and Ingram, D. K. (2004). Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. *Proc. Natl. Acad. Sci. U.S.A.* 101, 18171–18176.
Mattson, M. P. (2000). Neuroprotective signaling and the aging brain: take away my food and let me run. *Brain Res.* 886, 47–53.
Mattson, M. P., Duan, W., Chan, S. L., Cheng, A., Haughey, N., Gary, D. S., Guo, Z., Lee, J., and Furukawa, K. (2002). Neuroprotective and neurorestorative signal transduction mechanisms in brain aging: modification by genes, diet and behavior. *Neurobiol. Aging* 23, 695–705.
Milgram, N. W., Head, E., Muggenburg, B., Holowachuk, D., Murphey, H., Estrada, J., Ikeda-Douglas, C. J., Zicker, S. C., and Cotman, C. W. (2002). Landmark discrimination learning in the dog: effects of age, an antioxidant fortified food, and cognitive strategy. *Neurosci. Biobehav. Rev.* 26, 679–695.
Molteni, R., Barnard, R. J., Ying, Z., Roberts, C. K., and Gomez-Pinilla, F. (2002). A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience* 112, 803–814.
Molteni, R., Wu, A., Vaynman, S., Ying, Z., Barnard, R. J., and Gomez-Pinilla, F. (2004). Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. *Neuroscience* 123, 429–440.
Morcom, A. M., Good, C. D., Frackowiak, R. S., and Rugg, M. D. (2003). Age effects on the neural correlates of successful memory encoding. *Brain* 126(Pt 1), 213–229.
Morrison, J. H., and Hof, P. R. (1997). Life and death of neurons in the aging brain. *Science* 278, 412–419.
Mouret, A., Gheusi, G., Gabellec, M. M., de Chaumont, F., Olivo-Marin, J. C., and Lledo, P. M. (2008). Learning and survival of newly generated neurons: when time matters. *J. Neurosci.* 28, 11511–11516.
Mozolic, J. L., Hayasaka, S., and Laurienti, P. J. (2010). A cognitive training intervention increases resting cerebral blood flow in healthy older adults. *Front. Hum. Neurosci.* 4:16. doi: 10.3389/neuro.09.016.2010.
Naylor, A. S., Bull, C., Nilsson, M. K., Zhu, C., Bjork-Eriksson, T., Eriksson, P. S., Blomgren, K., and Kuhn, H. G. (2008). Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse brain. *Proc. Natl. Acad. Sci. U.S.A.* 105, 14632–14637.
Nichol, K. E., Parachikova, A. I., and Cotman, C. W. (2007). Three weeks of running wheel exposure improves cognitive performance in the aged Tg2576 mouse. *Behav. Brain Res.* 184, 124–132.
Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., and Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol. Aging* 17, 299–320.
Paulus, M. P., Hozack, N., Frank, L., and Brown, G. G. (2002). Error rate and outcome predictability affect neural activation in prefrontal cortex and anterior cingulate during decision-making. *Neuroimage* 15, 836–846.
Pearson, K. J., Baur, J. A., Lewis, K. N., Peshkin, L., Price, N. L., Labinskyy, N., Swindell, W. R., Kamara, D., Minor, R. K., Perez, E., Jamieson, H. A., Zhang, Y., Dunn, S. R., Sharma, K., Pleshko, N., Woollett, L. A., Csiszar, A., Ikeno, Y., Le Couteur, D., Elliott, P. J., Becker, K. G., Navas, P., Ingram, D. K., Wolf, N. S., Ungvari, Z., Sinclair, D. A., and

de Cabo, R. (2008). Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab.* 8, 157–168.

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., Sloan, R., Gage, F. H., Brown, T. R., and Small, S. A. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc. Natl. Acad. Sci. U.S.A.* 104, 5638–5643.

Pfluger, P. T., Herranz, D., Velasco-Miguel, S., Serrano, M., and Tschop, M. H. (2008). Sirt1 protects against high-fat diet-induced metabolic damage. *Proc. Natl. Acad. Sci. U.S.A.* 105, 9793–9798.

