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Effects of Aerobic Fitness Training on Human Cortical Function

A Proposal

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Abstract

We briefly review the extant human and animal literature on the influence of fitness training on brain, cognition and performance. The animal research provides clear support for neurochemical and structural changes in brain with fitness training. The human literature suggests reliable but process specific changes in cognition with fitness training for young and old adults. We describe a research program which examines the influence of aerobic fitness training on the functional activity of the human using event-related functional magnetic resonance imaging, of humans in fitness interventions.

Index Entries: Executive control; fitness; fMRI; neuroimaging.

Introduction

Research on the relationship between physical and mental fitness dates back several decades and is exemplified by the research program of Spirduso and her colleagues. Spirduso (1975) found that older racquet sportsman were significantly faster on simple, choice and movement response times than older nonexercisers. In a follow-up study, Spirduso and Clifford (1978) found similar results for runners as compared to nonrunners. Results of other cross-sectional studies have produced similar patterns of performance benefits for life-time exercisers compared to nonexercisers. The cross-sectional nature of these studies, however, complicates their interpretation. Thus, the positive effects of physical activity on perceptual, cognitive, and motor performance may reflect a predisposition of the exercisers towards fast and accurate responding rather than a benefit of aerobic fitness achieved through exercise. A number of researchers have at least partially circumvented the problem of self-selection by employing longitudinal exercise interventions. However the data obtained from longitudinal studies has been somewhat equivocal (Dustman et al., 1994). Clearly, there have been some notable successes in that aerobically trained individuals have outperformed non-aerobically trained control subjects on a variety of cognitive tasks (Dustman et al., 1984; Hawkins et al., 1992). On the other hand, some intervention studies have failed to observe such benefits to performance (Blumenthal et al., 1991; Hill et al., 1993). Thus, an important unanswered question concerns why some studies find improvements in performance with enhanced aerobic fitness while other studies have failed to observe such a relationship.

Research with animals has made it clear that physical and mental exercise can affect the brain in a

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number of important ways. Rats raised in complex environments, such as those which included toys for exploration and play, developed a greater density of synapses and higher capillary volume per nerve cell than those raised in less enriched environments (Black et al., 1987). Subsequent work has separately addressed consequences of physical activity and exercise and learning, both of which occur in the complex environment. Black, Isaacs, Anderson, Alcantara, and Greenough (1990) provided different groups of rats motor skill learning with minimal exercise, exercise in a running wheel or treadmill with minimal learning, or neither. They found that the exercise groups increased capillary density without significant change in synapse number, whereas the motor skill learners added synapses with no change in capillary density. This result indicated that these two responses, synapse formation to store new learning and capillary formation to provide stamina, were relatively independent in their responses to the demands of the animal's surroundings. Subsequent work has extended these findings to regions of the cerebral cortex involved in motor performance, learning, and memory (Kleim et al, 1996; van Praag et al., 1999).

The animal and human research reviewed above suggests a link between fitness; performance on a subset of perceptual, cognitive, and motor tasks and skills; and brain function and structure. However, as previously discussed, such relationships are not always observed nor have all of the links been established in humans (i.e., particularly the links between fitness and brain function and structure).

Recently we (Kramer et el., 1999) proposed and tested a new hypothesis that improvements in aerobic fitness would be associated with selective improvements in neurocognitive function and in particular in executive control processes such as coordination, inhibition, scheduling, planning, and working memory. We based this hypothesis on the reports in the literature, which suggest that neither cognitive nor brain function and structure decline uniformly during the course of aging. Within the realm of aging and cognition, large and disproportionate age-related deficits have been reported in tasks that require subjects to retain and manipulate information in working memory (Verhaeghen et al., 1997), perform two or more tasks concurrently (Korteling, 1991; Kramer et al., 1999), switch rapidly between two tasks (Kramer et al., 1999; Merian, in press), and inhibit prepotent responses (Olincy et al., 1997). All of these skills fit under the heading of executive control processes.

On a similar note, researchers have reported substantially larger reductions in gray matter volume with aging in association areas of cortex, and in particular in the prefrontal and frontal regions, than in sensory cortical regions (Raz, 2000). Studies of functional brain activity employing Positron Emission Tomography (PET) have reported similar trends, with prefrontal regions showing substantially larger decreases in metabolic activity than sensory areas of cortex (Azari et al., 1992). The majority of executive control processes appear to be supported, in large part, by the frontal and prefrontal regions of the brain.

