

Behavioral interventions to benefit cognition: intervenciones cognitivas para beneficiar la cognición

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Abstract:

With the growing population of older adults, the identification of treatment strategies to prevent or ameliorate age-related cognitive decline has been an important topic in recent years. After reviewing cross-sectional, longitudinal, and experimentally designed studies, as well as evidence from narrative and meta-analytic reviews, the authors concluded that behavioral approaches such as physical activity, cognitive training, and dietary interventions show promising results. In addition, given the likelihood that multiple underlying mechanisms support cognitive function, research is currently focusing on how to combine lifestyle factors into multi-component interventions to generate greater and more meaningful effects. Though evidence for these enhanced benefits exists from animal studies, few multi-component studies have been performed with humans. However, the findings from these studies are promising and a continued pursuit of multi-component behavioral interventions to benefit cognitive performance is warranted. Given the world's aging population and accompanying age-related health issues such as cognitive decline and dementia, future research should focus on understanding the biological mechanisms responsible for these effects in order to allow for the development of behavioral lifestyle prescriptions to benefit cognitive performance.

Keywords: aging | cognitive function | exercise intervention | oxidative stress | cognitive engagement

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Behavioral interventions to benefit cognition

Intervenciones cognitivas para beneficiar la cognición

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Abstract. With the growing population of older adults, the identification of treatment strategies to prevent or ameliorate age-related cognitive decline has been an important topic in recent years. After reviewing cross-sectional, longitudinal, and experimentally designed studies, as well as evidence from narrative and meta-analytic reviews, the authors concluded that behavioral approaches such as physical activity, cognitive training, and dietary interventions show promising results. In addition, given the likelihood that multiple underlying mechanisms support cognitive function, research is currently focusing on how to combine lifestyle factors into multi-component interventions to generate greater and more meaningful effects. Though evidence for these enhanced benefits exists from animal studies, few multi-component studies have been performed with humans. However, the findings from these studies are promising and a continued pursuit of multi-component behavioral interventions to benefit cognitive performance is warranted. Given the world's aging population and accompanying age-related health issues such as cognitive decline and dementia, future research should focus on understanding the biological mechanisms responsible for these effects in order to allow for the development of behavioral lifestyle prescriptions to benefit cognitive performance.

Keywords. aging, cognitive function, exercise intervention, oxidative stress, cognitive engagement

Resumen. Con la creciente población de adultos mayores, la identificación de las estrategias de tratamiento para prevenir o mejorar el deterioro cognitivo relacionado con la edad ha sido un tema importante en los últimos años. Después de revisar estudios con diseños transversales, longitudinales y experimentales, así como la evidencia de revisiones de literatura narrativa y meta-analítica, los autores concluyen que los enfoques conductuales como la actividad física, el entrenamiento cognitivo y las intervenciones dietéticas muestran resultados prometedores. Además, dada la probabilidad de que múltiples mecanismos subyacentes apoyan la función cognitiva, las investigaciones se enfocan actualmente en la manera de cómo combinar factores del estilo de vida en las intervenciones con múltiples componentes para generar efectos mayores y más significativos. Aunque existe evidencia de estos beneficios a partir de estudios en animales, se han realizado pocos estudios de componentes múltiples en humanos. Sin embargo, los resultados de estos estudios son prometedores y se garantiza un seguimiento continuo de las intervenciones conductuales de componentes múltiples para beneficiar el rendimiento cognitivo. Teniendo en cuenta el envejecimiento de la población mundial y los problemas de salud relacionados con la edad que la acompañan, tales como el deterioro cognitivo y la demencia, la investigación futura debería centrarse en la comprensión de los mecanismos biológicos responsables de estos efectos con el fin de permitir el desarrollo de las prescripciones de comportamiento de estilo de vida para beneficiar el rendimiento cognitivo.

