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GENETICS AND PREVENTION

Enhancing Brain and Cognitive Function of Older Adults Through Fitness Training

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Abstract

The present article provides a brief review of the human and animal literature that has investigated the relationship between fitness training and brain and cognitive function. The animal research clearly suggests that improvements in fitness can lead to both morphological and functional changes in the brains of older animals. Results of a recent meta-analysis suggest that fitness training can also have beneficial effects on human cognition, particularly on tasks requiring executive control processing. These effects are also moderated by a number of factors, including the proportion of men and women in the intervention studies, the length of training sessions, the age of the participants, and the combination of fitness training regimes. The article also discusses preliminary results that link, for the first time, fitness training and differences in human brain structure and function. Finally, we discuss the important issue of participant adherence to fitness training programs and the factors that influence fitness participation.

Index Entries: Aging; cognitive and cortical plasticity; meta-analysis; executive control; fitness.

Introduction

Over the past several decades, an increasing body of literature has begun to characterize the nature of cognitive and brain changes across the human life span. Within the domain of "cognitive aging" it has become clear, from both cross-sectional and longitudinal studies, that some deficits in a variety of perceptual, cognitive, and motor functions can be observed beginning during young adulthood and others not realized until the 60s or even 70s (Schaie, 2000; Park et al., 2003). Indeed, some of the most striking findings from longitudinal studies are the vast individual differences in the timing and pattern of decline.

Observations of changes in human cognition across the adult life span are mirrored by observations of nonpathological age-related changes in brain function and structure. For example, there is a body of research that documents nonspecific or global changes in brain volume across the adult life span. In most cases, these studies, which have employed computerized tomography (CT) or magnetic resonance imaging (MRI) scanning techniques, have been cross-sectional in nature and have found decreases in gray and white matter and increases in the size of the ventricles across the adult life span (Coffey et al., 1992; Pfefferbaum et al., 1994; Murphy et al., 1996). Similar findings have been obtained in relatively short-term longitudinal studies of morphological

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changes in brain structure (Davatzikos and Resnick, 2002; Resnick et al., 2000; Shear et al., 1995).

An association between changes in brain structure and cognition has been established through a number of reports of significant statistical relationships between global age-related differences in cortical morphology and measures of cognitive function. For example, Albert et al. (1987) reported that increases in global brain atrophy resulted in decreases in performance on a battery of neuropsychological tests. More recently, MacLullich et al. (2002) reported a significant relationship between MRI-based measures of brain volume and a general cognitive factor comprised of memory, attention, and decision-making tests. Similar types of relationships have been reported for regional measures of brain volume changes and selective aspects of cognition (Raz, 2000; Head et al., 2002). Finally, human neuroimaging studies, employing positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have also provided a number of insights into the relationship between brain function and cognition (see Cabeza [2000] and Park et al. [2003] for in-depth reviews of this literature). This literature has documented both reduced activation and nonselective activation of brain regions of older versus younger adults as they perform a variety of different memory and attentional tasks (Madden et al., 1996; Reuter-Lorenz et al., 2000; Cabeza, 2002; Logan et al., 2002).

Enhancing the Brain Function and Structure of Older Animals

Although human research has not yet addressed the question of whether changes in brain structure and function of older adults can be slowed or reversed through training or other interventions, such data are available in the animal literature. For example, although early research that examined the influence of enriched versus impoverished environments with rats and mice was confined to young animals, given the belief that brain plasticity existed only for young organisms, later research discovered that morphological changes could also be obtained with older animals (Riege, 1971; Black et al., 1990; Rosenzweig and Bennett, 1996; Kempermann et al., 1997). The changes engendered by enriched environments include increased dendritic branching, capillary development, the development of new neurons—presumably from adult stem cells—as well as a cascade of neurochemical changes. Indeed, many of these changes have also been observed when older animals are involved in fitness training (Black et al., 1990; Van Praag et al., 1999; Cotman and Berchtold, 2002). Such data, when viewed in terms of the human neuroimaging data which argues for a close coupling between cognition and brain function and structure, suggests that it is indeed conceivable that age-related brain and cognitive decline might be modifiable through intellectual and fitness training.

