Kinesiology and Mental Health: The Promise of Exercise Neuroscience Research for Diseases and Disorders of the Brain

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The relevance of kinesiology to the major issues of public health facing the nation is increasing with time. Of great importance is the area of exercise neuroscience in which remarkable developments have occurred in the past 35 years. The primary investigative efforts to date have been devoted to the impact of exercise on normal brain aging and recent efforts have also focused on the neurocognitive benefit to brain development in children. However, little work has been conducted in those with neurological disorders. The literature includes a number of animal studies that offer biological plausibility for the positive influence of exercise observed on brain structure and cognition in normal human subjects and, collectively, these studies provide a foundation on which to examine the role of exercise treatment in some of the major brain disorders that afflict adults and children today. These include the dementias, stroke, traumatic brain disorder (TBI), post-traumatic stress disorder (PTSD), and attentional deficit and hyperactivity disorder (ADHD). A role for exercise in building resilience to such disorders is discussed here that may assist in reducing the financial and emotional burden of these afflictions.

The purpose of this paper is to discuss the relevance of the research in exercise neuroscience to public health imperatives facing the nation in the area of neuropathology—that is, the benefits of exercise to diseases and disorders of the brain. Scientific studies of the influence of exercise on normal aging of the brain and cognition largely began to appear in the literature approximately 35 years ago and employed both animal and human subjects (see review by Spirduso, 1983). However, studies of the benefits of exercise to neurocognitive function in clinical populations (with animal subjects as analogs) have only recently appeared in the literature largely in the past eight years (Griesbach, Hovda, Molteni, Wu, & Gomez-Pinilla, 2004). The work with patients and human subjects is even more recent (Baker et al., 2010). Collectively, the corpus of work that has emerged offers great promise for prevention and treatment of some of the major disorders of the human brain. More specifically, there is compelling evidence to authorize investigation of exercise in the treatment of Alzheimer’s disease (AD), Mild Cognitive Impairment (MCI), Traumatic Brain Injury (TBI), Stroke, Post-Traumatic Stress Disorder (PTSD), and Attention Deficit Hyperactivity Disorder (ADHD) in children. In fact, the role of physical activity in the development of children’s brains, which holds significant implications for their academic performance, may promote resilience to such brain disorders and trauma in later life.

For clarity, it is important to differentiate among the terms physical activity, exercise, and physical fitness (i.e., cardiovascular and muscular) although these are often used interchangeably in the literature. Physical activity is “any bodily movement produced by skeletal muscles that results in energy expenditure” (Caspersen, Powell, & Christenson, 1985, p.126) while exercise is a process characterized by “physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective” (Caspersen et al., p.128). Physical fitness characterizes the status of an individual as comprised by a set of attributes, specifically: cardiorespiratory endurance, muscular endurance, muscular strength, body composition, and flexibility (Caspersen et al.). Investigations of exercise interventions allow for determination of the causal influence of such physical activity on brain structure and function whereas studies of comparative fitness levels are limited to correlational relationships and only suggestive of influence. Assessment of physical fitness is typically conducted in intervention studies to determine the effect of exercise on cardiovascular fitness and to address the dose-response relationship. Although less examined, the impact of exercise in the form of resistance training bears consideration, too, in light of the release of growth hormone and insulin-like growth factors IG-F that may also provide a benefit to the nervous system. In this manner, randomized clinical trials (RCT) of exercise interventions on brain and/or behavior are the sine qua non of the scientific literature to guide policy and practice.

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The major issue discussed in this paper is the contribution of a physically active lifestyle of sufficient intensity to the development of resilience and tolerance to brain aging, pathology, and insult. Such a preventive medicine perspective is distinguished from a rehabilitative effect, but it is reasonable to speculate, based on both logic and empirical findings, that exercise also contributes directly to recovery from disease or insult (e.g., concussive trauma) in some cases. In this sense, physical activity and exercise may promote overlapping preventive and restorative neural processes that alleviate suffering, but the major role is likely the promotion of resilience. As an illustration of exercise-induced resilience, the amyloid plaques and neurofibrillary tangles associated with AD may not be ‘cured’ by an aerobic exercise intervention or treatment. However, the contribution of exercise to thickening of the cerebral cortex (i.e., gray matter) (Colcombe et al., 2003) and any angiogenic effects that enhance the vasculature of the brain before disease onset (Rogers, Meyer, & Mortel, 1990) could reasonably enhance one’s tolerance to the pathology and delay any symptoms of cognitive impairment. In this manner, the individual builds sufficient neural integrity or reserve capacity to ‘absorb’ the pathology present in the brain and maintains cognitive performance as illustrated in Figure 1. A financial analogy would be the availability of cash reserves when loss of income occurs such that expenses can be met. On the other hand, as an illustration of rehabilitation, it may be that the neurotrophic (i.e., brain nourishing) effect of exercise on the central nervous system (CNS) directly counters trauma due to impact (i.e., TBI) through restoration of the injured blood vessels and neurons, thus allowing for healing and recovery to normal neurocognitive function (Molteni, Zheng, Ying, Gomez-Pinilla, & Twiss, 2004).

