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PREVENTION

Neurocognitive Aging and Cardiovascular Fitness

Recent Findings and Future Directions

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Abstract

In the first century, CE, the Roman satirist Juneval famously observed *Orandum est, ut sit mens sana in corpore sano*, or "A sound mind in a sound body is something to be prayed for." This implicit link between mental and physical health, also paralleled by Eastern philosophies and practices such as tai chi, has survived the millennia since Juneval and his contemporaries. More recently, controlled examinations of the effects of physical fitness on cognitive performance have shown that improving cardiovascular fitness (CVF) can help to reduce the deleterious effects of age on cognition and brain structure. Thus, as we age, it may well be the case that a sound mind is a natural concomitant of a sound body. Numerous cross-sectional and longitudinal studies have examined the effects of aerobic exercise on cognitive performance in aging humans since earlier studies, which found that physically fit older adults performed better on simple cognitive tasks than their less-fit counterparts. This base of knowledge recently has been furthered through examinations of cortical structure (Colcombe et al., 2003) and neurocognitive function in aging humans via functional and structural magnetic resonance imaging techniques. In this manuscript, we will briefly review some of our recent research on the effects of CVF on brain function, structure, and behavior in older adults. We will then outline some of our current and future directions in this area.

Index Entries: Aging; fitness; cognitive; brain; plasticity.

Cardiovascular Fitness and Cognition

Early cross-sectional studies of the effects of cardiovascular fitness (CVF) on cognitive performance in older adults showed that highly fit elders substantially outperformed less-fit elders (for review, *see* Etnier et al., 1997). However, longitudinal interventions in which older adults were randomly assigned to either receive aerobic training or some other control met with somewhat less consistent results, with some studies finding significant improvements in the aerobically trained group and others finding no difference between trained and untrained individuals.

In a recent meta-analysis, Colcombe and Kramer (2003) found that when aggregating the results from intervention studies conducted from 1966 through 2001, several interesting findings emerged. For example, older adults who received aerobic training showed a significantly greater improvement in cognitive performance than control subjects did, across a wide variety of cognitive tasks. Interestingly, these improvements were greatest on measures of

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executive control (i.e., scheduling, planning, inhibition, task coordination, etc.), which are largely subserved by the frontal lobes of the brain (West, 1996).

CVF and Brain Structure

Although it seems relatively clear that current levels of CVF, or improvements in CVF through aerobic training regimens, can positively impact cognitive function in aging individuals, it is not yet clear how these improvements might be instantiated in the aging brain. However, data from animal models has suggested several possibilities. For example, aerobic training in aging animals can increase levels of key neurochemicals that improve plasticity and neuronal survival, such as brain-derived neurotrophin factor (BDNF [Neeper et al., 1995]) and serotonin (Blomstrand et al., 1989), as well as reduce corticosteroid levels, which can increase cell proliferation rates in aged animals (Cameron and McKay, 1999).

A recent cross-sectional study examining the effects of CVF levels on cortical density in aging humans (Colcombe et al., 2003) has shown that the beneficial effects of CVF seen in the brains of aging animals might extend to aging humans. Colcombe et al. (2003) examined the density of cortical gray and white matter in a sample of adults ranging from 55 to 79 yr of age and related these measures to the CVF levels of the subjects in their sample. They found that CVF levels moderated the trajectory of age-related tissue loss significantly. Older adults with greater levels of CVF suffered significantly less loss of gray matter in the frontal, temporal, and parietal lobes and significantly less loss of tissue in the anterior and posterior white matter tracts. It is noteworthy that these findings remained highly statistically significant even after correcting for potential moderating effects such as socioeconomic status, tobacco, caffeine, and alcohol consumption, as well as hypertension.

These cortical density findings are highly consistent with findings from the behavioral literature that show CVF has its greatest impact on executive functions (Colcombe and Kramer, 2003), which are subserved by the frontal and parietal regions of cortex. The corroboration between the behavioral changes that result from improvements in CVF and the regional differences in brain morphology seen as a function of the participants' current fitness status suggests that improvements in behavioral functioning resulting from aerobic training protocols are instantiated at a relatively low biological level. Specifically, CVF can help to maintain the structural integrity of both the local cortical processing units (gray matter) and the pathways by which these processing units coordinate themselves to accomplish complex computations (white matter tracts). This supposition is bolstered further by recent findings that suggest both high levels of CVF and improvements in CVF through aerobic training can impact cortical recruitment in aging individuals. We turn to those results in the next section.