Palabras claves. envejecimiento, funcionamiento cognitivo, intervención con ejercicio, estrés oxidativo, participación cognitiva

Introduction

Age-related cognitive decline is a public health concern because of its association with clinical cognitive impairment (Flicker, Ferris, & Reisberg, 1991; Larson & Langa, 2008; Myers, Kluger, Golomb, Gluck, & Ferris, 2008) and because its prevalence is expected to surge with the growing population of older adults (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). Thus, it is important to identify treatments that maintain cognitive performance with advancing age. Several promising behavioral approaches have been identified with recent studies focusing on the potential benefits of physical activity, cognitive training, and dietary interventions.

Physical activity

Numerous studies have explored the relationship between chronic physical activity and cognitive performance through the use of cross-sectional, prospective, and experimental designs. This literature has been reviewed meta-analytically on several occasions with results generally supporting a positive relationship between physical activity and cognitive performance. Etnier et al. (1997) conducted the first comprehensive meta-analytic review of studies on physical activity and cognition, which included 134 cross-sectional, correlational, and experimental studies. They concluded that physical activity had a small but significant positive effect on cognitive function, with an overall mean effect size of 0.25. An important finding from this review was that experimental design was a significant moderator of the effect of physical activity on cognition, with less rigorous studies being associated with larger effects. This finding highlighted the need for more rigorous studies to be performed in order to elucidate the effect.

Prospective epidemiological studies examine the effects of baseline physical activity on subsequent cognitive performance and provide a stronger level of evidence than cross-sectional and correlational studies.

In general, studies using this design report that higher levels of physical activity at baseline protect against subsequent cognitive decline. This relationship is seen whether cognitive function is assessed using standardized cognitive tests (Lytle, Vander Bilt, Pandav, Dodge, & Ganguli, 2004; van Gelder et al., 2004; Weuve et al., 2004; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001) or clinical measures of cognitive impairment (Abbott et al., 2004; Larson et al., 2006; Podewils et al., 2005; Rovio et al., 2005). When explored meta-analytically (Sofi et al., 2011), prospective studies that investigated the association between physical activity and risk of cognitive decline in non-demented people, showed that physical activity had a protective effect against cognitive decline. This protective effect was similar for those who performed high levels compared to low-to-moderate levels of physical activity.

Randomized control trial studies provide an even higher level of evidence for the effects of physical activity on cognitive performance because they allow for the establishment of causation. Colcombe and Kramer (2003) performed a meta-analysis to explore the effect of chronic aerobic exercise training on cognitive performance by older adults specifically limiting their review to randomized control studies. Findings from their review revealed that aerobic exercise training produced a moderate overall positive effect on cognitive performance ($g=0.48$). Importantly, although effects were largest for executive function tasks ($g=0.68$), beneficial effects were observed across a variety of cognitive domains, suggesting global benefits of exercise on cognitive performance. The results from this review provided strong evidence for a beneficial effect of aerobic exercise training on cognitive performance by older adults.

Heyn, Abreu, and Ottenbacher (2004) specifically focused their review on whether physical activity was beneficial for older adults with dementia and related cognitive impairments. As with the study conducted by Colcombe and Kramer (2003), this meta-analysis only included studies that used randomized control trials. Results showed that the overall mean effect size between exercise and non-exercise groups for cognitive performance was 0.57. Therefore, they concluded that exercise training increases cognitive function in older adults with dementia and related cognitive impairments. Findings from this study are important

because they suggest that the mechanisms responsible for the beneficial effect of exercise on cognitive performance are still functional in individuals with cognitive impairment and degenerative brain disease. These findings are support for a continued effort to explore the use of exercise to benefit those with, or at risk for, dementia.

Much of the early research in this area was conducted using the cardiovascular fitness hypothesis as a foundation. The cardiovascular fitness hypothesis asserts that cardiovascular (or aerobic) fitness is a causal factor that explains the relationship between physical activity and cognitive performance. However, Etnier and colleagues used meta-regression techniques to specifically test the cardiovascular fitness hypothesis of cognitive performance (Etnier, Nowell, Landers, & Sibley, 2006) and concluded that there was no support for this hypothesis. Specifically, analyses showed that there was no relationship between changes in aerobic fitness and changes in cognitive performance for studies with cross-sectional designs or when making comparisons of data at post-test. Surprisingly, changes in aerobic fitness from pre-test to post-test were found to be negatively related to changes in cognitive performance from pre-test to post-test indicating that increases in aerobic fitness actually predicted decreases in cognitive performance. Given that the cardiovascular fitness hypothesis was not supported, the authors suggested that other causal mechanisms for the relationship between physical activity and cognitive performance should be explored.

