# Capitalizing on Cortical Plasticity:
# Influence of Lifestyle Factors on Cognition and Brain Health

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*Introduction*

The mantra of "successful aging" appears to be ever present in our fast paced high tech society. A visit to your local electronics store will quickly reveal an increasing number of computer games, such as Nintendo's Brain Age and Mattel's Brain Games, that are touted to train your brain and keep you mentally young. Of course, these products, and many others, are also easily downloadable, for a fee, from a multitude of web sites. The number of books offering solutions to age-related declines in cognitive function, including many aspects of memory, are also proliferating at a rapid pace. Claims in the media, and on the shelf's of health food stores, also abound with regard to the beneficial effects of nutraceuticals and supplements on health and functioning throughout the lifespan.

The increasing interest in products and lifestyle factors that engender successful aging is driven, in large part, by the aging of populations in many industrialized nations as well as the change in our conception of aging. For example, as of 2004 there were 36.3 million Americans over the age of 65, 12.4% of the population. This number is projected to grow to 71.5 million individuals, approximately 20% of the population, by 2030. Increasing numbers of 65+ year olds have been entering the workforce, both out of financial necessity and in search of continuing intellectual and social stimulation, and are expected to continue to do so in the future (Administration on Aging, 2005). Hence the desire to maintain cognitive as well as physical health.

In the present document we primarily focus on one factor that has been suggested to have a positive influence on cognition and brain function, that is, physical activity and exercise. However, other factors such as intellectual engagement, social interactions, and nutrition are also discussed, albeit to a lesser extent, with regard to their potential beneficial effects on cognition and brain function. We evaluate the claim that staying physically active can maintain and even enhance cognition and brain function as well as reduce the risk of age-associated neurological disorders such as Alzheimer's disease. We begin our review by examining the epidemiological or prospective observational literature which has explored this issue, often with middle age and older adults. Next, we examine randomized clinical trials which have examined the influence of fitness training programs on cognition and less frequently, measures of brain function and structure. We then provide a brief review of the ever expanding animal literature which has begun to elucidate the cellular and molecular mechanisms of physical activity effects on brain and cognition. Next, we briefly examine the role of other lifestyle factors such as the pursuit of intellectually engaging activities and social engagement in the maintenance of cognition and reduction in risk for age-related neurological disorders such as Alzheimer's disease. We then discuss a small but growing literature which examines the combination of different lifestyle factors, including intellectual engagement, social engagement, physical activity and nutrition as a means for enhancing cognitive and brain health of older adults. Finally, we conclude with a brief prescription of future directions for research on maintaining cognitive vitality across the adult lifespan.

*Human Observational Studies of Physical Activity & Exercise*

In recent years there has been an increasing interest in the relationship between physical activity and exercise at one point in the lifespan and cognition or the diagnosis of age-associated neurological diseases at a later point in time. Clearly, one reason for this interest is the burgeoning literature on the reduction in risk for a multitude of diseases, including cardiovascular disease, breast and colon cancer, obesity, and type II diabetes, associated with physical activity (Dishman et al., 2006). However, another important factor influencing the interest in physical activity and cognition is the animal research on the positive effects of enriched environments, which often include a physical activity component, on learning, memory and brain function (Rosenzweig & Bennett, 1996).

Observational studies generally assess physical activity and exercise with self-report questionnaires and then follow-up, often 2 to 9 years later, with an examination of cognitive function or diagnosis of Alzheimer's and other forms of dementia. Given that the decision to partake in physical activity is often related to other lifestyle choices and medical conditions these studies also assess such factors which are then are used as covariates in the examination of physical activity effects on cognition.

A number of prospective observational studies have found a reduction of risk for Alzheimer's disease and other forms of dementia for more physically active individuals. For example Larson el al (2006) assessed 1740 adults over the age of 65 on the frequency of participation in a variety of physical activities (e.g. walking, hiking, bicycling, swimming). After a mean follow-up of 6.2 years 158 of the original participants had developed dementia. After adjusting for age, sex and medical conditions, individuals who exercised more than 3 times per week during initial assessment were found to be 34% less likely to be diagnosed with dementia than those who exercised fewer than 3 times per week. Similar relationships between exercise and dementia have been reported in other studies (Laurin et al., 2001; Podewils et al., 2005; Scarmeas et al., 2001). Some studies have focused specifically on walking and its relationship to dementia. Abbott et al (2004) examined the distance that 2257 physically capable men, aged 71 to 93, walked on a daily basis and then followed up an average of 4.7 years later with an assessment of dementia. After adjusting for cognitive ability, education and medical conditions at baseline, both walking speed and distance were associated with a reduced risk for dementia.