CVF and Cortical Recruitment

As indicated above, the results of animal studies, human behavioral paradigms, and studies of human brain morphology all suggest that CVF should positively influence neurocognitive functioning in aging humans. In a recent series of studies, we (Colcombe et al., 2004) investigated this possibility using an event-related functional magnetic resonance imaging (fMRI) technique. Specifically, we asked older adults to perform a modified version of the flanker paradigm (Botvinick et al, 1999) while we assessed regional blood flow using a T2* echo-planar imaging scanning protocol. Participants were asked to identify the orientation of a central arrow cue (< or >) by depressing a left or right button. These central cues were flanked on either side by two arrow cues that pointed in the same direction (e.g., <<<<<) or a different direction (e.g., >><>>). To make a correct response in the presence of inconsistent flanking cues, participants were required to inhibit or filter the information provided by the inconsistent cues in favor of the central cue.

In study 1, participants completed the fMRI portion of the study, after which their current levels of CVF were assessed. In study 2, participants were assigned randomly to participate in either a 6-mo aerobic training group or a nonaerobic control group. Participants in study 2 completed the fMRI portions of the study both prior to and subsequent to the training intervention.

If CVF positively impacts cortical functioning, we expect that the recruitment of areas involved in selective attentional allocation would show increased activity associated with greater levels of CVF (in study 1) and as a result of aerobic training (in study 2). Additionally, the increased performance of these regions should lead to (1) less interference from the inconsistent flanking items, and (2) a reduction in activity in regions of cortex sensitive to the behavioral conflict engendered by the inconsistent flanking cues.

The results of the studies were consistent with the predictions discussed above. In study 1, high-level CVF older adults showed significantly less behavioral conflict than their lower CVF counterparts, as measured by the relative amount of time it took them to respond to the central cue in the presence of the inconsistent flanking items, compared with congruent stimuli. Similarly, aerobically trained individuals in study 2 showed significantly less behavioral interference after the 6-mo training protocol, whereas control participants showed no such benefit. Additionally, high-level CVF participants in study 1 showed greater activity in attentionally relevant regions of cortex of the frontal and parietal lobes than low-level CVF participants, and less activity in the dorsal anterior cingulate cortex, a region of cortex sensitive to behavioral conflict. Also, aerobically trained individuals in study 2 showed an increase in the recruitment of attentional circuitry and a reduction in activity in the dorsal anterior cingulate after the 6-mo training protocol, compared with control participants. Moreover, these regions overlapped spatially with those identified in study 1.

Taken together, the observed effects of CVF levels on brain structure and function are clearly encouraging. They suggest that chronically high levels of CVF can protect the brain from the ravages of time (Colcombe et al., 2003; 2004, study 1). Additionally, it appears that even relatively short aerobic training interventions might begin to repair or restore the aged brain (Colcombe et al., 2004, study 2), as well as performance on a variety of cognitive tasks (Kramer et al., 1999; Colcombe and Kramer, 2003).

However, the exact mechanisms that underlie these improvements are not clearly established in humans. It is possible, perhaps even likely, that the same effects resulting from aerobic exercise seen in other animal models, such as increased neuronal number, interconnections, and so forth, underlie both the differences in volume and cortical recruitment seen in the studies reviewed in this paper.

Future Directions

Thus far, the investigation of CVF on neurocognitive functioning in aging humans has proved quite productive. However, several avenues of investigation might prove valuable in both understanding the mechanisms that underlie the influence of CVF on neurocognitive function in older adults, as well as conjunctive approaches that might enhance or broaden the benefits of CVF for aging humans.

One interesting finding from the Colcombe and Kramer (2003) meta-analysis was that studies whose sample had a high proportion of females showed greater overall effects of aerobic training on cognitive performance. Although this finding is quite indirect, it suggests the possibility that females benefit to a greater degree from aerobic training than males. Several explanations for this type of effect exist. For example, it could be that gender differences exist in baseline CVF levels, which might lead to differentially efficacious outcomes of aerobic training. However, research from animal models suggests that estrogen also might play a role in these effects. Berchtold et al. (2001) have shown that estrogen can increase the rate of BDNF transcription in aged animals; again, BDNF is one of the neurotrophic factors thought to play a key role in instantiating the beneficial effects of exercise on cortical tissue. This possibility is tentatively supported by observations in our own lab. In the Colcombe et al. (2003) data set, we found a trend for increased cortical density in females who exercised, with the greatest effect in females who were currently undergoing hormone replacement therapy (HRT). Unfortunately, the number of HRT females in the sample was somewhat small. We are currently collecting additional data from HRT and non-HRT females to examine these effects more closely.

Another potentially useful finding from the Colcombe and Kramer (2003) meta-analysis was that aerobic training interventions that also included an anaerobic (strength) training protocol showed greater overall benefits on cognitive performance than those that only had an aerobic training component. One possibility is that the additional strength gained in the anaerobic training simply provides greater physical resources to facilitate the aerobic training component. But strength training is known to increase levels of human growth hormone (HGH) and insulin-like growth factor 1 (IGF-1), which in turn are known to have positive effects on neuronal growth, differentiation, and performance (Carro et al., 2001; Cotman and Berchtold, 2002; Godfrey et al., 2003; Yasuno et al., 2003). Therefore, much in the same way that estrogen might work synergistically with exercise training to facilitate brain health in aging adults, HGH and IGF-1 might help to accentuate the effects of aerobic training in older individuals. Future research that includes assessments of strength training history or interventions that compare aerobic training alone with combined aerobic and strength training to investigate brain morphology and/or cortical functioning are likely to prove informative.