More recently, Angevaren, Aufdemkampe, Verhaar, Aleman, and Vanhees (2008) conducted a Cochrane systematic review of 11 studies to assess the effects of chronic aerobic exercise programs on cognitive function with nonclinical older adults. They found that the largest effects were on motor function, auditory attention, and delayed memory. However, the authors suggest that care be taken in interpreting the effect on delayed memory as it was obtained from a single study. In addition, they observed moderate positive effects on cognitive speed and visual attention. Similar beneficial effects of exercise on cognitive function were also observed for cognitively impaired older adults.

In sum, when reviewed meta-analytically, results from studies testing the effects of chronic exercise on cognitive performance consistently support that there are benefits. These results are evident in older adults and in older adults who are already experiencing cognitive decline. Further, these results are evident when using laboratory-based measures of cognitive performance and when using clinical measures of cognitive performance.

Cognitive training

Cognitive training is another behavioral intervention that has been examined for its effect on cognitive performance in clinical and non-clinical populations. Systematic and meta-analytic reviews consistently show that cognitive training has positive effects on cognitive performance. In a meta-analytic review of published studies with randomized control trial designs, Zehnder, Martin, Altgassen, and Clare (2009) revealed significant training effects for paired associate learning and immediate and delayed recall in healthy older adults and significant training effects for immediate recall in adults with mild cognitive impairment (MCI). Other reviews support cognitive training benefits for memory (Gates, Sachdev, Fiatarone Singh, & Valenzuela, 2011; Teixeira et al., 2012), learning (Simon, Yokomizo, & Bottino, 2012), and various aspects of cognitive function, including objective and subjective measures of cognitive functioning, memory performance, executive functioning, processing speed, attention, and fluid intelligence (Reijnders, van Heugten, & van Boxtel, 2013). Results have also shown that the effects of computer-based cognitive interventions are comparable to or better than the effects of traditional, paper-and-pencil cognitive training approaches (Kueider, Parisi, Gross, & Rebok, 2012). Recently, Jak, Seelye, and Jurick (2013) conducted a systematic review of electronic cognitive training programs (e.g., computer and video game based) and found that most studies showed significant improvements in trained cognitive tasks, specifically processing speed. Thus, there is substantial evidence supporting the use of cognitive training to improve cognitive performance.

Despite the evident benefits of cognitive training, Jak et al. point out that there is a short-coming in this scientific literature because the benefits of cognitive training programs are typically only observed in the specific tasks that have been trained. Hence, more work is needed to determine the potential benefits of cognitive training programs on more general outcomes such as age-related cognitive decline. One intriguing direction for future research is to combine cognitive training with physical activity with the hopes of producing larger effects on a broad array of cognitive tasks.

Dietary intervention

Another promising approach to protect or improve cognitive performance is through dietary interventions. The focus of this research thus far has largely been on understanding how diet can be used to reduce oxidative stress by enhancing the antioxidant-prooxidant balance through an increase in antioxidants. The reduction of oxidative stress is important because when the production of reactive oxygen species (or free radicals) exceeds the capacity of the antioxidant defense system, oxidative stress markers are elevated in the systemic circulation and result in the activation of the inflammatory process (Giunta, 2008). According to the free-radical theory of aging (Harman, 1994), as the human body ages there is an increase in the production of free radicals and/or a decrease in the quantity or quality of antioxidants resulting in an overall increase in oxidative stress and inflammation. The brain is particularly vulnerable to oxidative insults, so this theory posits that the damage caused by increased oxidative stress plays a role in age-related cognitive decline and the risk of Alzheimer's disease (Berr, 2000; Clausen, Doctrow, & Baudry, 2010; Hasnis & Reznick, 2003).

