CHAPTER

4

Aging, Physical Activity, and Neurocognitive Function

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Over the past several decades, numerous researchers have examined age-related differences and changes in perception, cognition, and motor function. Cross-sectional studies have, for the most part, shown relatively linear declines in the great majority of these processes from the 20s through the end of life (Park et al., 2002). Furthermore, the slope of the linear functions is quite similar across different cognitive processes. The potential problem with cross-sectional studies, however, is that age effects are confounded with cohort effects. That is, age-related differences in cognition could be due, in part, to differences in nutrition, medical care, education, and other factors among the different age groups in the studies (Hofer, Sliwinski, & Flaherty, 2002). One way around these potential interpretative difficulties is to examine age-related changes in a within-individual fashion in longitudinal studies. Indeed, there are currently a number of such studies under way. The general consensus from such studies is that while age-related decrements are observed across a wide variety of perceptual, cognitive, and motor abilities, many of these deficits are not observed until after 60 years of age (Schaie, 2004).

Despite the different trajectories observed in cognitive processes in cross-sectional and longitudinal studies of aging, an interesting common observation is that age-related decline is quite broad. However, there are some notable exceptions. For example, it has generally been observed that knowledge-based or crystallized abilities (i.e., the extent to which a person has absorbed the content of culture) such as verbal knowledge and comprehension continue to be maintained or improve over the life span. This is in contrast to process-based or fluid abilities (i.e., reasoning, speed, and other basic abilities not dependent on experience), which display earlier and more dramatic age-related declines. Another interesting observation in the literature on cognitive aging is that there is a large amount of variability in the rate of change of cognitive abilities among older adults (Wilson et al., 2002). An important question, one that we will address in the present chapter, is why such variability is observed.

However, before turning to the main topic of the chapter—the influence of physical activity differences and aerobic fitness training on brain and mind—we provide a brief overview of the literature that has addressed neuroanatomical and neurophysiological changes during the course of aging. Mirroring the cognitive literature, recent studies have shown differences in the time course and magnitude of age-related changes in brain structure. Correlations between age and cortical volume have been reported to be largest for prefrontal regions, somewhat smaller for temporal and parietal areas, and small and often nonsignificant for sensory and motor cortices (Head et al., 2002; Raz, 2000). In general, the disproportionate changes in brain structure across the adult life span parallel findings of age-specific changes in executive control (i.e., processes that involve scheduling, planning, working memory, coordination, and inhibitory control), which are supported in large part by prefrontal and temporal regions of the brain (Robbins et al., 1998; Schretlen et al., 2000).

Changes in human brain function, as indexed by positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies, have also recently been examined; and these studies have resulted in a number of tentative general observations. For example, it has often been reported that older adults show lower levels of activation in a wide variety of tasks and brain regions than younger adults (Logan et al., 2002; Madden et al., 1996). Two different interpretations have been offered for such data. One is that aging is associated with an irreversible loss of neural resources. Another possibility is that resources are available but inadequately recruited. Although the reason or reasons for underrecruitment remain to be determined, some evidence points toward the second possibility. Logan and colleagues (2002) found that underrecruitment of prefrontal regions could be reduced when older adults were instructed to use semantic association strategies during word encoding.

Another frequent observation in PET and fMRI studies is that older adults show nonselective recruitment of brain regions. That is, relative to younger adults performing the same task, older adults often show the recruitment of different brain areas in addition to those activated in the younger adults. Indeed, one variety of nonselective recruitment, the bilateral activation of homologous brain regions, has been codified into a model of neurocognitive aging proposed by Cabeza (2002). The model, referred to as Hemispheric Asymmetry Reduction in Older Adults (HAROLD), suggests that under similar circumstances, cortical activity tends to be less lateralized in older than in younger adults. An important question with regard to this asymmetry is whether the additional activity observed for the older adults is compensatory or a marker of cortical decline (i.e., a failure to recruit specialized neural processors). At present, this is an open question, with some studies indicating that older adults who perform better on a task show bilateral recruitment of homologous areas while older adults who perform more poorly show unilateral activation (Cabeza et al., 2003; Reuter-Lorenz et al., 2000). Other studies have either failed to find a relationship between laterality and performance (Logan et al., 2002) or have shown unilateral prefrontal activation for better-performing older adults and bilateral activation for poorer-performing older adults (Colcombe et al., 2002). However, studies thus far have examined performance–brain activation pattern differences across subjects. Clearly, future studies are needed to examine these relationships within individuals as a function of levels and types of cognitive challenges as well as a function of training and practice. Finally, as with the cognitive literature already described, it has become clear from the human neuroimaging literature that a good deal of individual variability exists in both brain structure and function during the course of aging (see, for example, O'Sullivan et al., 2001).