A reduction of risk for cognitive decline, often measured with a general test of cognitive function such as the mini-mental state examination (MMSE), has also been found for physically active individuals who have not been diagnosed with dementia (Almeida et al., 2006; Lytle et al., 2004; Weuve et al., 2004; Yaffe et al., 2001). A particularly noteworthy study was reported by Barnes et al (2003) who obtained both subjective and objective measures of cardiorespiratory fitness in a sample of 349 individuals over 55. Six years later these individuals were tested on both the MMSE and more focused tests of executive control, attention, verbal memory and verbal fluency. Higher fit individuals at time 1 showed benefits on tests of all of these abilities at the

final assessment and the relationship between fitness and cognition was stronger for the objective than for the subjective measure of fitness.

Although in general the majority of the observational studies have found that physical activity has beneficial effects on cognition, it is important to note that some observational studies have failed to find a relationship between fitness and cognition or dementia (Sturman et al., 2006; Verghese et al., 2003; Wilson et al., 2002; Yamada et al., 2003). It is difficult to know, given the current scientific literature, which factors are most important in moderating the influence of physical activity on later life cognition and dementia. However some possibilities that merit further research include: the distinction between aerobic and non-aerobic physical activities (Barnes et al., 2003), the utility of self-report versus more objectively measured physical activities and fitness, the relative contribution of social, intellectual and physical factors to different everyday activities (Karp et al., 2006), the role of physical activity duration, intensity, and frequency (van Gelder et al., 2005), the nature of the components of cognition that serve as the criterion variables (Colcombe & Kramer, 2003; Hall et al., 2001), the age of participants at initial and final assessment, and genetic factors (Etinier et al., 2007; Podewilis et al., 2005, Rovio et al., 2005; Schuit et al., 2001).

*Beyond Observation: Randomized Clinical Trials in Humans*

Observational studies have provided intriguing support for the relationship between physical activity and cognition. However, such studies cannot establish causal links between these constructs. Over the past several decades there have been a relatively small but increasing number of clinical trials in which relatively sedentary individuals, often over the age of 60, are randomized to an aerobic training group (i.e. walking, swimming, bicycling) and a control group that often entails non-aerobic activity such as toning and stretching. Training is usually conducted for an hour a day for several days a week and can last from several months to two years. Cognition, and less frequently brain function and structure, is examined prior to and subsequent to the interventions.

Results of such studies have been mixed with some reporting that aerobic exercise differentially benefits aspects of cognition while other studies have failed to observe such a relationship. Several potential reasons for this mixed pattern of results include: (1) the manner in which cardiorespiratory fitness was characterized from resting heart rate to the gold standard, $VO_2$ max, (2) the length, duration and intensity of exercise training, (3) the cognitive processes examined in the studies, and (4) the age, health, sex, and fitness levels of participants. Given the substantial variability in individual and experimental characteristics several meta-analyses have been conducted in recent years to determine, first, whether a robust relationship between exercise training and cognition can be discerned and second, which factors moderate such a relationship (Etnier et al., 2006; Heyn et al., 2004; Kramer & Colcombe, 2003).

The results are clear with respect to the first question, exercise training positively influences cognition. Several additional results are noteworthy. First, the effect size of exercise training, approximately .5 over analyses, is quite similar for both normal and

cognitively impaired adults. Thus, older adults with early dementia appear able to benefit from exercise training, albeit from a different cognitive baseline. Second, studies with more women generally show a larger effect of exercise training on cognition than studies with fewer women. Third, while fitness training has relatively broad effects across a variety of perceptual and cognitive processes, the benefits of exercise training appear to be larger for executive control processes (e.g. planning, scheduling, working memory, dealing with distraction, multi-tasking). This observation is quite interesting given that executive control processes show substantial declines over the adult lifespan. Fourth, overall there was little evidence of a significant relationship between fitness change and cognitive change. At first glance this observation appears perplexing. However, upon further consideration this may not be surprising given that the measures of fitness obtained in these studies are global in nature (i.e. sensitive to both peripheral and central nervous system changes) and not specific to brain function.