Piguet, O., Double, K. L., Kril, J. J., Harasty, J., Macdonald, V., McRitchie, D. A., and Halliday, G. M. (2009). White matter loss in healthy ageing: a post-mortem analysis. *Neurobiol. Aging* 30, 1288–1295.

Pontifex, M. B., Hillman, C. H., Fernhall, B., Thompson, K. M., and Valentini, T. A. (2009). The effect of acute aerobic and resistance exercise on working memory. *Med. Sci. Sports Exerc.* 41, 927–934.

Poo, M. M. (2001). Neurotrophins as synaptic modulators. *Nat. Rev. Neurosci.* 2, 24–32.

Rakic, P. (1985). Limits of neurogenesis in primates. *Science* 227, 1054–1056.

Rakic, P. (2002). Adult neurogenesis in mammals: an identity crisis. *J. Neurosci.* 22, 614–618.

Rapp, P. R., and Amaral, D. G. (1991). Recognition memory deficits in a subpopulation of aged monkeys resemble the effects of medial temporal lobe damage. *Neurobiol. Aging* 12, 481–486.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., Loken, W. J., Thornton, A. E., and Acker, J. D. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb. Cortex* 7, 268–282.

Renaud, S., and de Lorgeril, M. (1992). Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 339, 1523–1526.

Reuter-Lorenz, P. A., Jonides, J., Smith, E. E., Hartley, A., Miller, A., Marshuetz, C., and Koeppe, R. A. (2000). Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. *J. Cogn. Neurosci.* 12, 174–187.

Ro, T., Noser, E., Boake, C., Johnson, R., Gaber, M., Speroni, A., Bernstein, M., De Joya, A., Scott Burgin, W., Zhang, L., Taub, E., Grotta, J. C., and Levin, H. S. (2006). Functional reorganization and recovery after constraint-induced movement therapy in subacute stroke: case reports. *Neurocase* 12, 50–60.

Rodrigue, K. M., and Raz, N. (2004). Shrinkage of the entorhinal cortex over five years predicts memory performance in healthy adults. *J. Neurosci.* 24, 956–963.

Rolland, Y., Pillard, F., Klapouszczak, A., Reynish, E., Thomas, D., Andrieu, S., Riviere, D., and Vellas, B. (2007). Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. *J. Am. Geriatr. Soc.* 55, 158–165.

Rosenzweig, M. R., and Bennett, E. L. (1972). Cerebral changes in rats exposed individually to an enriched environment. *J. Comp. Physiol. Psychol.* 80, 304–313.

Rugg, M. D., Otten, L. J., and Henson, R. N. (2002). The neural basis of episodic memory: evidence from functional neuroimaging. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* 357, 1097–1110.

Rypma, B., and D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nat. Neurosci.* 3, 509–515.

Saxe, M. D., Malleret, G., Vronskaya, S., Mendez, I., Garcia, A. D., Sofroniew, M. V., Kandel, E. R., and Hen, R. (2007). Paradoxical influence of hippocampal neurogenesis on working memory. *Proc. Natl. Acad. Sci. U.S.A.* 104, 4642–4646.

Scalf, P. E., Colcombe, S. J., McCarley, J. S., Erickson, K. I., Alvarado, M., Kim, J. S., Wadhwa, R. P., and Kramer, A. F. (2007). The neural correlates of an expanded functional field of view. *J. Gerontol. B. Psychol. Sci. Soc. Sci.* 62, 32–44.

Scarmeas, N., Luchsinger, J. A., Schupf, N., Brickman, A. M., Cosentino, S., Tang, M. X., and Stern, Y. (2009). Physical activity, diet, and risk of Alzheimer disease. *JAMA* 302, 627–637.

Scholz, J., Klein, M. C., Behrens, T. E., and Johansen-Berg, H. (2009). Training induces changes in white-matter architecture. *Nat. Neurosci.* 12, 1370–1371.

Shamosh, N. A., Deyoung, C. G., Green, A. E., Reis, D. L., Johnson, M. R., Conway, A. R., Engle, R. W., Braver, T. S., and Gray, J. R. (2008). Individual differences in delay discounting: relation to intelligence, working memory, and anterior prefrontal cortex. *Psychol. Sci.* 19, 904–911.