Despite the picture of aging painted by the literature just discussed, in recent years a number of studies have begun both to characterize the factors that lead to successful aging and to examine interventions that can improve cognition, brain structure, and function of older adults. An extensive review of this literature is clearly beyond the scope of the present chapter (see Kramer et al., 2004, for a discussion of this literature); however, cognitive and aerobic exercise training are two interventions that have been found to improve the cognitive and brain function of older humans.

Fitness and Behavioral Indices of Cognition

As discussed in the preceding section, although decrements in cognition occur during aging, certain lifestyle factors and interventions have been found to moderate age-related changes in selective aspects of cognition. One such moderating factor, and the central topic of this chapter, is physical activity or exercise. There is a relatively extensive history of studies examining the influence of aerobic exercise training on the cognitive function of older adults. Unfortunately, however, the results of these studies, with regard to whether or not beneficial effects of exercise training are observed on behavioral indices of cognition, have been mixed. The ambiguous nature of these results could be due to a number of factors, including relatively small sample sizes and therefore low statistical power in the great majority of intervention studies. Colcombe and Kramer (2003) performed a meta-analysis of randomized intervention trials in an effort to increase the power to detect potential effects of fitness training, most notably aerobic exercise training, and also to examine the influence of moderating factors on the relationship between fitness and cognition.

Physical activity intervention studies published 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 exercise

training was found. Thus, when one aggregates across studies, exercise training does indeed have positive effects on the cognitive function of older humans. Second, exercise training had both general and selective effects on cognitive function. Although exercise effects were observed across a wide variety of tasks and cognitive processes, the effects were largest for those tasks that involved executive control processes (Kramer et al., 1999; i.e., planning, scheduling, working memory, interference control, task coordination). 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 exercise training and cognition. For example, aerobic exercise training programs that were combined with strength and flexibility training regimens had a greater positive effect on cognition than exercise 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. Insulin-like growth factor-1 is a neuroprotective factor involved in neuronal growth and differentiation (Carro et al., 2001; Cotman & Berchtold, 2002). Exercise training programs also had a larger impact on cognition if the study samples included more than 50% females. This effect may be due, 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 & Berchtold, 2002). Estrogen has been found to upregulate BDNF, a neurotrophic molecule that is also increased by exercise. Apparently, a normal estrogen level in exercising animals is necessary for maintaining voluntary activity levels (Berchtold et al., 2001). Both estrogen and BDNF are important for synaptogenesis and neurogenesis, especially in the hippocampal region (Klintsova & Greenough, 1999; Tanapat et al., 1999). Finally, exercise effects on cognition were found to be largest for exercise training interventions that exceeded 30 min per session.

A number of recent prospective studies with fairly large numbers of older participants have also shown that fitness training and physical activity are beneficial for maintaining cognitive vitality in old age. For example, Yaffe and colleagues (2001) reported a study of 5,925 high-functioning community-dwelling women, all greater than 65 years of age, who reported their activities including the number of blocks that they walked per week. The central question addressed in the study was whether higher levels of activity, particularly the number of blocks walked per week, would serve a protective function for cognition six to eight years in the future. Indeed, women with greater physical activity levels at baseline were less likely to experience cognitive decline as assessed with the mini-mental status exam (MMSE) during six to eight years of follow-up. This effect remained even after adjustment for age, educational level, health status, depression, stroke, diabetes, hypertension, smoking, and estrogen use. A similar study (Barnes et al., 2003) with a smaller male and female sample of older adults (349 participants 55 years of age and older at time 1) also showed that fitness level at baseline predicted higher levels of cognitive performance six years later. This study was noteworthy in that it used an objective measure of aerobic fitness, $\dot{V}O_2$peak, and also assessed a wider variety of cognitive processes. Indeed, higher levels of aerobic fitness at baseline predicted sparing of a number of different measures of attention and executive function.