As compared to the study of the relationship between exercise training and cognition relatively few studies have been conducted to examine exercise training influences on human brain structure and function. Colcombe et al (2004) investigated changes in the neural network which supports attentional control, as indexed by fMRI activation obtained in a high field magnet, over the course of a 6 month aerobic exercise program. Older adults performed the flanker task, which entails focusing on a subset of information presented on a visual display and ignoring task-irrelevant distractors, before and after the exercise training interventions. Individuals in the aerobic training group (i.e. walking) showed a reduced behavioral distraction effect and change in pattern of fMRI activation similar to that displayed by younger controls (i.e. increased right middle frontal gyrus and superior parietal activation). Participants in the toning and stretching control group did not show such behavioral and fMRI changes. More recently, Colcombe et al (2006) reported increases in brain volume, as indexed by a semi-automated image segmentation technique applied to high resolution MRI data, for an aerobic but not for a non-aerobic exercise training group. The individuals who walked three days a week for approximately 1 hour per day displayed increases in gray matter volume in the frontal and temporal cortex as well as increases in the volume of anterior white matter. Finally, Pereira et al (2007) reported increases in MRI measures of cerebral blood volume (CBV) in the dentate gyrus of the hippocampus for a group of 11 middle aged individuals who participated in a 3 month aerobic exercise program. These CBV changes were related to both improvements in cardiorespiratory fitness and performance on a test of verbal learning and memory. Increases in CBV in a parallel study of exercising mice was found to be related to enhanced neurogenesis. Therefore, the results of this study are particularly exciting in suggesting that CBV may serve as a biomarker for neurogenesis in humans.

*Animal Research: Cellular and Molecular Mechanisms*

Research using non-human animals complements human research in several ways. First, many of the uncontrolled variables in human research can be more easily controlled or systematically manipulated in non-human animal research, thereby allowing for a more precise examination of some of the factors influencing brain and cognition.

Second, the capabilities to assess the molecular and cellular mechanisms of exercise are substantially greater in non-human animals than in humans. Therefore, animal research provides an important translational approach to understanding neurocognitive plasticity in humans.

In rodents, voluntary exercise enhances the rate of learning on hippocampal dependent tasks such as the Morris Water maze, a task that requires the use of extra-maze cues to determine the location of a submerged platform (Adlard et al., 2004; Vaynman et al., 2004). For example, in older animals, van Praag et al. (2005) reported that 45 days of access to a running wheel resulted in faster acquisition and greater retention on the water maze than age-matched sedentary controls. Other tasks, such as the passive avoidance task, in which animals are trained via foot-shock to refrain from entering into a dark chamber, also show performance improvements with exercise (Alaei et al., 2006). Similar behavioral benefits of exercise have been reported in rodent models of Alzheimer's disease (Adlard et al., 2005) and Huntington's disease (Pang et al., 2006). Therefore, there is ample evidence that exercise promotes faster rates of learning and improved retention on hippocampal-dependent tasks.

Enhanced learning on water maze tasks has been associated with an increased production of neurotrophic molecules such as brain-derived neurotrophic factor (BDNF). BDNF is involved in neuroprotection and promotes cell survival, neurite outgrowth, and synaptic plasticity (Cotman & Berchtold, 2002). For example, direct administration of BDNF increases cell proliferation in the hippocampus, whereas blocking BDNF activity reduces cell proliferation. Voluntary exercise increases both mRNA and protein levels of BDNF in the hippocampus, cerebellum, and frontal cortex and blocking the binding of BDNF to its tyrosine kinase receptor abolishes the exercise-induced performance benefits on the Morris water maze (Vaynman et al., 2004). Therefore, exercise increases BDNF levels, which seem to be inextricably related to the behavioral improvements observed with an exercise treatment.

BDNF is not the only molecule in the brain affected by exercise. For example, insulin-like growth factor-1 (IGF-1) is critical for both exercise-induced angiogenesis (Lopez-Lopez et al., 2004) and neurogenesis (Trejo et al., 2001). By blocking IGF-1 influx into the brain, exercise-induced cellular proliferation and BDNF production are effectively rescinded. In addition, IGF-1 also moderates the secretion of other molecules such as vascular endothelial growth factor (VEGF), a prominent growth factor involved in blood vessel growth. For example, Lopez-Lopez et al., (2004) reported that blocking IGF-1 blocked the secretion of VEGF, which resulted in a significant suppression of new capillaries. Furthermore, by blocking the influx of VEGF into the brain, exercise-induced neurogenesis is abolished, but baseline levels of neurogenesis are unaffected (Fabel et al., 2003). Therefore, a plethora of molecules and molecular cascades are up-regulated with exercise that influence learning and memory operations, cortical morphology, angiogenesis, and cell proliferation.