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., Evans, A., Rapoport, J., and Giedd, J. (2006). Intellectual ability and cortical development in children and adolescents. *Nature* 440, 676–679.

Shi, L., Adams, M. M., Linville, M. C., Newton, I. G., Forbes, M. E., Long, A. B., Riddle, D. R., and Brunso-Bechtold, J. K. (2007). Caloric restriction eliminates the aging-related decline in NMDA and AMPA receptor subunits in the rat hippocampus and induces homeostasis. *Exp. Neurol.* 206, 70–79.

Shors, T. J., Miesegaes, G., Beylin, A., Zhao, M., Rydel, T., and Gould, E. (2001). Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 410, 372–376.

Smiley-Oyen, A. L., Lowry, K. A., Francois, S. J., Kohut, M. L., and Ekkekakis, P. (2008). Exercise, fitness, and neurocognitive function in older adults: the "selective improvement" and "cardiovascular fitness" hypotheses. *Ann. Behav. Med.* 36, 280–291.

Song, H. J., Stevens, C. F., and Gage, F. H. (2002). Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons. *Nat. Neurosci.* 5, 438–445.

Springer, M. V., McIntosh, A. R., Winocur, G., and Grady, C. L. (2005). The relation between brain activity during memory tasks and years of education in young and older adults. *Neuropsychology* 19, 181–192.

Sterr, A., Muller, M. M., Elbert, T., Rockstroh, B., Pantev, C., and Taub, E. (1998). Changed perceptions in Braille readers. *Nature* 391, 134–135.

Straube, T., Korz, V., and Frey, J. U. (2003). Bidirectional modulation of long-term potentiation by novelty-exploration in rat dentate gyrus. *Neurosci. Lett.* 344, 5–8.

Takasawa, K., Kitagawa, K., Yagita, Y., Sasaki, T., Tanaka, S., Matsushita, K., Ohstuki, T., Miyata, T., Okano, H., Hori, M., and Matsumoto, M. (2002). Increased proliferation of neural progenitor cells but reduced survival of newborn cells in the contralateral hippocampus after focal cerebral ischemia in rats. *J. Cereb. Blood Flow Metab.* 22, 299–307.

Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., Yamanouchi, T., Suzuki, S., and Kawashima, R. (2010). Training of working memory impacts structural connectivity. *J. Neurosci.* 30, 3297–3303.

Taub, E., Uswatte, G., and Elbert, T. (2002). New treatments in neurorehabilitation founded on basic research. *Nat. Rev. Neurosci.* 3, 228–236.

Teri, L., Gibbons, L. E., McCurry, S. M., Logsdon, R. G., Buchner, D. M., Barlow, W. E., Kukull, W. A., LaCroix, A. Z., McCormick, W., and Larson, E. B. (2003). Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. *JAMA* 290, 2015–2022.

Toni, N., Laplagne, D. A., Zhao, C., Lombardi, G., Ribak, C. E., Gage, F. H., and Schinder, A. F. (2008). Neurons born in the adult dentate gyrus form functional synapses with target cells. *Nat. Neurosci.* 11, 901–907.

Trejo, J. L., Carro, E., and Torres-Aleman, I. (2001). Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J. Neurosci.* 21, 1628–1634.

Tschop, M., and Thomas, G. (2006). Fat fuels insulin resistance through Toll-like receptors. *Nat. Med.* 12, 1359–1361.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia* 42, 1394–1413.

Van Petten, C., Plante, E., Davidson, P. S., Kuo, T. Y., Bajuscak, L., and Glisky, E. L. (2004). Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia* 42, 1313–1335.

van Praag, H., Kempermann, G., and Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* 2, 266–270.

van Praag, H., Shubert, T., Zhao, C., and Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *J. Neurosci.* 25, 8680–8685.

Vaynman, S., Ying, Z., and Gomez-Pinilla, F. (2004). Exercise induces BDNF and synapsin I to specific hippocampal subfields. *J. Neurosci. Res.* 76, 356–362.