Fitness, Aging, and Cognition

The study of the relationship between fitness, aging, and cognition dates back several decades to the pioneering research of Spirduso and colleagues (Spirduso, 1975; Spirduso and Clifford, 1978). These researchers found that older athletes were significantly faster on a variety of different reaction time and movement time tasks than older nonathletes. Indeed, in many cases, the older athletes' performance was similar to that exhibited by younger low-fit adults. These initial observations were confirmed in numerous subsequent studies on cross-sectional differences in fitness on the performance and cognition of older adults (*see* Etnier et al. [1997] for a review of this literature).

However, longitudinal studies in which older adults were randomly assigned to either aerobic fitness or control groups produced a more varied pattern of results, with some studies reporting improvements in aspects of cognition with fitness training (e.g., Dustman et al., 1984; Rikli and Edwards, 1991; Hawkins et al., 1992; Kramer et al., 1999). However, other investigators failed to observe a relationship between improvements in fitness and cognition (e.g., Madden et al., 1989; Blumenthal et al., 1991; Hill et al., 1993). Interpretation of these data is complicated by the variety of differences among the studies in the length, intensity, and type of fitness training regimens; the age, health, and beginning and ending fitness levels of the study participants; the methods used for the assessment of cardiorespiratory fitness; and the tasks used to index perceptual, cognitive, and motor function improvements.

Recently, Colcombe and Kramer (2003) conducted a meta-analysis to ask whether (1) a fitness effect on cognition could be discerned when aggregating data across longitudinal studies, and (2) whether this effect, if observed, is moderated by other variables such as age, length, and intensity of fitness training, the nature of the tasks used to assess cognition, and so forth. Fitness intervention studies conducted from 1966 through 2001 were included in the analysis. Several interesting and potentially important results were obtained in the meta-analysis. First, a clear and significant effect of aerobic fitness training was found. Thus, when aggregating across studies, fitness training does indeed have positive effects on the cognitive function of older humans. Second, fitness training had selective effects on cognitive function. Although fitness effects were observed across a wide variety of tasks and cognitive processes, the effects were greatest for those tasks that entailed executive control (i.e., planning, scheduling, working memory, interference control, task coordination) processes. Executive control processes have been found to decline substantially as a function of aging (Kramer et al., 1994; West, 1996) as have the brain regions that support them (Raz, 2000). Therefore, the results of the meta-analysis suggest that even processes that are quite susceptible to age-related changes appear to be amenable to intervention.

The meta-analysis also revealed that a number of other moderator variables influenced the relationship between fitness training and cognition. For example, fitness training programs that were combined with strength and flexibility training regimens had a greater positive effect on cognition than fitness training programs that included only aerobic components. This effect may be the result of increases in the production of insulin-like growth factor 1 (IGF-1), which has been shown to accompany improvements in strength. IGF-1 is a neuroprotective factor that is involved in neuronal growth and differentiation (Carro et al., 2001; Cotman and Berchtold, 2002). Fitness training programs also had a greater impact on cognition if the study samples included >50% females. Although highly speculative, this effect may be attributable, in part, to the positive influence of estrogen (in the present case, estrogen replacement therapy) on both brain-derived neurotrophin factor (BDNF) and increased exercise participation (Cotman and Berchtold, 2002). Estrogen has been found to up-regulate BDNF, a neuroprotective molecule that is also increased by exercise. Finally, exercise effects on cognition were found to be greatest for exercise training interventions that exceeded 30 min per session.

To summarize thus far, although many questions concerning the relationship between fitness and cognition remained to be examined, the results of our recent meta-analysis, when viewed in the context of the animal research, suggest that this intervention can indeed enhance performance and cognition, even for older organisms.

Beyond Cognition: Beginning to Establish Fitness-Cognition-Brain Relations in Older Humans

Structure

The research into the effects of cardiovascular fitness on brain health markers using adult animal models suggests a low-level biological basis for the improvements in human cognition with cardiovascular training. Colcombe et al. (2003), recently explored the implied relationship between cardiovascular fitness and brain health in aging humans using a voxel-based morphometric (VBM) approach. In VBM analyses, high-resolution brain scans are segmented into gray and white matter maps, spatially warped into a common coordinate system, and examined for systematic changes in tissue density as a function of some other variable (e.g., age, cardiovascular fitness, etc.). This technique allows examination of the entire brain in a point-by-point fashion, revealing spatially precise estimates of systematic variation in brain tissues. The technique also provides a substantial advantage over other techniques, such as global estimates of gray and white matter volume, in that it allows researchers to localize the effects of a given variable to a specific region of the brain.