Other studies have also shown that physical activity can have protective effects on the cognition function of middle-aged individuals. Richards, Hardy, and Wadsworth (2003) reported that physical activity level at 36 years of age was predictive of higher levels of verbal memory in a sample of 1,919 participants from 43 to 53 years of age. Interestingly, spare time activities such as game playing, attending religious services, or playing a musical instrument were not predictive of memory performance in these individuals from 43 to 53 years of age. Finally, Laurin and colleagues (2001) reported that compared to no exercise, physical activity level at baseline was associated with lower risks of cognitive impairment, Alzheimer's disease, and dementia of any type five years after assessment. All of the participants in this study (4,615 individuals) were high-functioning 65^{+}-year-olds at the baseline assessment (see also Teri et al., 2003).

The results of these investigations suggest that modest levels of physical activity and aerobic fitness can have beneficial effects on a number of cognitive processes, especially executive control processes, of middle-aged and older individuals.

Fitness Effects on Brain Function and Structure

We turn now to an examination of the literature that has gone beyond performance-based measures of cognition in an effort to examine the influence of fitness levels and training on brain function and structure.

Event-Related Brain Potentials

As first discovered by Berger (1929/1969), neural activity in the cerebral cortex and subcortical areas produces electrical potentials at the scalp, and the electroencephalogram (EEG) can be recorded as a time series of the fluctuating voltages. The recorded neuroelectric activity (i.e., EEG) can be decomposed along two basic properties, frequency and amplitude. The amplitude of EEG, which is the topic of the current section, is measured in microvolts (μV) and is indicative of the relative size of the bioelectrical signal. The frequency of the recorded EEG signal is discussed in detail in chapter 8 of this volume.

Research on the temporal dynamics of the neuroelectric system has further focused on a class of EEG activity known as event-related brain potentials (ERPs), which have been found to be particularly susceptible to physical activity and aerobic exercise participation. ERPs reflect neuroelectric activity time-locked to a stimulus or response. In particular, the P3, a positive waveform that peaks approximately 300 to 800 msec after stimulus onset, is an endogenous component of an ERP that has captured considerable attention in the literature and has been related to attentional allocation and updating of memory. The amplitude of the P3 component reflects changes in the neural representation of the environment and is proportional to the amount of attentional resources needed to engage in a given task, with more attention increasing P3 amplitude (Polich & Heine, 1996). The latency of P3 is a measure of stimulus classification speed, with longer latencies reflecting increased processing time (Duncan-Johnson, 1981).

To the best of our knowledge, only a few studies have been conducted that have examined acute aerobic exercise effects on the P3 (see table 4.1). Specifically, two of the studies examined the effects of an acute bout of running on cognitive function using an auditory discrimination paradigm, known as the oddball task. This task requires participants to discriminate between two stimuli with differing probabilities and to respond selectively to the infrequent stimulus while ignoring the more frequent stimulus. Results indicated an increase in P3 amplitude (Magnie et al., 2000; Nakamura et al., 1999) and a decrease in P3 latency (Magnie et al., 2000) following acute aerobic exercise when compared to baseline. These results suggest that acute bouts of aerobic exercise may aid cognitive function related to both attentional allocation and memory updating, as well as increase stimulus-processing speed. Hillman, Snook, and Jerome (2003) measured the same relationship using a flanker task, which requires variable amounts of inhibitory control—one component of executive control. This task requires participants to respond as quickly as possible to a centrally presented target letter that appears among an array of distracting letters. In the Hillman, Snook, and Jerome (2003) study, neutral and incompatible conditions were presented to examine variable amounts of inhibitory control. In the neutral condition, the target letter was flanked by other letters with no response assignment. In the incompatible condition, the target letter was flanked by other letters requiring an alternate response. Hillman, Snook, and Jerome (2003) found an increase in P3 amplitude following exercise, suggesting that acute aerobic exercise may enhance attentional allocation. P3 latency was unchanged for the condition requiring less inhibitory control (i.e., neutral flanker condition) and decreased for the condition requiring greater inhibitory control (i.e., incompatible flanker condition) following exercise. The increase in P3 latency in the neutral condition may be the result of fatigue, while the decrease in P3 latency in the incompatible condition suggests enhanced inhibitory control. It is important to point out that in all three studies, posttesting occurred only after participants' heart rate had returned to preexercise baseline levels; hence, the observed differences in the P3 measures can be associated with the beneficial effects of exercise participation rather than a more general physiological arousal.