Volkow, N. D., Gur, R. C., Wang, G. J., Fowler, J. S., Moberg, P. J., Ding, Y. S., Hitzemann, R., Smith, G., and Logan, J. (1998). Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. *Am. J. Psychiatry* 155, 344–349.

Voss, H. U., Uluc, A. M., Dyke, J. P., Watts, R., Kobylarz, E. J., McCandliss, B. D., Heier, L. A., Beattie, B. J., Hamacher, K. A., Vallabhajosula, S., Goldsmith, S. J., Ballon, D., Giacino, J. T., and Schiff, N. D. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *J. Clin. Invest.* 116, 2005–2011.

Waddell, J., and Shors, T. J. (2008). Neurogenesis, learning and associative strength. *Eur. J. Neurosci.* 27, 3020–3028.

Walford, R. L., Mock, D., MacCallum, T., and Laseter, J. L. (1999). Physiologic changes in humans subjected to severe, selective calorie restriction for two years in biosphere 2: health, aging, and toxicological perspectives. *Toxicol. Sci.* 52(2 Suppl), 61–65.

Walhovd, K. B., Fjell, A. M., Dale, A. M., Fischl, B., Quinn, B. T., Makris, N., Salat, D., and Reinvang, I. (2006). Regional cortical thickness matters in recall after months more than minutes. *Neuroimage* 31, 1343–1351.

Weindruch, R., and Sohal, R. S. (1997). Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. *N. Engl. J. Med.* 337, 986–994.

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychol. Bull.* 120, 272–292.

Whitlock, J. R., Heynen, A. J., Shuler, M. G., and Bear, M. F. (2006). Learning induces long-term potentiation in the hippocampus. *Science* 313, 1093–1097.

Willis, S. L., and Schaie, K. W. (1986). Training the elderly on the ability factors of spatial orientation and inductive reasoning. *Psychol. Aging* 1, 239–247.

Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., Morris, J. N., Rebok, G. W., Unverzagt, F. W., Stoddard, A. M., and Wright, E. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA* 296, 2805–2814.

Wingfield, A., and Grossman, M. (2006). Language and the aging brain: patterns of neural compensation revealed by functional brain imaging. *J. Neurophysiol.* 96, 2830–2839.

Witte, A. V., Fobker, M., Gellner, R., Knecht, S., and Floel, A. (2009). Caloric restriction improves memory in elderly humans. *Proc. Natl. Acad. Sci. U.S.A.* 106, 1255–1260.

Wu, A., Molteni, R., Ying, Z., and Gomez-Pinilla, F. (2003). A saturated-fat diet aggravates the outcome of traumatic brain injury on hippocampal plasticity and cognitive function by reducing brain-derived neurotrophic factor. *Neuroscience* 119, 365–375.

Wu, A., Ying, Z., and Gomez-Pinilla, F. (2008a). Docosahexaenoic acid dietary supplementation enhances the effects of exercise on synaptic plasticity and cognition. *Neuroscience* 155, 751–759.

Wu, W., Brickman, A. M., Luchsinger, J., Ferrazzano, P., Pichiule, P., Yoshita, M., Brown, T., DeCarli, C., Barnes, C. A., Mayeux, R., Vannucci, S. J., and Small, S. A. (2008b). The brain in the age of old: the hippocampal formation is targeted differentially by diseases of late life. *Ann. Neurol.* 64, 698–706.

Xu, T., Yu, X., Perlik, A. J., Tobin, W. F., Zweig, J. A., Tennant, K., Jones, T., and Zuo, Y. (2009). Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature* 462, 915–919.

Yu, E. S., Liu, W. T., Levy, P., Zhang, M. Y., Katzman, R., Lung, C. T., Wong, S. C., Wang, Z. Y., and Qu, G. Y. (1989). Cognitive impairment among elderly adults in Shanghai, China. *J. Gerontol.* 44, S97–S106.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 02 April 2010; accepted: 22 October 2010; published online: 29 November 2010.

*Citation: Greenwood PM and Parasuraman R (2010) Neuronal and cognitive plasticity: a neurocognitive framework for ameliorating cognitive aging. Front. Ag. Neurosci. **2**:150. doi: 10.3389/fnagi.2010.00150*