Exercise induces the development of new capillaries in the hippocampus, cerebellum, and motor cortex of young rats (Black et al., 1990; Kleim et al., 2002; Swain

et al., 2003) and reduces the volume of cortical damage caused by the induction of stroke (Ding et al., 2004). One function of new capillaries is to deliver necessary nutrients to existing or newly dividing neurons. In relation to this, exercise increases both cell proliferation and cell survival, which has been related to enhanced learning rates on the Morris water maze (van Praag et al., 1999). Neurogenesis is diminished with age, but exercise reliably reverses the normal decline in neurogenesis accompanied by improved Morris water maze performance (van Praag et al., 2005; Kronenberg et al., 2006).

It is clear from this review that rodent research provides strong support for the positive effects of exercise on the brain and cognition. Voluntary wheel running in rodents results in enhanced learning and retention on hippocampal-dependent tasks, the induction of a variety of molecular cascades including BDNF, IGF-1, VEGF, and an increase in neurotransmitter release in dopaminergic, cholinergic, and serotinergic systems. In addition, both angiogenesis and neurogenesis are up-regulated with exercise in young and old animals. This evidence provides an important mechanistic and molecular basis for understanding the effects of exercise on the human brain and cognition.

*Beyond Physical Activity & Exercise: The Influence of Intellectual and Social Engagement in Promoting Healthy Minds throughout Adulthood*

Similar to the studies of physical activity there have been an increasing number of longitudinal human studies to examine the influence of participation in intellectually stimulating activities such as reading, playing cards or chess, attending a play, doing crossword puzzles, taking classes, going to museums and other similar activities on the maintenance of cognitive health and reduction in risk for Alzheimer's disease in older adults. These studies generally assess number and frequency of participation in intellectually engaging activities at one point in time, in populations of adults between 60 and 80 years of age, and then follow up six or more years later with an assessment of cognition and age-associated neurological disorders. The great majority of such studies conducted over the past decade have found that participation in a greater number (and with greater frequency) of intellectually engaging activities is associated with higher levels of cognitive function and reduced risk of dementia in older adults (Bosma et al. 2002; Verghese et al, 2003, 2006; Wang et al., 2006; Wilson et al., 2002, 2003).

A similar approach has been taken to examine the influence of participation in social activities and maintaining social interactions on cognition and brain health of older adults. Studies that have examined social activities such as meeting friends, participating in cultural or social groups, engaging in family and charitable activities, and attending church activities have generally produced positive results both in terms of maintenance of cognition in normal elderly and in reducing the risk for Alzheimer's dementia (Barnes et al., 2004; Lovden et al., 2005; Wang et al., 2002). The size of social networks has produced a mixed pattern of results with some studies finding benefits for individuals with larger social networks and other studies failing to observe relationships between social network size and cognition or dementia risk (Fratiglioni et al., 2000; Helmer et al.,

1999). Indeed, social relationship quality rather than social network size may be more important with regard to maintaining healthy minds and brains.

One potential concern with these longitudinal studies, however, is whether reduced intellectual or social engagement at initial assessment may be an early sign of decline or dementia rather than a predictor of latter function. While reverse causation is always a concern in studies that do not involve randomized trials, the fact that some of the studies have found relationships between cognitive or social engagement over 15 or 20 years considerably reduces this concern (Crowe et al. 2003)

*Effects of Multimodal Lifestyle Factors on Cognition and Brain Health*

As described in the sections above, the great majority of laboratory studies of factors that influence the level and trajectories of cognitive function focus on single factors. This is a reasonable scientific approach given the potential complexity and cost of simultaneously studying multiple interacting factors. However, clearly a disadvantage of such an approach is that it may miss the potential power of interactions for maintaining and enhancing cognition.