Of course, physical fitness intervention is only one type of approach to offset the effects of normal aging on human cognition. Many other factors, such as expertise (Salthouse, 1984; Masanuga and Horn, 2002) and cognitive training protocols (e.g., Baron and Mattila, 1989; Kramer et al., 1999c; Scialfa et al., 2000), can benefit older adults to an equal or even greater extent than younger adults. But most of the beneficial effects of these factors tend to be highly domain specific. For example, expertise in typing has little or no effect on one's ability to drive a car, and training in visual search paradigms has little effect on working memory performance. However, several recent studies that have implemented a kind of dual task training protocol in which older adults were taught, over the course of several sessions, to flexibly allocate processing resources to different stimulus and task dimensions have shown greater general benefits on cognitive performance than more traditional training protocols.

Kramer et al. (1999c; see also Kramer et al., 1995) asked young and old adults to perform two tasks concurrently, a pattern-learning task and a tracking task, with either of two training strategies. In the fixed priority training strategy, subjects were asked to treat each of the tasks as equal in importance; in the variable priority training procedure, subjects were required to constantly vary their priorities between the two tasks. On-line performance feedback was presented in both training conditions. Consistent with previous studies, young and old adults improved their dual-task performance at the same rate with the fixed priority training strategy. Additionally, variable priority training led to faster acquisition and a higher level of mastery in performing the tasks together than did fixed priority training. Moreover, individuals trained in the variable priority condition also displayed superior transfer to untrained tasks and better retention of time-sharing skills, over a 2-mo period, than did those individuals trained in the fixed priority condition.

The fact that variable priority training participants showed generalization to new tasks suggests that they gained efficacy in more general higher-order cognitive management skills, rather than simply learning to respond to a particular stimulus set, as in a visual search paradigm. Of course, the underlying mechanisms, in terms of cortical recruitment, that instantiate these general improvements in cognition are of interest in and of themselves. But it is also interesting to consider the implications of these results in combination with aerobic training. Presumably, the additional plasticity and focused activity engendered by aerobic fitness in aged brains should facilitate adaptation and perhaps increase the general effect of cognitive training in older adults. Utilizing such general cognitive training in the favorable cortical environment provided by aerobic fitness training might prove to be a powerful approach to remediate age-related decline in cognition.

Finally, models of neurocognitive aging have implicated age-related changes in gray and white matter as major factors in age-related declines in cognition. Some models (e.g., HAROLD, Cabeza, 2002) suggest that gray matter declines reduce the efficacy of specialized cortical processing units, which in turn leads to under-recruitment of these areas and concomitant activation of nonspecialized regions of cortex to compensate for the loss of tissue in the specialized regions. Others have suggested that deterioration of the anterior white matter tracts results in an effective disconnection between the hemispheres of the brain (O'Sullivan et al., 2001), thereby impairing cognition. Of course, these are not mutually exclusive propositions and could differentially impact cognitive performance in aged individuals.

The observations on which these proposals are based are derived by examining static differences among individuals and not through any manipulation of these factors. However, CVF is known to affect both gray and white matter densities and might therefore provide a mechanism to parcel out the relative contributions of gray and white matter health to cognitive performance in aging individuals. A number of methodological obstacles still remain in the pursuit of such an endeavor. For example, although animal models have shown differences in neuron health after only 1 wk of aerobic training, it is unclear whether even a 6-mo intervention would yield detectable effects in humans. Future research addressing these issues seems warranted.

Conclusions

We believe that CVF holds great promise as a largely noninvasive but potentially powerful moderator of neurocognitive senescence. Our recent and current research programs have begun to elucidate the effects of CVF on cortical recruitment and brain structure in aging humans. Future research that combines both structural and functional assessments to model the changes in cognitive benefits of aerobic fitness training are likely to prove highly fruitful in understanding the mechanisms that underlie these changes. Furthermore, these assessments might tell us something about the factors that affect individual differences in cognitive performance of older adults more generally, as well as speak to models of neurocognitive aging. It also seems likely that cognitive training interventions that leverage the increased plasticity engendered by aerobic training will be effective in remediating cognitive decline. Finally, an understanding of the roles of estrogen, BDNF, IGF-1, and HGH in moderating cortical decline, and perhaps even the restoration of brain health, might help to guide future research in targeted drug therapies and clinical recommendations for hormone replacement. We believe that research into the effects of aerobic training in aging humans provides a number of promising avenues for both applied interventions and theoretical guidance in offsetting the effects of age on neurocognitive function. Future research endeavors are likely to provide deeper insights into this issue.

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