In a cross-sectional examination of 55 older adults, Colcombe et al. (2003) found that consistent with previous findings, age-related losses in gray and white matter tended to be greatest in the frontal, prefrontal, and temporal regions (e.g., Raz, 2000; O'Sullivan et al., 2001). Moreover, consistent with predictions derived from the human and animal literature, there was a significant reduction of declines in these areas as a function of cardiovascular fitness. That is, older adults who had better cardiovascular fitness also tended to lose much less tissue in the frontal, parietal, and temporal cortices as a function of age. Subsequent analyses, factoring out other potential moderating factors, such as hypertension, hormone replacement therapy, caffeine, tobacco, and alcohol consumption, confirmed that none of these other variables moderated the effect of cardiovascular fitness.

Function

A preliminary cross-sectional analysis of the relationship between cardiovascular fitness and brain function in older adults has shown promising results and is consistent with the notion that cardiovascular fitness tends to spare the brain from the aging process. Participants in this study performed a modified version of the Ericksen flanker task, in which they were asked to identify the orientation of a central arrow presented among an array of distracting stimuli while brain function was recorded using fMRI. In 50% of the trials, the orientation of the distracting stimuli was consistent with the central cue (e.g., <<<<<), whereas in the other 50%, the distracting stimuli were oriented inconsistently with the central cue (e.g., >><>>). In inconsistent trials, participants were required to suppress the information provided by the flanking stimuli in order to make a correct response. In these trials, highly fit older adults, much like young adults, tended to show less activity in the left prefrontal regions of cortex than did their low-fit older counterparts. These results, although preliminary, suggest that cardiovascular fitness may provide a prophylactic effect to the functional integrity of the older adult brain.

Longitudinal Assessments

The data emerging from cross-sectional assessments of fitness on older adult brain function and structure are both promising and encouraging. However, no matter how well controlled such assessments might be, the cross-sectional nature of these studies minimizes the degree to which causal claims might be made about the relationship between fitness and brain structure or function. To make such claims, randomized intervention trials, in which participants are randomly assigned to participate in cardiovascular training or control groups, are necessary.

However, longitudinal assessments of brain structure and function present unique challenges in terms of the accurate spatial coregistration that is critical for such measures. For example, recalibrations of the magnetic field in the scanner can induce slight alteration in the apparent geometry of acquired images. Additionally, the soft tissue in the brain may itself change over time. Both of these effects, if not taken into account, can result in noisy or misleading data.

In our ongoing longitudinal projects, we have adopted a variant of the registration approach used in structural image evaluation using normalization of atrophy (SIENA), a tool for assessing global atrophy in a longitudinal sample (Smith et al., 2002). This technique uses information derived from the soft tissues (the brain), which might well change over time, as well as the skull, which is unlikely to change over time, to constrain the coregistration of MRI images collected at different time points. Any alteration detected in the morphology of the skull can likely be attributed to changes in the geometry of the scanner and not to changes in the bone tissue itself. This allows for a relatively unbiased basis to correct for changes in scanner geometry over time and to constrain soft tissue coregistration.

Additionally, it is important to ensure that when the images taken from two time points are resampled into a common space, the resampling process itself does not differentially impact either time point. For example, it would be possible to register the time1 image to match that of the time2 image, but then the time1 image would have undergone an alteration that was not applied to the time2 image. Because of slight errors in the resampling processes, this would systematically add error to one time point over another. Another approach might be to register time1 to time2 for half of the participants, and time2 to time1 for the other half. This, however, is also a suboptimal solution, as it would rely on the participant by session variance in registration errors to balance out the within-subject differences in image sampling. A more optimal approach would be to register time1 to time2, and, vice versa, compute the exact midpoint of the transformation between the two images and then transform both time1 and time2 images to that space. This way, the images are registered into a common space and have undergone equivalent transformation and resampling. This is the approach adopted in SIENA (Smith et al., 2002), and modified in our lab to coregister both functional and structural images across time.