Research has shown that low plasma levels of molecular antioxidants such as plasma α -tocopherol, vitamin C, vitamin E, carotenoids, and selenium, are linked to detriments in cognitive performance (Berr, Richard, Roussel, & Bonithon-Kopp, 1998; Gale, Martyn, & Cooper, 1996; Goodwin, Goodwin, & Garry, 1983; Jama et al., 1996; Perkins et al., 1999; Perrig-Chiello, Perrig, Ehrensam, Staehelin, & Krings, 1998; Schmidt et al., 1998; Tucker et al., 1990) as well as a greater risk of cognitive decline or impairment (Berr, 2000; Engelhart et al., 2005; La Rue et al., 1997; Perrig, Perrig, & Staehelin, 1997). Conversely, correlational studies have shown that people whose diets are high in antioxidants have lower levels of oxidative stress (Covas et al., 2006; Kang, Ascherio, & Grodstein, 2005; Rondanelli, Trotti, Opizzi, & Solerte, 2007; Senthilmohan, Zhang, & Stanley, 2003), perform better on cognitive tests (Kang et al., 2005; Rondanelli et al., 2007), and experience less cognitive decline over time (Wengreen et al., 2007). Interventions with older non-human animals report that those on a high antioxidant diet experienced reductions in oxidative stress and improvements in cognitive performance (Cartford, Gemma, & Bickford, 2002; Joseph et al., 1999; Milgram et al., 2002; Reme et al., 2008). Findings from intervention studies with humans in which dietary supplements have been used are more equivocal (Grodstein, Kang, Glynn, Cook, & Gaziano, 2007; Petersen et al., 2005). However, it has been suggested that this may be due to the variability in the antioxidant potency of various supplements, individual differences in the metabolism of supplements, and/or adherence issues. With regards to the effects of dietary interventions on cognitive performance, several researchers have shown benefits in cognitive functioning or reduced risk of Alzheimer's disease with increased intake of vegetables (Kang et al., 2005), fruit and vegetable juices (Dai, Borenstein, Wu, Jackson, & Larson, 2006), and fruit and vegetable extracts in rats (Joseph et al., 1999) and canines (Milgram et al., 2002). More comprehensive dietary changes like those associated with the Mediterranean diet have also been shown to reduce cognitive decline in humans (Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006; Weih, Wiltfang, & Kornhuber, 2007).

In sum, the free-radical theory of aging implicates the antioxidant/prooxidant balance as being a critical determinant of age-related cognitive decline. Correlational evidence with humans and experimental evidence with non-human animals support the potential role of diet in mitigating age-related cognitive decline. Intervention studies with humans provide

some promising findings, but future studies are necessary to better understand how diet can be reliably manipulated to positively impact cognitive performance.

Multi-component interventions

Based on the abovementioned evidence, there is support for the efficacy of individual behavioral interventions to benefit cognitive performance. However, a limitation of all of these interventions is that their effects tend to be relatively modest in size and the cognitive training interventions are particularly limited in that their benefits do not transfer across cognitive domains. Given these limitations and that multiple mechanisms likely contribute to cognitive function (Etnier, 2008), it has been suggested that «a cocktail of multiple interventions» may be necessary to attain larger, more generalizable effects (Droge & Schipper, 2007). In fact, recent calls for proposals from the United States National Institutes of Health (RFA-AG-09-009 and RFA-AG-14-016) focus explicitly on this expectation that combined interventions may be necessary to elicit larger, meaningful effects. The rationale behind a multi-component intervention is that the various components of the intervention might impact multiple mechanisms or might have a larger combined (i.e., synergistic) effect on a single mechanism (Rebok, Carlson, & Langbaum, 2007). Although there are several studies which have assessed the effects of multi-component interventions on non-human animals, there are only a few studies with humans which have used this approach (Benloucif et al., 2004; Masley, Weaver, Peri, & Phillips, 2008; Small et al., 2006; van Uffelen, Chinapaw, van Mechelen, & Hopman-Rock, 2008).