Coping with injury- or pathology-induced impairment to normal function may also be enabled by compensatory activity of the brain, either in the form of elevated neural activity or the recruitment of ‘new’ neural networks (or both) during cognitive challenge, which could also maintain or approach normal cognitive performance. Based on these examples, exercise may be conceived both as preventive and rehabilitative medicine, but in either case evidence is emerging that ‘exercise is medicine’ in the case of neural disease and trauma.

A number of concepts will be introduced in the paper that can serve to explain the role of physical activity as well as aerobic and resistance exercise in the emergence and management of the neurological disorders listed above. Specifically, the contribution of physical activity and exercise to cognitive reserve will be highlighted below as a process that will extend or delay the threshold for the expression of symptoms of neural decline (Scarmeas & Stern, 2003; Stern, 2002). The notion of synchronous exercise-induced benefit, which refers to positive neurobiological adaptations in the presence of advancing pathology will also be described as a process that can attenuate the emergence of cognitive impairment. In addition, the notion of compensation will be discussed and how the measurement of this process with neuroimaging tools can provide a forecast of future cognitive performance (Sperling, 2007). The notion that exercise is ‘essential medicine’ for some, such as those who are genetically at risk for neurocognitive decline, will be discussed, as will the concept of exercise as an investment hypothesis against future decline—this notion has particular implications for children who are characterized by remarkable brain plasticity and who may derive long-term benefit from exercise during this critical developmental phase.

Figure 1 — Cognitive function in individuals characterized by low and high cognitive reserve over time after presence of neuro-pathology. Adapted from B.D. Hatfield and P. Kaplan (2012), Exercise psychology for the personal trainer. In NSCA’s Essentials of personal training (2nd ed.), edited by J.W. Coburn and M.H. Malek (Champaign, IL: Human Kinetics).
That we are poised to consider the treatment of brain disorders with exercise is a testament to the landmark studies and pioneering investigators who conducted innovative research in this area. The accrual of scientific developments over a relatively short span of time is remarkable and largely began with the work of Spirduso and colleagues (1975; 1980; 1983) who first reported the relationship between physical activity and reaction time such that those who were more active exhibited superior speed of reaction relative to age-matched individuals who were sedentary. The importance of the finding was eloquently articulated by Birren, Woods, & Williams, (1979) who described reaction time as an “indicator of central nervous system integrity in the aged (p. 654).” Spirduso’s work also addressed the relevance of physical activity to the management of Parkinson’s disease (PD), via the maintenance of the central neurotransmitter dopamine (DA) as PD results when DA levels drop abnormally low (Spirduso, 1983). This program of research was followed by that of Dustman and colleagues (1984) who reported the results of one of the first exercise interventions and noted numerous cognitive and sensory-perceptual benefits induced via training in older men and women after six months of cardiovascular conditioning. Dustman et al. (1990) later published findings from a seminal psychophysiological study in which event-related potentials (ERPs), derived from electroencephalography (EEG), were employed to contrast the speed and efficiency of the brain’s response to sensory and cognitive challenge between high-fit and low-fit older and younger men (i.e., four groups measured for cardiovascular fitness). Importantly, the study revealed that older men who were characterized by high fitness exhibited similar neural responses to those of young men for a number of the tests employed. This was the first study to my knowledge that examined the benefits of cardiovascular fitness employing an imaging measure of human brain function—a noteworthy development of only 20 years ago!