Other factors, such as participant movement while being scanned in fMRI can impact longitudinal studies to a greater extent than cross-sectional studies. In the simplest case, participants are exposed to double jeopardy, in that they are required to restrain from movement during two sessions, rather than one. This, of course, results in a higher attrition because of movement artifacts in longitudinal studies. Additionally, preliminary results in our lab, perhaps not surprisingly, suggest that there tends to be less movement during the second session than the first. Given that in fMRI studies, the signal intensity changes due to motion are relatively great compared to typical signals of interest (Friston et al., 1996), motion-related artifacts must be carefully controlled both by spatially realigning the raw images and controlling for differences in motion parameters during the statistical assessment of the data.

In summary, we are in the process of applying the techniques discussed above, as well as others, to the longitudinal data set that we are collecting in an effort to examine, within individuals, the influence of fitness training on brain and cognitive function.

Maintaining and Enhancing Participation in Exercise Trials

Although the numerous health benefits of regular physical activity for older adults are well established, ~40% of adults are sedentary (*Healthy People 2010*, 2000) and only 32% of adults 65 and older engage in regular exercise (*Fitness Facts for Older Americans*, 2000). Colditz (1999) has estimated the direct cost of inactivity to be 2.4% of the nation's health care expenditures. Equally serious is the 50% attrition rate that is typically associated with most exercise programs. Consequently, if the promise of improved cognitive function and possible brain changes through improved cardiovascular fitness is to be realized, it is imperative that exercise programs be designed to maximize adherence. In this section, we briefly review the literature relative to some of the more reliable correlates of adherence and describe how we have implemented this knowledge into the Institute for the Study of Aging (ISOA) trial to influence adherence.

Self-Efficacy

One of the most consistently reported correlates of exercise behavior is self-efficacy (McAuley and Blissmer, 2000). An integral component of social cognitive theory (Bandura, 1986, 1997), self-efficacy expectations concern the individual's beliefs relative to his/her capabilities to execute necessary courses of action to satisfy situational demands. Individuals with high self-efficacy expectations tend to approach more challenging tasks, put forth more effort, and persist longer in the face of aversive stimuli. When faced with stressful stimuli, low efficacious individuals tend to give up, attribute failure internally, and experience greater anxiety or depression (Bandura, 1986). As individuals age, performance of everyday functions becomes more challenging and requires greater effort and perseverance. Therefore, a robust sense of efficacy appears to be of particular importance to older adults.

Self-efficacy has been found to be predictive of adherence to exercise regimens in asymptomatic (McAuley, 1993) and clinical (Kaplan et al., 1984) populations, recovery from conditions associated with aging (e.g., cardiovascular disease; Carroll, 1995), and survival rates of individuals with chronic disease (Kaplan et al., 1994). McAuley et al. (1994) conducted a randomized controlled trial employing efficacy-enhancement strategies to improve exercise adherence and reported a significantly greater attendance rate (67%) for the intervention group compared to the control group (55%) over the 5-mo trial. Additionally, twice as many participants in the intervention group exercised two or more times per week than in the control group. Integrating similar efficacy-enhancement strategies into a recent randomized controlled exercise trial of 174 older adults, we were able to hold attrition to 13% over a 6-mo program (McAuley et al., 1999). It appears, therefore, that the correlational evidence that suggests self-efficacy to be a consistent determinant of exercise participation is supported by more stringent intervention data.

Social Support

Social interactions have been demonstrated to play an important role in physical and psychological health (Uchino et al., 1996) and such interactions are known to decrease with aging. Indeed, social support is one of the most frequently studied psychosocial determinants of exercise as a health behavior. Social support can be characterized as either perceived or actual assistance given by others in the acquisition of behaviors. Although typically assessed as a unidimensional construct in the exercise literature, there is good theoretical reason to consider social support as multidimensional (Weiss, 1974; Cutrona and Russell, 1987). In the context of physical activity, social support has consistently been shown to be related to exercise behavior (Chogahara et al., 1998), and the general conclusion is that social support has a direct effect on such behavior. However, a social cognitive perspective (Bandura, 1997) would argue that this relationship is indirect and mediated by self-efficacy. Such a position views social support as a potent source of self-efficacy information. Indeed, convincing support for this theoretical assumption comes from the work of Duncan and his colleagues (Duncan and McAuley, 1993; Duncan et al., 1993). In these studies, physical activity was related to both self-efficacy and social support in cross-sectional and longitudinal analyses. However, latent growth analyses were able to demonstrate that the effect of social support on adherence to older adults' exercise behavior operated through its influence on self-efficacy. Thus, whereas group activities might be reasonably expected to enhance social support and self-efficacy, the subsequent impact of these variables on physical activity behavior is not as straightforward as is often portrayed in the literature.