In an effort to test our executive control/fitness hypothesis, we (Kramer et el., 1999) trained 124 sedentary but healthy older adults (age range 60–75) for a period of 6 mo with either an aerobic (walking) or anaerobic (toning and stretching control) exercise protocol. Each of the subjects was tested in a variety of attention and memory tasks. We chose particular behavioral tasks because components of a subset of these tasks have been shown, either through human lesion, neuroimaging, or animal studies, to entail executive control processes and be supported, in large part, by the frontal or pre-frontal regions of the brain. The main question was whether the task components that entailed executive control processes would show improvements, over the course of the exercise intervention, for the walkers but not for the stretching group Additionally, we were interested in whether nonexecutive control processes would show equivalent performance trends for both of the exercise groups. To a large extent, this is the pattern of results that were observed in our study (see Kramer et al., 1999 for additional details).

In the present research, which has recently begun, we extend our previous studies by examining the influence of improvements in aerobic fitness on executive control processes as reflected by both performance on computerized tasks as well as by changes in the pattern of brain activation indexed by event-related functional magnetic resonance imaging (fMRI). More specifically we will test the hypotheses that: 1) a 6-mo aerobic fitness intervention will selectively improve aspects of cognition that depend on executive control; and 2) that improvements in executive control processes exhibited by aerobically trained older adults will be related to differences in brain function, particularly in the frontal and prefrontal regions of the cortex. These hypotheses will be examined by collecting high-resolution structural MRI images and patterns of functional activation (fMRI), both before and after a 6-mo fitness intervention, from healthy but sedentary older adults as they perform attention and memory tasks in a 1.5 Tesla MRI.

Methods

We will investigate the relationship between aerobic fitness, cognitive function (particularly executive control), and brain function with a 6-mo intervention study. Seventy-two healthy but low fit adults will be recruited from the Champaign area. Thirty-six of the low fit adults will be randomly assigned to an aerobic training group, the other 36 will be assigned to a nonaerobic toning and stretching control group. Subjects will perform a series of cognitive tasks in the MRI system (with collection of structural and function data) before and after the 6 mo exercise intervention. Subjects will also participate, before and after the exercise intervention, in cardiorespiratory assessments in order to establish the degree of improvement in aerobic function.

Subjects will practice the cognitive tasks prior to fMRI recording in our laboratory at the Beckman Institute and also for a brief time in the magnet before scanning commences. Each subject will participate in one behavioral training session (approx 1.5 h with frequent breaks for task familiarization and practice and other brief assessments including vision tests, mini-mental state test) and two 1-h fitness assessment sessions before and after the 6-mo intervention. The neuroimaging session will last approx 2 h and will include completion of two tasks. Task performance, which occurs during fMRI recording, will take no longer than 1 h and 15 min, with the other 45 min being devoted to obtaining structural scans, system set-up, and subject re-familiarization with the tasks.

Each of the paradigms that subjects will perform in the magnet have been chosen because at least one component has previously been shown: 1) to produce disproportionate age-related performance decrements; 2) entail some aspects of executive control such as scheduling, planning, coordination, working memory, or inhibition; and 3) require effective frontal lobe function for successful performance. Furthermore, at least one component of each of the tasks will be used to provide a nonexecutive control (non-frontal) baseline against which to compare fitness effects on executive control (and frontal and prefrontal) processes.

Exercise Training Interventions

Basic principles and guidelines for exercise programming will be followed, including adequate warm-up and cool-down periods, progressive and gradual increments in exercise duration and energy expenditure, and instruction regarding avoidance of exercise-related injury. The exercise program will be conducted three times per week for 6 mo. As these participants will be sedentary at onset, the prescribed intensity component of the exercise program will begin at a light to moderate intensity level over the first 2 mo progressing to a moderate to high level for the remaining duration of the intervention.

Aerobic Exercise Group

The aerobic exercise intervention is designed to improve physical fitness as typified by cardiorespiratory endurance. Levels of exercise intensity will be prescribed based upon peak heart rate (HR) responses during the initial graded exercise treadmill test. The light exercise intensity level will require HR responses between 40–50% HR reserve. The moderate level will elicit a HR of 60–70% HR reserve. This group will follow a walking routine beginning at 10–15 min per session and increasing by a minute per session. After 3 mo the participants will be walking for 40–45 min per session and will continue at this duration until the end of the study. Frequent assessment of heart rate and ratings of perceived exertion will be made to ensure appropriate levels of intensity are met during each exercise session.