Non-human animal studies have shown that rodents exposed to cognitively engaging exercise demonstrate beneficial adaptations in cerebral structure (which are sometimes shown to be concomitant with improvements in behavioral measures of cognition) compared to animals that receive exercise alone (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996; Kleim et al., 1998; Kleim, Vij, Ballard, & Greenough, 1997; Klintsova, Dickson, Yoshida, & Greenough, 2004). In these studies, «cognitively engaging exercise» is typically defined as physical activity in stimulating environments in which the objects/toys in an animal's cage are changed on a regular basis to encourage exploratory physical activity while «exercise alone» is defined as access to a running wheel. In light of these positive findings, it has been proposed that more cognitively engaging forms of physical activity might result in larger cognitive gains for older adults (Colcombe, Kramer, McAuley, Erickson, & Scalf, 2004; Fabre, Chamari, Mucci, Masse-Biron, & Prefaut, 2002). However, few human studies report on the cognitive effects of interventions that include physical activity and cognitive training components in combination.

Fabre et al. (2002) tested the effects of a 2-month combined intervention on cognitive performance. Sedentary older adults were randomly assigned to one of four groups: an exercise group (two sessions per week of walking or running for 45 min), a mental training group (one 90-min session per week of performing mentally challenging tasks), a combined group that performed both the exercise sessions and the mental training session each week, or a leisure activity group. Participants in the combined group showed a significantly larger gain in memory quotient (Cohen's $d=5.22$) than participants any other group (exercise: Cohen's $d=1.64$; mental training Cohen's $d=3.15$; control Cohen's $d=0.20$). However, there were no significant benefits for any of the training groups on 5 of the 8 cognitive measures and improvements were comparable for all three training groups on the other 2 cognitive measures. Although the multi-component program resulted in a larger improvement in cognitive performance on 1 of the 8 cognitive measures, the general lack of a difference between the combined group and the single intervention groups might indicate that combining this type of cognitive training with physical activity in this specific fashion does not result in a broad synergistic effect on cognitive performance.

Benloucif et al. (2004) used a repeated measures cross-over design to compare the effects of two (morning vs evening) 2-week daily activity

interventions on the cognitive performance and sleep quality of older adults. The intervention consisted of physical activity and social cognitive activities performed in small groups for 90 min. Specifically, participants performed 30 min of stretching and low to moderate intensity physical activity, 30 min of social game playing, and another 30 min of low to moderate intensity physical activity. Results showed that participants in both the morning and evening interventions experienced significant improvements in cognitive performance as compared to their own performance during baseline. Significant benefits ranged in effect size from 0.598 to 1.235 and were evident for tasks assessing mathematical processing, memory, logical reasoning, and working memory/information processing. These effects are promising and certainly suggest that this combined intervention benefits cognitive performance, however the failure to use a randomized control trial limits the conclusions that can be drawn from this study.

Given that one of the mechanisms by which chronic physical activity may improve cognitive performance is through effects on antioxidants, it is logical to also consider combining exercise and dietary interventions that focus on reducing oxidative stress. Non-human animal studies show that chronic exercise training reduces oxidative stress. This evidence comes from studies showing that exercise reduces free radical production at rest, increases antioxidant defenses (Aksu, Topcu, Camsari, & Acikgoz, 2009; Harris, Mitchell, Sood, Webb, & Venema, 2008; Leeuwenburgh, Fiebig, Chandwaney, & Ji, 1994; Leeuwenburgh et al., 1997; Powers et al., 1994; Powers et al., 1993; Radak et al., 2001; Radak, Sasvari, Nyakas, Taylor, et al., 2000; Venditti, Masullo, & Di Meo, 1999), and enhances the repair and elimination of oxidized molecules (Radak et al., 1999; Radak et al., 2002; Radak, Sasvari, Nyakas, Pucsek, et al., 2000). Although research with humans is more limited, there is evidence that chronic exercise improves antioxidant defenses in younger men and women (Evelo, Palmen, Artur, & Janssen, 1992; Sato, Nanri, Ohta, Kasai, & Ikeda, 2003) and in older men (Fatouros et al., 2004). Based upon this evidence and the aforementioned evidence supporting that dietary changes can influence cognitive performance and Alzheimer's disease risk, one might expect that combining exercise with an antioxidant diet would result in maximal reductions in oxidative stress and, concomitantly, larger cognitive benefits. Researchers have tested the effect of multi-component interventions (described as behavioral enrichment that includes physical activity, opportunity for exploratory behavior, and social interactions through group housing) and an antioxidant diet on the cognitive performance of canines (Milgram et al., 2005; Nippak, Mendelson, Muggenburg, & Milgram, 2007) with results supporting cognitive benefits. There are two studies with humans in which the effects of interventions combining physical activity with diet on cognitive performance have been examined.