Enjoyment

Although Bandura (1997) identifies the interpretation of affective responses as a source of efficacy information, very little research has been conducted examining the relationship between effect and exercise adherence in older adults. Stevens et al. (2000) conducted a cross-sectional study examining 266 Dutch adults aged 49 and older, reporting that enjoyment of exercise significantly discriminated between those participants who were not considering the adoption of exercise and those who were considering or preparing to adopt exercise. Additional support for the role of enjoyment comes from Johnson and Heller (1998), who followed 459 older adult cardiac rehabilitation patients and found that enjoyment of home-based exercise 6 wk after discharge was predictive of exercise levels 6 mo after discharge. Again, a social cognitive perspective would hold that social support and enjoyment/affective influences on maintenance of exercise behavior operate indirectly through their effects on self-efficacy. McAuley et al. (2003) have presented prospective evidence of such relationships in older adults engaged in a 6-mo exercise trial.

Maintaining Adherence in the ISOA Trial

The ISOA trial employs the primary sources of self-efficacy as integral parts of the exercise experience. These sources of information are personal accomplishments (mastery), vicarious experience (modeling), verbal persuasion, and interpretation of physiological states. To maximize mastery experiences throughout the program, the importance of regular attendance to the program is emphasized, and daily attendance is monitored by exercise logs and corroborated by exercise leaders. Each participant is provided with a personal exercise prescription, based on a preintervention fitness assessment, which serves as a guide for setting individualized goals. Exercise leaders are instructed to focus on and encourage task-oriented goals, with an emphasis on mastery experience and personal improvement. Additionally, the participants are provided with monthly reports of their individualized goals, accompanied by graphic displays of their progress.

Because of the recruitment process, new participants enter the trial in waves. This has led to the creation of a heterogeneous group of participants with varying skill and fitness levels determined by the length of their stay in the program, which allows for successful social modeling. Coupling this peer modeling with strong leader-participant communication and encouragement provided an important source of guidance or instrumental support for the participants, as well as an important motivational influence. Additional social support is provided through the formation of buddy groups and telephone trees.

Unrealistic or false expectations are one of the most common causes of exercise attrition. To avoid attrition owing to frustration or disappointment from unfulfilled expectations, extensive educational instruction is delivered at the beginning of the trial. Participants are familiarized with the extent of changes/improvements that regular physical activity might bring about over time. Similar effort is placed on the explanation of normal or adverse physiological responses to exercise. Given the nature of the sample (older sedentary individuals), it is of vital importance to explain the physiological adaptations and their relationships with exercise training over time. In an effort to educate participants about these issues, a booklet containing information relevant to the initiating of an exercise program (e.g., safety precautions, exercise tips) is provided for all participants prior to program onset.

In all, these behavioral science approaches to enhancing primary correlates of physical activity participation are crucial to the success of the trial. Poor adherence results in minimal or no fitness gains. Such an outcome negates a primary purpose of this trial, that is, to determine the extent to which fitness gains are associated with changes in brain structure and function. In the present phase of this trial, 43 participants were randomized. Six participants (14%) dropped out of the exercise program shortly after assignment with typical reasons for attrition being family illness and travel schedules. Of the six dropouts, three were willing to come back for post-trial testing. Using an intent to treat criteria and thus including all dropouts, we have an average adherence rate of 77% across the 6-mo exercise intervention. Those participants who completed the program attended ~86% of all possible exercise sessions. The combination of strong adherence rates and low dropout rates provide further support for efficacy-laden interventions.

Conclusions and Future Directions

We have attempted, in this brief exposition, to discuss the animal and human research of relevance to the understanding of the relationship among fitness differences/changes, cognition, and brain structure and function. In recent years the study of this relationship has undergone major enhancements, given the advent of nonintrusive techniques for the measurement of human brain structure and function. These developments have enabled researchers to begin to relate, in a meaningful fashion, studies of fitness-brain-cognition across molecular, cellular, and systems levels of analysis. Future studies will, we believe, continue this trend in an effort to explicate the mechanims that support interactions among these important domains of animal and human function.

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