Toning and Stretching Control Group

This group will serve as a control group against which to gauge the effects of aerobic conditioning on neurocognitive function. This group will meet on the same basis as the aerobic exercise group, will be led by an experienced exercise leader, and therefore receive the same amount of attention as our treatment group. The focus of the stretching and toning program will be on the provision of an organized program of stretching, limbering, and toning for the whole body and is specially designed for individuals 60 yr of age and older. Each stretch will be constant, controlled, and smooth and progressions will be gradual and steady. The stretches will be within each subject's range of motion and will be held to the point of slight discomfort. Each stretch will be held for approx 20–30 s and be repeated 5–10 times. Each stretching session will last for approx 20–30 min and meet 3 times per week. Each session will be preceded and followed by 10–15 min of warm-up and cool-down exercises.

Assessment of Aerobic Capacity

Aerobic endurance capacity will be determined for all subjects prior to the intervention and at the end of the program. Aerobic endurance capacity will be assessed on a motor-driven treadmill by employing a modified Balke protocol. The protocol involves walking at a speed of 3 mph with increasing grade increments of 2% every 2 min. Measurements of oxygen uptake, heart rate, and blood pressure will be continuously monitored. Peak oxygen uptake (VO_2) will be measured from expired air samples taken at 30-s intervals until the highest VO_2 is attained at the point of test termination due to symptom limitation and/or volitional exhaustion.

Neuroimaging Methods

We will rely on MRI procedures to provide information on brain structure and function. First, we will measure changes in brain activity (indirectly via the BOLD contrast mechanism) during cognitive challenge by using event-related fMRI. These measures will enable us to examine functional differences in hemodynamic response before and after the fitness intervention. Functional neuroimaging has been well-established in measuring regional changes in blood flow for neural areas that are active during cognitive challenges. Our previous work (Kramer et al., 1999) has suggested that an aerobic intervention program provides substantial improvements in older adults on tasks requiring executive control. Here, we propose to examine at the functional changes in the aging human brain that may accompany the cognitive improvements that we have already demonstrated.

Furthermore, given that we will record event-related fMRI data in our experimental tasks, we will be able to examine a number of important parameters of the hemodynamic response (HDR) including the shape and time course with respect to stimulation, the absolute and relative amplitude change across experimental conditions, the variability of the HDR within conditions, and the signal/noise ratio. We may observe increases in amplitude, decreases in variability, and increases in the signal/noise ratio of the HDR's as a function of fitness for the older adults, perhaps in a generalized manner. The degree to which specific changes beyond these general differences in hemodynamic response are observed in frontal and prefrontal regions in the conditions of the experimental tasks that rely, in large part, on aspects of executive control, will provide a test of our executive control/fitness hypothesis.

To acquire our functional and structural images, we will be using a 1.5 Tesla magnetic resonance imaging system (General Electric Co.) equipped for echo-planar imaging. For each functional run, the total number of EPI images acquired will depend on the nature of the experiment and the number of stimuli presented. The resulting EPI images (TR = 2017 ms, TE = 40 ms, flip angle = 90°), will consist of 20 contiguous slices (thickness = 7 mm, in-plane resolution = 3.75 mm), parallel to the AC-PC line. A high-resolution 3D anatomical set (T1-weighted three-dimensional spoiled gradient echo images) will be collected for each participant, as well as 20 inplane T1-weighted slices. The head coil will be fitted with a bite bar to minimize head motion during the session. Stimuli will be presented on a goggle system and responses acquired on a button response pad.

Task Description

Given limited space we will describe only one of several tasks, the response compatibility paradigm, that subjects will complete during fMRI scanning.

There is now a substantial body of research that suggests older adults have more difficulty than younger adults ignoring conflicting information. In our previous study of aging, fitness, and cognition, we found not only an age difference in the ability to ignore peripherally presented distractor items that were inconsistent with the response of a centrally located target, but also a significant improvement in the ability to ignore conflicting information following 6 mo of aerobic fitness training. The ability to successfully ignore or inhibit conflicting information in tasks such as these has been found to be associated with activation of a variety of prefrontal regions such as the DLPFC and the anterior cingulate (Carter et al., 1995).

Subjects will perform four 5.5-min blocks of trials with an equal number of randomly distributed compatible and incompatible trials (i.e., trials on which the target stimulus is flanked by distractors that prime either the same or different response from the target) in each of the experimental blocks. The stimuli will be presented for 1.5 s on each trial followed by 15-s intertrial interval. Thus, subjects will perform a total of 80 experimental trials in the magnet. Subjects will take a 2 min rest between each of the experimental blocks in the magnet. Subjects will also perform three 5.5-min blocks as practice prior to recording the fMRI data.

Progress to Date

Although we have only begun the project within the past few months, we have already developed the event-related fMRI protocols and begun to collect behavioral and functional imaging data. Preliminary data indicates robust frontal, parietal, and occipital activation for the older adults.

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