Masley et al. (2008) randomly assigned fifty-six older adults to either a no-treatment control or a multi-component intervention for 10 weeks. The multi-component intervention consisted of meal plans and recipes to increase dietary fiber and decrease saturated fat and encouragement to increase physical activity that was presented in weekly meetings. Participants in the intervention improved on 3 of 4 tests of cognitive performance ($ES = 0.26 - 0.41$). These effects are similar to what has been observed with physical activity alone and the modest effects may be due to the limitations of only recommending behavioral change, the relative brevity of the intervention, and the lack of a focus on a high antioxidant diet.

van Uffelen et al. (2008) performed a randomized placebo-controlled trial to explore the effects of 12 months of aerobic activity combined with the supplementation of folic acid and other B vitamins in older adults with MCI. The results showed that those in the aerobic activity group experienced improvements in cognitive function that positively correlated with higher levels of adherence to the exercise program. These findings suggest that those who walked more gained the biggest cognitive benefits. However, interpretation of the combined effects of aerobic activity and supplementation use is limited since the authors only presented results for the main effects of supplementation and physical activity.

To our knowledge, there is only one study which has tested the combined effects of physical activity, cognitive stimulation, and diet on cognitive performance. Small et al. (2006) examined the effects of a 14-day combined program on cognitive performance by older adults with mild age-related memory complaints. Participants were randomly assigned to a control condition or to the combined program. The combined program consisted of aerobic exercise, relaxation training, cognitive training to teach memory techniques and to give exposure to mental puzzles, and suggested meal plans that included an emphasis on fruits and vegetables high in antioxidants. They found that participants in the intervention program improved significantly on a measure of verbal fluency compared to participants in the control group.

Clearly, research on the efficacy of multi-component interventions is still in its infancy. Support for the «cocktail» hypothesis from non-human animal studies is promising and demonstrates benefits both behaviorally and mechanistically that exceed benefits from physical activity in isolation. However, research exploring multi-component interventions for humans is extremely limited. Further, human studies exploring physical activity and cognitive stimulation have not mimicked the animal research because the animal studies have typically simultaneously combined physical activity and cognitive stimulation while, by contrast, the human studies have presented these intervention components asynchronously. This may be an important distinction because the asynchronous presentation may not result in the same synergistic impact on mechanisms as might be observed with a synchronous presentation. Further, as described above, we are aware of only one short-term intervention which has tested the combined effects of physical activity, cognitive stimulation, and diet on cognitive performance. This is an important direction for future research because interventions that encompass many lifestyle factors may affect multiple mechanisms, which may in turn lead to an exponential increase in the magnitude of beneficial effects on cognitive performance. Considering additional mechanisms that explain the benefits of physical activity on cognitive performance is a logical place to begin when designing multi-component interventions that include physical activity and are hypothesized to achieve larger benefits.