Subsequently, several significant developments occurred during the 1990s that propelled the field of exercise neuroscience forward. In the area of cerebral circulation, Rogers and colleagues (1990) published a truly provocative paper, using positron emission tomography (PET), which revealed higher cerebral perfusion (regional cerebral blood flow) in older physically active men and women relative to their less active counterparts. The longitudinal study approach strongly suggests that a physically active lifestyle positively impacts the vascular integrity of the human brain. The first animal studies directed by William Greenough and colleagues at the University of Illinois (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Isaacs, Anderson, Alcantara, Black, & Greenough,1992) also appeared in the literature at this time and revealed that exercise training in the form of running exerted a significant angiogenic influence on the brain—that is, an enhancement of capillary density, while coordinated movement activities specifically affected synaptogenic activity in the cerebellum. Such an effect implies specificity of brain adaptation to exercise as the impact of fitness on various structures seems to be constrained to certain regions and by the nature of the exercise (e.g., endurance running vs resistance training vs complex coordinated movement).

In addition, the lines of investigation directed by Carl Cotman and Fred Gage revealed remarkable effects of exercise on brain plasticity in animals. For example, Neuper, Gomez-Pinilla, Choi, and Cotman (1995), working under the direction of Cotman, first reported the neurotrophic effects of exercise in animals owing to the enhanced release of brain-derived neurotrophic factor (BDNF), which can facilitate synaptogenesis and repair of axons resulting in greater tissue density and enhanced neuronal interconnectivity in the brain. The neurotrophic effect can be mediated via upregulation of BDNF (Neuper et al.) insulin-like growth factor (IGF-1) (Trejo, Carro, & Torres-Aleman, 2001), nerve growth factor (NGF; Neuper et al.), and vascular endothelial growth factor (VEGF; Ding, Li, Zhou, Rafols, Clark, & Ding, 2006). This work was joined by that of vanPraag, Kempermann, & Gage, (1999), who reported that running increases cell proliferation and neurogenesis in the dentate gyrus of the adult mouse, a brain region in the hippocampus that is a critical target of pathology in the early stages of AD. In the same year, vanPraag, Christie, Sejnowski, and Gage (1999) reported superior learning as a result of exercise in mice indicative of the translation of brain adaptations to behavior.

Although the findings in animals cited above were suggestive of remarkable benefits of exercise to the human brain, it was the work of Arthur Kramer and colleagues in the first decade of the 21st century who provided such evidence through the innovative employment of functional magnetic resonance imaging (fMRI). For example, Colcombe et al. (2003) first observed that aerobic fitness was positively associated with tissue density and white matter integrity in several regions of the cerebral cortex and forebrain in middle-aged men and women, with the observed relationship most pronounced in those regions most susceptible to normal brain aging, namely the frontal cortices that mediate critical executive processes such as working memory, planning, scheduling and coordinating actions. More recently, Erickson et al. (2011) conducted a RCT with older men and women and concluded that one year of aerobic exercise training increased the size of the hippocampus and improved memory, while accompanied by increased levels of circulating BDNF! This finding also supports a causal influence of exercise on the health of the human brain with specific benefit to the region that is most susceptible to disease during the early stage of AD.

It was also during this decade that the first studies to reveal the benefits of physical activity in those who are genetically more susceptible to AD, that is, the carriers of the Apolipoprotein E4 (APOE e4) allele, were published. For example, Schuit, Feskens, Launer, and Kromhout, (2001) noted the arrest of cognitive decline over a three-year period, as measured by the Mini-Mental States exam (MMSE), in older men who carried a copy of the e4 allele,
but were physically active. Of great clinical relevance, Rovio et al. (2005) examined leisure-time physical activity at midlife and noted the attenuated risk of dementia and Alzheimer’s disease), via an epidemiological study. Furthermore, Deeny et al. (2008) were the first to employ neuroimaging in the form of magnetoencephalography (MEG) to determine the benefit of physical activity in APOE e4 carriers by assessment of the cerebral cortical response to working memory challenge in middle-aged men and women. More specifically, physically active e4 carriers showed similar amplitude and speed of brain response during a test of working memory (i.e., modified Sternberg letter-recognition task) relative to noncarriers who are at reduced risk for the development of AD, while inactive e4 carriers exhibited inefficient and slowed cortical responses during recognition.

It is also noteworthy that the notion of specificity of the neurocognitive adaptation to exercise received support during the 1990s and the decade beyond beginning with the work of Chodzko-Zajko and Moore (1994) who noted a robust benefit of cardiovascular fitness on fluid intelligence relative to crystallized intelligence. This theme was developed further by Kramer and colleagues (1999) who reported the positive impact of exercise training on the frontally-mediated executive processes in their seminal paper, which was reinforced by a meta-analytic review (Colcombe & Kramer, 2003). Their finding seems reasonable in light of the accelerated decline of the frontal brain region, relative to other brain regions, during normal aging as noted by West (1996). In this manner, the neurobiological benefits of exercise appear most apparent in the brain region that suffers the greatest decline with age. Therefore, superior executive function is revealed in those who are aerobically fit compared with those who are less fit.