The majority of research examining the influence of chronic exercise participation on cognition has done so with older adults. The goal in these studies was to determine whether greater amounts of aerobic exercise participation can reduce age-related cognitive decline. Aging effects on the P3 component have been found to be robust. For example, Picton and colleagues (1984) employed auditory stimuli to elicit the P3 from participants

Table 4.1 Summary of Event-Related Brain Potential Studies on Acute and Chronic Physical Activity Influences on Cognition

Investigators	Subjects	Design	Procedure and task	Findings
			Acute exercise	
Hillman et al. (2003)	20 males and females (M = 20.5 yr)	Within-subjects; pre-post design	E: 30 min treadmill run C: preexercise baseline Eriksen flanker task	*P3 amplitude:* increased at all sites *P3 latency:* condition effect at baseline, no condition effect following exercise
Magnie et al. (2000)	20 males (18-30 yr)	Pre-post design; cross-sectional	E: graded exercise stress test on cycle ergometer C: preexercise baseline P3—auditory oddball task N4—sentence task	*P3 amplitude:* increased amplitude at all sites for posttest regardless of fitness level *P3 latency:* decreased latency at all sites for posttest regardless of fitness level *N4 amplitude:* increased amplitude at posttest regardless of fitness level; effect observed only for incongruent sentences
Nakamura et al. (1999)	7 males (29-44 yr)	Within-subjects; pre-post design	E: 30 min self-paced jogging C: preexercise baseline Auditory oddball task	*P3 amplitude:* increased amplitude at central and parietal sites for posttest *P3 latency:* no exercise effect
			Chronic exercise	
Bashore (1989)	90 older males (60-84 yr) 50 younger males (20-35 yr)	Age × fitness; cross-sectional	Speeded perceptual task	*Statistical analyses were not performed, descriptive results only* *P3 amplitude:* increased amplitude for high- compared to low-fit older males *P3 latency:* faster latency for high- compared to low-fit older males
Hillman et al. (2005)	24 male and female children (7-11 yr), 27 male and female adults (18-22 yr)	Age × physical activity; cross-sectional	Visual oddball task	*P3 amplitude:* increased amplitude for high-fit children compared to other groups *P3 latency:* faster latency for the high-fit compared to the low-fit group
Dustman et al. (1990)	30 older (50-62 yr) and 30 younger (20-31 yr) males	Age × fitness; cross-sectional	Visual oddball task	*P3 amplitude:* not reported *P3 latency:* faster latency for older high- compared to low-fit males *A/I slope:* larger for low- compared to high-fit males

(continued)

Table 4.1 *(continued)*

Investigators	Subjects	Design	Procedure and task	Findings
		Chronic exercise		
Hillman et al. (2002)	48 older (64.2 yr) and younger (22.8 yr) males and females	Age × fitness; cross-sectional	Speeded perceptual task	*P3 amplitude:* no fitness effect *P3 latency:* faster for older fit adults compared to older sedentary adults *CNV amplitude:* decreased amplitude for fit compared to sedentary adults *SPN amplitude:* no fitness effect
Hillman et al. (2004)	32 older (M = 66.8 yr) and younger (M = 20.4 yr) males and females	Age × physical activity; cross-sectional	Eriksen flanker task	*P3 amplitude:* increased amplitude at frontal sites for moderate- and high-active older adults compared to younger adults *P3 latency:* increased physical activity related to decreased latency in older adults
Hillman et al. (in press)	66 older (M = 64.8 yr) and younger (19.4 yr) males and females	Age × physical activity; cross-sectional	Task switching	*P3 amplitude:* increased amplitude at frontal sites for high-active compared to low-active older adults and high- and low-active younger adults *P3 latency:* faster latency for active compared to sedentary, regardless of age
McDowell et al. (2003)	36 older (M = 67.7 yr) and 37 younger (22.7 yr) males	Age × fitness; cross-sectional	Visual oddball task	*P3 amplitude:* increased amplitude for high- compared to low-fit subjects, regardless of age *P3 latency:* no fitness effect *P3 AUC:* increased AUC for older low- compared to high-fit males
Polich & Lardon (1997)	11 high- (M = 30.0 yr) and 11 low-active (M = 34.7 yr) adults	Physical activity; cross-sectional	Visual and auditory oddball tasks	*P3 amplitude:* increased amplitude for high compared to low active *P3 latency:* no physical activity effects

Note: A/I slope: Amplitude/Intensity slope; CNV: Contingent Negative Variation; SPN: Stimulus Preceding Negativity; AUC: Area Under the Curve.

of different age groups (20-79 years, 12 from each decade). P3 amplitude declined with age at a rate of 0.18 μV per year after age 40, and the scalp distribution became more frontal due to age-related decreases in amplitude at the vertex (Cz) of the scalp. Further, P3 latency was observed to increase at a rate of 1.36 msec per year, indicating decreased stimulus classification speed with age.