Mechanisms

There is evidence supporting that chronic physical activity has beneficial effects on cerebral structure, cerebral function, and neurotrophic factors which may explain the benefits for cognitive performance. With magnetic resonance imaging techniques, Colcombe et al. (2003) observed age-related decreases in brain volume, in both white and grey matter of the frontal, parietal, and temporal cortices, in older adults. More importantly, they revealed that losses in these areas were smaller in older adults with higher levels of cardiovascular fitness. Relatedly, Colcombe et al. (2004) found that elderly individuals with higher levels of fitness showed different activation patterns in the middle frontal gyrus, superior frontal gyrus, anterior cingulate cortex, and superior parietal cortex relative to lower fit individuals. Other researchers have also provided evidence that aerobic fitness is positively associated with hippocampal volume (Bugg & Head, 2011; Erickson et al., 2009; Szabo et al., 2011). Prospective evidence is limited, but one study has shown that baseline physical activity is predictive of hippocampal volume nine years later (Erickson et al., 2010). To further understand whether aerobic fitness training can increase brain volume in regions associated with age-related decline in both brain structure and cognition, Colcombe et al. (2006) randomly assigned older adults to either an aerobic training group or a toning and stretching control group. After the 6-month intervention, individuals in the aerobic fitness training group showed significant increases in brain volume in both gray and white matter regions that were not observed in control group participants. Similarly, Erickson et al. (2011) found that participation in a 1-year exercise intervention resulted in an increased hippocampal volume in older adults. These results provide strong support for a causal effect of aerobic exercise on measures of cerebral structure and function that are indicative of central nervous system health in older adults, and extend the findings

from Colcombe et al. (2004) by showing that aerobic exercise may not only ameliorate age-related declines in brain volume, but actually increase brain volumes in older adults who begin long-term aerobic exercise.

In non-human animal studies, exercise has also been shown to increase levels of brain-derived neurotrophic factor (BDNF) and other growth factors, stimulate neurogenesis, increase resistance to brain insult and improve performance on cognitive tasks including learning (Cotman & Berchtold, 2002). Gomez-Pinilla, Ying, Roy, Molteni, and Edgerton (2002) demonstrated that exercise could promote changes in neuronal plasticity via BDNF and Neeper, Gomez-Pinilla, Choi, and Cotman (1996) showed that BDNF concentration in the hippocampus was elevated after exercise. Importantly, Vaynman, Ying, and Gomez-Pinilla (2003) showed that BDNF actually acts as a mediator of the effects of exercise on hippocampal synaptic-plasticity. Even though there is strong evidence in the non-human animal literature that BDNF is a causal mechanism in the physical activity / cognitive performance relationship, this hypothesis has not been empirically tested in humans.

That being said, research with humans has shown a positive relationship between physical activity and basal BDNF concentrations, as well as an increased BDNF response to maximal exercise following five weeks of aerobic training (Zoladz et al., 2008). However, a study that assessed the relationship between a 6-month aerobic activity program, cognitive performance, and BDNF in older adults with MCI has shown that while there seems to be no effect of physical activity on cognitive performance or BDNF concentrations in men, for women there is a positive effect on cognitive performance and a decrease in BDNF concentration compared to controls (Baker et al., 2010). More research is needed to elucidate the potential causal relationship between physical activity, BDNF concentrations, and cognitive performance.

Conclusions

Research has established simple relationships between various lifestyle factors (e.g., physical activity, diet) and cognitive performance and there is evidence supporting that these relationships are causal. Research has also begun to establish mechanisms that explain the benefits of physical activity and specific dietary interventions for cognitive performance. The focus of current studies is on furthering our understanding of how to best combine lifestyle factors to achieve larger, more robust effects on cognitive performance. In so doing, the elucidation of mechanisms is an important emphasis for future research because of the potential to use this information to help identify the most promising combined interventions. Additionally, understanding mechanisms is likely to contribute to our ability to prescribe physical activity in a specific dose (intensity, duration, mode) to maximally benefit cognitive performance. Lastly, understanding mechanisms may bring to light ways to combine pharmacological or nutritional interventions (e.g., BDNF supplementation, antioxidant supplements) with behavioral interventions to, again, produce stronger cognitive benefits. With regards to the design of multi-component interventions, it is our contention that it is most efficacious to base their design on existing empirical evidence, theory, and the understanding of mechanisms. Specifically, multi-component interventions combining physical activity and cognitive training would likely benefit from more closely mimicking the extant literature with non-human animals; i.e., the combination of physical activity and cognitive training should be a synchronous experience rather than an asynchronous experience. Similarly, given the shared mechanism of antioxidants, interventions combining diet and physical activity should like focus on an antioxidant diet as a way to maximize effects. Given the projected increase in the population of older adults and the anticipated coincident increase in the prevalence of age-related cognitive decline and dementia, the identification of interventions to benefit cognitive performance is a public health imperative.

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