There are at least two different approaches that have been pursued in the literature to the study of multi-factor influences on cognition. One approach is represented by the early study of complex or enriched environments on brain function and performance of non-human animals (Black, Isaacs, Anderson, Alcantara & Greenough, 1990; Ehninger & Kempermann, 2003; Jones, Hawrylak, & Greenough, 1996; Kempermann, Kuhn & Gage, 1997; Rosenzweig & Bennett, 1996). Such an approach can establish the influence of some combination of either separately acting or interacting factors such as social interaction, cognitive challenge, physical activity and nutrition on performance and brain. However, this approach can not assess the relative contribution of individual factors (or their interaction). Nonetheless such an approach has been instrumental in establishing the importance of potential lifestyle factors in cognitive maintenance and enhancement. A second approach which has been represented in observational studies for some time and is beginning to evolve in human and non-human interventions is the orthogonal examination of multiple factors and their interactions in separate groups of subjects. Such an approach is costly in terms of time and the number of subjects required. However, this approach also has the potential to decompose the relative benefits of different factors and their potential mechanisms. Studies that have pursued each of these approaches will be discussed below.

**Prospective Observational Studies.** A number of prospective observational studies, some of which have been reviewed above in the context of single lifestyle factors, have investigated the relative contribution of intellectual, physical and social engagement as predictors of cognitive change and transition to dementia. For example, Wilson et al (2002a&b) reported that while participation in cognitive activities (such as reading, listening to the radio, playing games) reduced the risk of succumbing to Alzheimer's Disease participation in physical activities (such as jogging, gardening, bicycle riding, dancing) was unrelated to the development of AD four years in the future

(see also Verghese et al., 2005; Wang et al, 2006). Both the cognitive and physical activities were assessed via self report and while the cognitive activities were assessed relative to a one year time frame, physical activities were referenced to a two week period prior to the assessment.

A study by Sturman et al (2006) is particularly interesting in that these investigators addressed the question of whether, over a 6.4 year period, participation in physical activities by older adults reduces the rate of cognitive decline after accounting for participation in cognitively stimulating activities. Prior to adjustment for cognitive activities, each additional hour per week of physical activity was associated with a slower rate of cognitive decline. However, this relationship was no longer significant after adjusting for cognitive activities. On the other hand, Richards et al (2003) reported that physical activity at 36 years of age was associated with a slower rate of decline in memory from 43 to 53 years of age and this relationship was unchanged after adjusting for cognitive activities. Cognitive activities were not associated with change in memory over this interval.

The studies described above generally employ different activities to represent cognitive or physical demands. However, a recent study by Karp and colleagues (2006) has taken a different approach to examining the relative contribution to cognitive, physical and social engagement to cognitive change and dementia. They argue that most leisure activities engage some combination of these three types of demands. On this basis they had the researchers and a panel of older adults rate the relative intensity, on a scale of 0 to 3, of social, cognitive and physical demands of a set of thirty leisure activities. Agreement was quite high among raters. As an example of the ratings attending courses was rated 3,1 and 2 for mental, physical and social demands, respectively (with 3 being the most intense). These ratings were then applied to the activities pursued by 776 individuals over the age of 75 years of age to predict diagnosis of dementia six years in the future. After adjusting for a variety of covariates social, cognitive and physical activities were each found to be associated with a reduced risk for dementia. In any event, characterizing leisure activities in terms of their multidimensional nature is an interesting and potentially important alternative to the dichotomous approach adopted by other observational studies.

In summary, in observational studies that examine more than one lifestyle factor, cognitive activities appear to be the strongest predictor of cognitive change. However, this could be the result of the several factors including: (1) rarely are physical activities characterized in terms of intensity, frequency and duration, (b) the period across which activities are assessed has been different for cognitive and physical activities, (c) with one exception, activities have been treated as unidimensional in nature. Clearly, these issues require additional consideration in future studies.

**Human Intervention Studies.** To our knowledge there have been only two randomized trials that have examined the separate and combined influence of multiple lifestyle factors on the cognitive function of older adults. Both of these studies were conducted by the same research group and involved two months of training with eight 60

to 75 year old participants in each of four experimental groups. In both studies subjects either participated in an aerobic training group (walking & jogging), a memory training group (including general encoding & retrieval instructions, association & attentional training), a combined group, and a control group. Fabre et al (1999) found that all three training groups but not the control group showed improved performance on logical and paired associate memory tasks across the 2 month intervention. However, combined training did not show additional benefits as compared to the aerobic or memory training. Fabre et al (2002) used an elaborated memory training protocol and a similar physical training protocol as compared to their previous study. A more thorough assessment of changes in memory was also used in this study. Results indicated improvements in a general memory metric in all three of the training groups. However, in this experiment benefits were largest for the combined training group.