Finally, at the other end of the age spectrum, a number of studies conducted during the past decade have also revealed exercise-induced benefits to brain development in children, particularly in the frontal lobes. A recent report by Davis et al. (2011) of a RCT revealed that exercise improves executive function and academic achievement and elevates brain activation in the frontal region during executive challenge in overweight children. Such a finding suggests enhancement of neural integrity in the developing frontal region, an area that is essential to attentional processes, working memory, and behavioral control and which is characterized by great plasticity that does not achieve maturity until the mid to late twenties. This notion suggests a critical role for exercise in the healthy development of the brain. Collectively, these foundational studies in healthy animals and humans, accompanied by the overall volume of work in exercise neuroscience, provide a strong foundation from which to speculate on the public health significance of physical activity, exercise, and fitness for the management of brain disorders.

As a starting point to build this case, the link between physical activity and the quality of cognition in aging was addressed by Hendrie (2006) in a report appearing in Alzheimer’s and dementia. The report summarized the NIH Cognitive and Emotional Health Project (CEHP), which was sponsored by the National Institute of Aging, National Institute of Mental Health, and the National Institute of Neurological Disorders & Stroke. The goal of CEHP was to identify the demographic, biological, and psychosocial factors that can help people to maintain or enhance their cognitive and emotional health as they grow older, which was cited as a major public health goal for the United States. The conclusions were based on a comprehensive review of the literature in this area and the criteria for survey inclusion were large cohorts, longitudinal in design, including participants predominantly 65 years of age or older, containing measurements of both cognition and emotion, as well as information on a wide variety of demographic, psychosocial, and biological factors. The protective factors for cognitive health that were most consistently reported in these large-scale high-quality studies included 1) higher education levels, 2) higher SES, 3) emotional support, 4) mastery, 5) better baseline cognitive function, 6) better lung capacity, 7) more physical exercise, 8) moderate alcohol use, and 9) use of vitamin supplements. The neurobiological basis for such benefit likely rests on the findings of the investigators described above.

**Dementia—Alzheimer’s Disease and Mild Cognitive Impairment**

The biological effects of exercise described above likely underlie the cognitive benefits to normal aging, which hold significant value to society, particularly in light of the advancing age of the American population. However, the purpose of the present paper is to discuss the implications of exercise for clinical neuropsychological disorders, such as dementia. According to Solomon and Budson (2003) dementia is the progressive decline in cognitive function due to damage or disease in the body beyond what might be expected from normal aging. Alzheimer’s disease (AD), also called Alzheimer disease and senile dementia of the Alzheimer type (SDAT), is the most common form of dementia. It is an irreversible and progressive brain disease that slowly destroys memory and thinking skills. First described by Alois Alzheimer in 1906, the most common complaint in the early stages is memory loss. The etiology of AD can be described by the progressive preclinical, mild and moderate, and severe stages that first destroy neurons in the hippocampal region by the presence of amyloid plaques and neurofibrillary tangles. The plaques are a product of cleavage of the amyloid precursor protein, which normally protrudes into the extracellular space from the neuronal membrane, and forms abnormally large clumps or plaques due to adhesions. The plaques appear to interfere with interneuronal communication. The tangles are located inside the neuronal membrane due to destruction of the tau protein causing collapse of the small canals that provide for intracellular transport of materials. First appearing in the hippocampal region and causing problems with the formation of new
memories, the histopathology becomes stronger over time promoting destruction of the hippocampal region and assumes a rostral progression until the entire forebrain is affected. The disease is also accompanied by the frontal decline associated with normal aging so, in essence, the individual experiences a double ‘hit’ to the integrity of the brain. In essence, the memory structures are destroyed.

In terms of prevalence, AD affects 10% of men and women over 65 and 50% of those over 85 years. The public health significance is remarkable as there are presently 5.4 million cases in the United States with 16 million cases projected by the year 2050. It is the 5th leading cause of death in those over 65 years of age. In terms of financial burden, it was estimated to be $76.3 billion in 1991, it then grew to $130 billion in 2011 and is conservatively projected to be $400 billion annually by 2050 (www.cdc.gov/mentalhealth/data_stats/alzheimers.htm). Importantly, any delay in the onset of symptoms of three to six years would reduce the incidence of AD by one-third. In terms of personal relevance, an earlier report from the Alzheimer’s Association predicts that 10 million baby boomers will develop Alzheimer’s disease in the United States that translates to one out of every eight. For the “baby boomers,” this is a frightening statistic to say the least (Alzheimer’s blog—March 25, 2008).