To date, few reports on the P3 potential have appeared in the physical activity and cognition literature, with two other reports from our laboratory that are currently under review (see table 4.1). The relationship between physical activity and P3 latency appears robust, since decreased latency has been related to increased aerobic exercise participation in most reports (Bashore, 1989; Dustman et al., 1990; Hillman et al., 2002, 2004, in press). As already noted, findings have revealed that older individuals show increased latency compared to younger adults (Polich, 1996), indicating slower processing speed. However, habitual participation in aerobic exercise or physical activity has been shown to decrease P3 differences between older and younger individuals, indicating that aerobic exercise, in part, may help to maintain overall central nervous system (CNS) health (Dustman et al., 1993). Dustman and colleagues (1990) observed that P3 latency was faster in aerobically trained, compared to sedentary, older men in response to an auditory oddball task. In fact, the decrease in P3 latency was observed between older fit and both fit and sedentary younger adults, suggesting that aerobic exercise may help to reduce age-related slowing of cognitive processing—supporting aerobic fitness as a potential mediator of CNS degradation in older adults. Other studies have supported this finding (Bashore, 1989; Hillman et al., 2002, 2004, in press); but most notably, Hillman and colleagues (2004) measured P3 latency in older adults with a history of low, moderate, and high amounts of physical activity participation and a younger adult control group using a flanker task. Results indicated that P3 latency decreased with increased levels of exercise participation.

However, two other studies failed to find physical activity effects on P3 latency using oddball tasks. In the case of Polich and Lardon's study (1997), the observed lack of relationship between physical activity and P3 latency may be explained by their participant sample, which was composed of young adults (i.e., 34.7 and 30.0 years for low and high exercisers, respectively) who were rather heterogeneous in their physical activity participation (i.e., aerobic exercisers, racket sport athletes, etc.). As mentioned earlier, previous P3 research has not evidenced slowing of P3 latency until approximately 40 years of age; thus the observed similarity between high and low exercisers may have been due to a ceiling effect related to CNS health in younger adults. McDowell et al. (2003) also failed to observe significant differences in P3 latency as a function of physical activity level. However, an explanation of this lack of significance is not readily obvious given that several other studies have observed this relationship using similar tasks.

P3 amplitude has also been found to be affected by chronic physical activity participation. In a sample of young adults, those who participated in greater amounts of exercise had larger P3 amplitude along midline recording sites in response to both visual and auditory oddball tasks (Polich & Lardon, 1997). Other researchers have corroborated these findings (Hillman et al., in press; McDowell et al., 2003). Specifically, Hillman and colleagues (in press) observed increased P3 amplitude, but only at electrode sites overlying the frontal and parietal scalp regions, using a task switching paradigm that requires individuals to alternate between two different tasks. In this study, high physically active older adults had increased amplitude at frontal scalp sites, and high physically active younger adults had increased amplitude at parietal scalp sites, when compared to the other three groups. Hillman and colleagues (2005) corroborated these findings in a sample of high- and low-fit preadolescent children and fitness-matched young adult groups, as increased P3 amplitude was observed across midline sites for the high-fit children compared to the other three groups using a visual oddball task. Taken together, the results of these studies indicate that increased participation in aerobic exercise is related to changes in the neuroelectric system that underlie improvements in cognitive processing.

Several mechanisms for the relationship between aerobic exercise and differences or changes in neuroelectric activity have been suggested. One mechanism by which physical activity has been theorized to affect the P3 component is through underlying EEG activity (Polich & Lardon, 1997). In support of this notion, Kubitz and her colleagues (Kubitz & Mott, 1996; Kubitz & Pothakos, 1997) showed increased spectral EEG alpha activation (8-13 Hz activity) following acute bouts of submaximal aerobic exercise and suggested that exercise may serve to increase neuronal

synchrony (also see Petruzzello, Ekkekakis, & Hall, chapter 8 in this text). Further, Polich (1997) has shown that interparticipant variations in spectral alpha power are related to individual variability in the P3 component, indicating that changes in resting EEG activity may directly influence ERPs. According to this view, aerobic exercise helps to increase the amount of alpha activity, which in turn increases P3 amplitude and decreases P3 latency. Some support for the relationship between the P3 component and resting EEG alpha has been reported (Bashore, 1989; Dustman et al., 1990; Lardon & Polich, 1996). Less clear, though, is the relationship between aerobic exercise and changes in alpha activity. Dustman and colleagues (1990, 1994) surmised that aerobic exercise promotes increased cerebral blood flow, which improves neurotransmitter function and cerebral vascularization among other neurobiological changes. Further discussion regarding potential mechanisms for aerobic exercise effects on cognitive function is presented later in this chapter.