The two studies described above attempted to decompose the relative contribution of cognitive and physical training to improvement in cognitive function. A number of other human intervention trials have taken a multimodal approach, much like enriched environment experiments with animals, in examining the influence of multiple lifestyle factors on cognition. The Experience Corps project, conducted at Johns Hopkins, is an example of one such project (Fried et al, 2004). This project places teams of older adults in inner city elementary schools to address unmet needs. The older adult participants are trained to provide literacy, numeracy, library and other support in kindergarten through 3rd grade. Once entering the program and completing training the older adults devote at least fifteen hours per week for an academic year to the schools. The Experience Corps program stresses a combination of social, cognitive and physical activity engagement in support activities in the schools. An intervention with 128 participants who were randomized to the Experience Corps program and a wait list control group found that individuals with poor baseline executive function showed a 44 to 51% improvement in executive function and memory in the post intervention follow-up. These improvements were not observed for the control participants (Carlson et al., submitted). In another small randomized intervention (Carlson et al., 2006) Experience Corps subjects, but not control subjects, displayed improved efficiency in brain activation, as indexed by event-related fMRI, and performance in an inhibitory control task.

Another recently completed multimodal intervention was conducted by Small and colleagues (2006). In this study a small group of middle aged participants were randomized either to a 2 week healthy lifestyle program or a wait list control group. Subjects in the healthy lifestyle group, which included a healthy diet, physical exercise, relaxation training and memory training, showed improvements in verbal fluency and decreases in activation in left dorso-lateral prefrontal cortex as assessed via Positron Emission tomography. Other multimodal interventions that have combined social and cognitive components have also shown training specific benefits as compared to wait list control groups in cognition and psychosocial function (Fernandez-Ballesteros, 2005; Stine-Morrow et al., in press).

In summary, thus far there are few studies that have systematically examined either the separate or combined contribution of multimodal interventions to enhanced

cognitive and brain function in older adults. Clearly, the nature and mechanisms of multimodal intervention programs, particularly those that can be implemented in community setting such as the Experience Corps project, are important topics for future longer-term studies.

**Multimodal Animal Research.** As described above the great majority of animal studies that have examined the influence of multimodal interventions on brain function, learning and memory have done so in the context of enriched or complex environments in which animals are often housed together with the opportunity for physical activity and exploration of a multitude of novel objects (Black, Isaacs, Anderson, Alcantara & Greenough, 1990; Ehninger & Kempermann, 2003; Jones, Hawrylak, & Greenough, 1996; Kempermann, Kuhn & Gage, 1997; Rosenzweig & Bennett, 1996). These studies have generally found beneficial effects of this multimodal environment on brain structure, function and performance. However, a smaller set of studies have examined the separate and joint contributions of different interventions to brain health and cognition.

Two studies have focused on the separate and combined effects of diet and cognitive training or exercise. Molteni et al (2004) examined the effects of a high fat diet and voluntary exercise on learning and a variety of molecules which support neural function. Female rats were randomized into four different groups created by combining a regular or high fat diet with voluntary exercise or a sedentary environment. After two months of the interventions the regular diet/exercise group was found to show the fastest spatial learning on the Morris Water maze task followed by the regular diet/sedentary and high fat/exercise groups, with the high fat/sedentary group showing the poorest learning. Additionally, a combination of a regular diet and exercise was observed to produce the largest increase in brain-derived neurotrophic factor (BDNF), a neuroprotective molecule that facilitates synaptic transmission, as compared to the regular diet/sedentary group. Furthermore, decreases in BDNF engendered by a high fat diet were abolished by exercise. Thus, these data suggest that the costs of a high fat diet can, under some conditions, be offset by regular exercise. Milgram et al (2005) conducted a two year intervention with separate and combined diet (regular & enhanced anti-oxidant) and enriched (including discrimination training and exercise & non-enriched control) conditions with older beagles. Both the antioxidant diet and enriched environment groups displayed a number of benefits in learning in memory across a variety of discrimination tasks. Furthermore, the group that received both the antioxidant diet and enriched environment should the most dramatic benefits in learning and memory. Indeed, these data suggest reduced cognitive decline, over the two year period of the study, for older dogs with behavioral enrichment and/or dietary fortification with antioxidants.