Exercise clearly benefits the animal brain, as summarized by Cotman and Engesser-Cesar (2002), and the observed neurotrophic effect is most pronounced in the brain regions devoted to episodic memory, including the dentate gyrus of the hippocampus, which is located within the medial temporal lobe. A critical issue is whether this neurobiological benefit occurs in humans. Such an effect in the human brain would hold major implications for the delay of dementia, particularly AD. The work of Colcombe et al. (2003) was suggestive of such an effect as greater amounts of fitness were associated with sparing of prefrontal and temporal regions, but the study lacked evidence of anatomical specificity regarding the hippocampal region and was correlational in nature. However, a subsequent paper from the same research team authored by Erickson et al. (2011), titled “Exercise training increases size of hippocampus and improves memory,” reported an exercise intervention that yielded a 2% increase in anterior hippocampal volume in men and women as well as an increase in circulating BDNF and memory improvement. This study provides strong evidence in support of the neurotrophic action of exercise in the human brain and is striking in light of the specificity of effect to the hippocampal region, biological plausibility in light of elevation in circulating BDNF, and translation to improved behavioral performance.

Incidentally, it is interesting to speculate why the hippocampus is ‘privileged’ in terms of neurotrophic effect and the answer may lie in the essential navigational role that the hippocampus plays in movement activity as observed in animal studies (Wills, Cacucci, Burgess, & O’Keefe, 2010). That is, when we move, we must process and remember where we moved (i.e., essential for survival in our remote ancestors!) such that there may be a natural stimulation of the hippocampus whenever we engage in large muscle locomotor activity.

In this manner, the specific exercise-induced hypertrophy of the hippocampus could serve as a buffer to any pathology of AD that might appear in this region and prevent or delay any symptoms of memory impairment. Such a role of exercise serves to build cognitive reserve—a concept described by Scarmeas and Stern (2003). The term cognitive reserve describes the mind’s resilience to neuropathological damage of the brain. The mind’s resilience is evaluated behaviorally, whereas the neuropathological damage is evaluated histologically, by using blood-based markers and imaging methods. In addition, passive reserve largely relates to the thickness of the cerebral cortex and the tolerance of cell death via the reserve capacity enabled by abundant synaptic interconnections that are sufficient to “absorb” the destructive effects of age and pathology. On the other hand, active reserve is largely expressed as compensatory activity through which the surviving population of neurons “works harder” to negotiate cognitive challenges or devises alternative strategies in an adaptive manner to achieve a desired cognitive performance outcome. Importantly, the reserve capacity extends the threshold for cognitive decline. The threshold concept implies that aging and pathology/insult are associated with degenerative processes that do not result in clinical symptoms until they accumulate to a critical level. This critical level would be delayed because of passive, active, or combined cognitive reserve.

Although there is an absence of reports of RCT with AD patients at this time, such studies are beginning to appear in men and women with mild cognitive impairment (MCI, also known as incipient dementia, or isolated memory impairment), which is a diagnosis given to individuals who have cognitive impairments beyond that expected for their age and education, but that do not interfere significantly with their daily activities. Baker et al. (2010) recently published a paper in which positive effects of aerobic exercise on executive function were reported in 55–85 year-old women and men who suffered from MCI as a result of engagement in high-intensity training. This benefit was largely confined to female participants and the limited positive findings are countered by the negative findings reported by Miller et al. (2011) who observed that exercise improved cardiovascular fitness in persons with MCI, but there was no improvement in cognitive function. Rather, they observed that MCI patients in this sample declined in performance on several tests sensitive to AD and concluded that exercise may be beneficial before the onset of MCI, but less helpful after its onset. Such a position is consistent with the preventive model described above while the positive effects reported by Baker et al. are suggestive of a synchronous appearance of neurobiological benefit in the presence of brain pathology thus attenuating the rate of decline and even reversing it such that the par-
participant achieves a level of cognitive performance that was typical at an earlier stage.