Aging, Fitness, and Brain Structure

As discussed previously, a number of age-related changes have been observed in both human gray (brain tissue composed of neuronal cell bodies and supporting structures) and white matter (brain tissue composed primarily of myelinated nerve fibers), and these changes have in turn been related to changes in the efficiency of cognitive processes. Regionally specific age-related decreases in the volume of gray matter have been related to declines in a variety of cognitive processes. For example, Raz and colleagues (1998) reported that age-related differences in frontal gray matter volume were predictive of increases in the number of preservative errors on the Wisconsin Card Sorting Test, while Head and colleagues (2002) reported that decreases in prefrontal cortical volume were associated with reduced solution speed on the Tower of Hanoi puzzle and working memory performance (see also Meguro et al., 2001). Changes in gray matter volume could be the result of a number of factors, including neuron loss, neuron shrinkage, reduction in dendritic arborization, and changes in glia (Scheibel, 1996; Vinters, 2001). Age-related decreases in white matter volume and therefore connectivity have also been reported. These changes relate to decreases in the performance on a number of cognitive tasks (Davatzikos & Resnick, 2002; O'Sullivan et al., 2001; Sullivan et al., 2002) and are likely the result of demyelination of axons.

Given previous reports (see van Praag, chapter 5 in this volume, for a detailed discussion of this literature) of cortical plasticity in older animals placed in enriched environments (Kempermann, Kuhn, & Gage, 1998; Kolb, Gibb, & Robinson, 2003; Rosenzweig & Bennett, 1996) and with aerobic exercise training interventions (Black et al., 1990; Cotman & Berchtold, 2002; van Praag, Kempermann, & Gage, 1999), one could ask whether similar changes would be observed in humans. Three recent studies suggest that this might indeed be the case. These studies employed a technique called Voxel-based morphology (VBM). 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 or volume as a function of some other variable. This technique allows examination of the entire brain in a point-by-point fashion, revealing spatially precise estimates of systematic variation in brain tissues. Voxel-based morphology 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 and colleagues (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 literatures, there was a significant reduction of declines in these areas as a function of aerobic fitness. That is, older adults who had better aerobic 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 aerobic fitness.

Draganski and colleagues (2004) asked whether change in brain structure could be observed when a group of young adults were trained to juggle. Voxel-based morphology analysis was applied to high-resolution magnetic resonance imaging (MRI) scans obtained before and after a three-month training period, as well as three months after the

cessation of training. Individuals who participated in the training were compared to individuals who were not trained to juggle. Bilateral increases in gray matter were found for the trained group in midtemporal regions (MT/V5) and in the left posterior intraparietal sulcus when the MRIs obtained before training were compared to those obtained immediately after the three-month training intervention. Both of the regions in which increased volume was observed have been related to the processing of motion. Interestingly, the volumes in these regions decreased at the last assessment, that is, when subjects were no longer juggling.

Finally, Colcombe and colleagues (2004) examined the influence of a six-month aerobic fitness training on the brain structure of older healthy but sedentary adults. High-resolution MRIs were obtained from 30 subjects in the aerobic exercise training group (i.e., walking) and from another 30 control subjects in a stretching and toning training group. Although preliminary, the results for changes in brain volume were quite similar to those obtained in the cross-sectional exercise training study conducted by Colcombe and colleagues (2003).

In summary, although there are still few studies on the influence of physical activity (i.e., both aerobic and motor skills) on human brain structure, the initial findings are quite promising. Of course, there is much left to discover, including the influence of the observed brain changes on selective components of perception, cognition, and motor processes; the amount and types of training required to induce changes in brain structure; the amount of training required to maintain increases in volume; and the nature of the morphological changes that underlie the measures obtained from the high-resolution MRIs.