In a recent study, Stranahan et al (2006) examined the interaction between social isolation and exercise on neurogenesis in the hippocampus of adult male rats. Animals were either housed individually or in groups and either did or did not have access to a running wheel. Several interesting results were observed. First, individual housing precluded the positive effects of short term running on adult neurogenesis in

hippocampus. Furthermore, in the presence of additional stressors the influence of short-term running was negative for the socially isolated animals, resulting in a net decrease in the number of neurons relative to sedentary animals. Second, group housed runners produced the largest number of new neurons in the hippocampus. Finally, longer duration running was able to enhance cell proliferation of the socially isolated animals but not to the level of group housed animals.

In summary, the studies reviewed above and others (Berchtold et al., 2001; Russo-Neustadt et al., 1999) suggest potentially mutually interdependent relationships of a number of different lifestyle factors on brain and cognitive health of both young and older organisms. Clearly, however, although the extant literature provides some clues concerning the molecular and cellular pathways that support the interactive effects of different factors much remains to be discovered in additional research on multimodal interventions (Gobbo & O'Mara, 2006; Wolf et al., 2006).

*Future Directions*

Our brief review of the literature suggests that a number of lifestyle factors provide multiple routes to enhancing cognitive vitality across the lifespan – through the reduction of disease risk and in the improvement in the molecular and cellular structure and function of the brain. Thus, as has been suggested for other factors such as education (Elkins et al., 2006; Stern, 2006), physical activity, intellectual engagement, social interaction and nutrition appear to provide a cognitive reserve which buffers us against the many challenges experienced during the course of aging. However, despite all that we have learned about the benefits of exercise much remains to be discovered in future research.

We present here several directions for future research to isolate and delineate the cognitive and neural effects of exercise. First, as reviewed in this manuscript, both animal and human research point to similar conclusions regarding the beneficial properties of exercise on the brain and cognition, but whether the underlying mechanisms are the same in both humans and rodents remains unresolved. An important avenue for future research will be to assess the concentration of molecular markers in human blood and brain tissue as a function of an aerobic exercise treatment (Pereira et al., 2007; Reuben et al., 2003). Such a link would provide compelling evidence that the same molecular mechanisms are functioning in both humans and rodents. Of course, the same issues are of interest for other lifestyle factors.

A few studies have reported that the effects of aerobic exercise are not independent of factors such as estrogen, diet, and intellectual and social engagement (Vanyman & Gomez-Pinilla, 2006). However, the study of interactions among lifestyle factors is in its infancy and the degree and direction of these interactions needs to be more fully elucidated. An important future direction is to examine the effects of lifestyle factors within a multi-factorial framework which also incorporates pharmacological treatments for age-associated disorders and diseases.

A third avenue involves determining the relationship between lifestyle factors and certain genetic profiles. For example, people with certain alleles have higher risks for dementia, disease, or cognitive dysfunction. Whether exercise, intellectual engagement, social engagement or good nutrition offsets or diminishes the risks associated with such genetic predispositions remains an understudied question. Characterizing the genetic profiles of those people who benefit the most and those that benefit the least from an particular lifestyle regimens is clearly needed.

In addition, the benefits and limitations of lifestyle factors in preventing or reversing the cognitive and neural deterioration associated with neurological diseases have not been fully investigated (Heyn et al., 2004). It will be important for future research to examine the efficacy of lifestyle factors such as exercise, intellectual, and social engagement in relation to symptom severity, duration of illness, comorbidity of diseases, the brain areas and molecular factors most affected in the disease, and possible interactions with pharmaceutical treatments. Given the medical and social significance of this research, these questions should be pursued with vigor.

Another direction for future research is to specify which cognitive operations are most affected by different lifestyle factors. For example, it appears that in humans aerobic exercise affects executive functions more than other cognitive processes (Colcombe & Kramer, 2003). However, what remains unaddressed is what aspect(s) of executive function is being most affected with exercise: response preparation, response selection, conflict detection, task-switching, task and goal maintenance in working memory, etc. The nature of exercise effects on tasks that rely on the temporal lobes, consistent with the demonstration of hippocampal neurogenesis in non-human animals (Pereira et al., 2007; Van Praag et al., 2005), is also an important research topic. Therefore, more refined task manipulations in the context of exercise and other interventions will allow for a detailed characterization of the relevant cognitive processes.

Finally, very few experimental studies investigate whether the benefits of lifestyle factors extend outside the laboratory to everyday cognitive functioning. Although the effects are often assumed to transfer outside the laboratory, evidence to support such a claim does not currently exist. It will be important for any future research to also investigate the transfer of such cognitive and neural benefits to everyday activities involved in independent living and workplace activities.

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