Aging, Fitness, and Brain Function

In recent years, both PET and fMRI have been increasingly used to examine changes in the cortical dynamics that underlie cognition and aging. Given their relatively high spatial resolution, both of these techniques provide an ideal complement to the high temporal but poor spatial resolution of EEG and ERP measures. Both PET and fMRI are used to image functional activity in the brain, often as an individual is performing a specific task. Both of these techniques involve inferring changes in neuronal activity from changes in blood flow or metabolic activity in the brain (Reiman et al., 2000). In PET, cerebral blood flow and metabolic activity are measured on the basis of clearance of radionuclides from cortical tissues. These radionuclides, which are either inhaled or injected, decay by the emission of positrons that combine with electrons to produce gamma rays, which are detected by a series of sensors placed around the head. Each PET image, which is acquired over an interval of anywhere from 1 to 45 min depending on the nature of the radionuclide employed, represents all of the brain activity during the integration period. These PET images are then coregistered with structural scans, often obtained from MRIs, to indicate the location of the functional activity. Functional MRI is similar to PET in that it provides a map of functional activity of the brain. However, fMRI activity can be obtained more quickly (within a few seconds), does not depend on the inhalation or injection of radioactive isotopes, and can be collected in the same system as the structural information. The blood oxygen level dependent technique (BOLD) of fMRI uses the perturbation of local magnetic fields due to changes in the oxygen content of blood during increased blood flow to image functional brain activity (Belliveau et al., 1991; Ogawa & Lee, 1990).

Neuroimaging techniques like those described earlier were used in two studies examining the relationships among fitness or activity level, cognition, and brain function. Rogers, Meyer, and Mortel (1990) conducted a prospective study with 90 older adults to determine the relationship between physical activity, cerebral blood flow, and cognition. Measures of regional cerebral blood flow and physical activity were obtained from 60^{+}-year-olds who were either still employed or retired. Over a four-year follow-up period, individuals who reduced their activity level were also found to have reductions in global measures of brain blood flow and on general measures of cognitive function. Although this study did not have the benefits of randomized assignment of subjects to experimental groups, it does suggest that further study of the relationship among physical activity, cognition, and brain function should be pursued.

To that end, Colcombe and colleagues (2004) examined the influence of a six-month program of exercise training designed to improve aerobic fitness, as compared to a program in which a control group of older adults were trained in stretching and toning, on brain function and cognition. Participants in the randomized intervention performed a 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. On 50% of the trials, the orientation of the distracting stimuli was consistent with the central cue (e.g. "<<<<<"), while on the other 50% the distracting stimuli were oriented inconsistently with the central cue (e.g. ">><>>"). On inconsistent trials, participants were required to suppress the information provided by the flanking stimuli in order to make a correct response. This paradigm was employed because it has previously been found to be sensitive to age-related decrements in attentional control as well as to show improvements in performance with increments in aerobic fitness (Kramer et al., 1999).

Results indicated that after six months of aerobic exercise training the older adults showed improved performance, particularly in terms of reducing their response times to the incompatible trials (in which subjects would need to selectively process the target and ignore the incompatible distractors), while the participants in the nonaerobic stretching and toning group did not. Furthermore, the aerobically trained participants showed increased activation in the superior parietal cortex and middle frontal gyrus, brain regions responsible for assisting in the focus of spatial attention and maintaining task goals in working memory, respectively. On the other hand, individuals in the nonaerobic group showed increased activation in the anterior cingulate cortex, a brain region that assists in resolving response conflicts. One interpretation of this pattern of results is that higher levels of aerobic fitness lead to more efficient prefrontal control of extrastriate and parietal regions of cortex that are responsible for the selective processing of stimulus attributes (Corbetta, 1998; Posner & DiGirolamo, 1998). Thus, these results suggest that exercise participation leading to improved aerobic fitness may provide a prophylactic effect to the functional integrity of the older adult brain.

Potential Mechanisms

An in-depth discussion of the mechanisms that underlie physical activity effects on brain and cognition is beyond the scope of this chapter (see van Praag in the present volume). However, there appear, at present, to be at least several different plausible biological mechanisms. First, a growing body of animal research has demonstrated a variety of molecular, vascular, and cellular changes in the brain in response to increased aerobic fitness (often engendered through wheel running). For example, aerobic exercise training in aging animals has been shown to increase levels of key neurochemicals that improve plasticity and neuronal survival, such as BDNF and IGF-1 (BDNF, Neeper et al., 1995; IGF-1, Carro et al., 2001), serotonin (Blomstrand et al., 1989), and dopamine (Spirduso & Farrar, 1981). Other studies have shown that aerobic exercise interventions increase the development of new capillaries, presumably to support increased neuronal firing, in rodents (Black et al., 1990; Isaacs et al., 1992) and primates (Rhyu et al., 2003). Indeed, this added vasculature has been demonstrated to be functional: Activity wheel–exercised rats have both a greater resting blood flow and a greater "reserve capacity" in response to increased oxygen demand compared with those not allowed to exercise (Swain et al., 2003). Finally, there have been a number of recent demonstrations of enhanced learning and memory (Anderson et al., 2000; van Praag, Kempermann, & Gage, 1999) and hippocampal neurogenesis (van Praag, Kempermann, & Gage, 1999; Rhodes et al., 2003; Trejo, Carro, & Torres-Aleman, 2001) with aerobic exercise training. These changes occur throughout the course of training and suggest a direct effect of fitness training on neurochemistry and brain structure.

Second, aerobic exercise training can exert its influence on cognition and brain through the reduction of vascular disease, including diabetes, hypertension, and heart disease. Each of these diseases can negatively influence cognition and hasten the development of Alzheimer's dementia (Fenster, Darley-Usmar, & Patel, 2002; Launer et al., 2000). Finally, inflammatory and immunological mechanisms are increasingly implicated in the pathogenesis of several age-related diseases including Alzheimer's (AD) and vascular dementias. Hallmarks of AD include chronic inflammation and significantly elevated levels of the acute-phase reactant C-reactive protein (CRP) and the proinflammatory cytokine interleukin-6 (IL-6) in amyloid plaques and microvessels. Furthermore, recent studies have indicated that elevated blood serum levels of CRP and IL-6 are also associated with cognitive deficits cross-sectionally and that they predict cognitive decline prospectively in nonpathological aged samples (Weaver et al., 2002; Yaffe et al., 2003). This suggests that elevated CRP and IL-6 may play a role in accelerating "normal" age-related neurocognitive decline or, conversely, that reducing CRP and IL-6

levels may slow deleterious changes in the aging brain. Although acute bouts of exercise transiently increase inflammatory markers, recent evidence suggests that chronic physical activity may reduce inflammatory markers in nonpathological humans (Ford, 2002; Reuben et al., 2003). Such findings hint that exercise may also exert positive effects on the CNS by reducing serum levels of proinflammatory molecules such as CRP and IL-6.

Thus, in summary, physical activity—and in particular exercise aimed at improving aerobic fitness—likely influences cognition and brain structure and function, both directly through its effects on brain structure and neurochemistry and indirectly by reducing inflammatory and other processes that are responsible, in part, for increased incidence of vascular disease.

Directions for Future Investigation

The studies reviewed in this chapter clearly suggest that physical activity and aerobic exercise training can serve to moderate undesirable age-related changes in cognition, brain function, and brain structure. Importantly, these data add substantially to the growing literature suggesting that cognitive and brain plasticity is maintained, albeit to a lesser extent than for younger individuals, well into old age. Such results have important implications both for our understanding of aging and from a public health standpoint.

There are, however, many unanswered questions with regard to the relationship between physical activity, aging, cognition, and the brain. For example, we do not yet know how much and what types of physical activity training produce the most rapid and robust effects on cognition and the brain. We are also ignorant about the extent to which the same or different biological mechanisms subserve exercise training and other interventions, such as cognitive training, social interventions, and nutritional programs, that have shown promise in reducing age-related declines in cognition and brain function. Indeed, to our knowledge there have been only two studies that contrasted the separate and joint effects of cognitive and fitness training on performance-based metrics of selective aspects of cognition, and these studies have come to opposite conclusions with regard to whether the effects of these two training modes are additive or interactive (Fabre et al., 1999, 2002).

There is also little knowledge about the moderating influences of specific genotypes on the magnitude of cognitive and brain effects of interventions such as aerobic exercise training. A recent study showed that physical activity level strongly interacted with the presence of an e4 allele on the APOE gene, a gene implicated in cognitive deficits and AD. Indeed, the researchers observed that high levels of activity reduced the negative effects of an e4 allele on the MMSE (Schuit et al., 2001). Given the rapidly developing knowledge about the relationship of allelic variation of genes with single nucleotide polymorphisms to neurotransmitter systems and neurotrophins and, in turn, the influence on specific aspects of cognition, the marriage of molecular genetics and intervention-based research is another fertile area for future inquiry (Greenwood & Parasuraman, 2003).

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