**Genetic Consideration in the Exercise/Dementia Relationship.** Some are at greater risk for this terrible disease (i.e., AD). Specifically, a gene on chromosome 19, APOE e4, is present in only 17% of the US population, but ~40% of late-onset AD patients. The absence of universal presence in AD patients suggests that the e4 allele interacts with other genes or lifestyle behaviors (e.g., exercise) in its contribution to decline. The increased prevalence of the e4 allele in AD patients suggests decreased resilience to the disease because of compromised amyloid plaque clearance and inefficient cholesterol transport that is essential in neuronal repair and axonal maintenance (Bu, 2009). Additional work has shown accelerated cognitive decline in nonclinical e4 carriers (Greenwood et al., 2005). As such, a compelling interest is whether exercise participation can alleviate such accelerated decline offering resilience to decline and delay of AD symptoms based on the building of cognitive reserve in those who have greater need than noncarriers. The evidence seems to provide support for such a proposition. The first investigation in this area was reported by Schuit et al. (2001) who contrasted the relative likelihood of cognitive decline over a three-year period, as quantified by the MMSE, in middle-aged men classified into four groups: 1) physically active e4 carriers, 2) inactive e4 carriers, 3) physically active noncarriers, and 4) inactive noncarriers. Although the incidence of decline was low and undifferentiated in noncarriers, the high incidence of decline in inactive carriers was remarkably reduced in e4 carriers who reported regular vigorous physical activity. This finding is consistent with an ameliorative interactional model, reported by Kayes et al. (2010). According to this model, sedentary e4 carriers exhibit inferior cognitive performance relative to activity- and age-matched noncarriers while a positive dose-response relationship with activity or fitness characterizes e4 carriers relative to noncarriers. In this manner, highly active and fit carriers exhibit similar cognitive performance to noncarriers of similar status (see Figure 2).

In essence, this model can also be described in terms of a delay of threshold for clinical symptoms of cognitive impairment in e4 carriers that would be proportionally greater relative to the delay of threshold proposed in noncarriers. It is noteworthy that Podewils et al. (2005) conducted a study in which they observed that the incidence of AD was reduced with physical activity only in noncarriers while no such effect was observed in e4 carriers. Although this seems like a contradiction of the findings reported by Schuit et al., careful consideration underscores that the two reports were focused on different outcomes (i.e., attenuation of cognitive decline vs incident AD) and, collectively, are supportive of the resilience model. On elaboration, it is unlikely that exercise would reduce the likelihood of AD in e4 carriers (in fact, it is more likely that noncarriers would not present symptoms of the disease before death as they are not penalized by the neurophysiological disadvantages of APOE e4), but it does seem plausible (and empirically supported) that exercise would hold significant implications for the delay of decline in e4 carriers.

Beyond the level of cognitive-behavioral analysis, the work of Reiman et al. (2004) illustrates the importance of neuroimaging to detect ‘invisible’ brain processes in e4 carriers. Specifically, Reiman and others have noted a number of differences in glucose metabolism between e4 carriers and noncarriers (i.e., hypometabolism in

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**Figure 2** — Cognitive performance in APOE e4 noncarriers and carriers as related to physical activity and/or aerobic fitness level.
exercise in the promotion of resilience to dementia, par-
attenuated decline and delayed onset of AD. In sum, there
in those genetically vulnerable to pathology to achieve
"window of opportunity" for beneficial effects of exercise
symptoms of dementia. This finding suggests a critical
lifestyle by e4 carriers may result in earlier decline and
ameliorated in the active carriers. A prolonged sedentary
time for such diagnostic tests for cardiovascular disease
routine assessment of brain health just as is the case at this
total cost in the U.S. is estimated at $43 billion per year (i.e., direct and
deficit appeared to costly compensation. However, the advanced stages
were undifferentiated, while inactive carriers exhibited
exaggerated in the early stages of MCI. However, relative
hypoactivation occurs during late-stage MCI which is
further and remarkably reduced on conversion to AD.
Such a model proposes a ‘hard working’ brain in those
who are at risk for dementia and during the early period
of decline, which would serve to mask any symptoms due
to costly compensation. However, the advanced stages
of pathology would ultimately preclude the ability to
compensate resulting in a hypoactive neural state and
a precipitous decline in cognitive ability and severe
neurocognitive impairment.

It is tempting to speculate that routine use of neuro-
imaging, such as positron emission tomography (PET)
and functional magnetic resonance imaging (fMRI),
would offer a ‘forecast’ of future cognitive decline and
possible clinical symptoms if such testing were conducted
time within an individual. It is possible that the
costs of such tests may be reduced in the future as new
and cheap technologies are developed that would enable
routine assessment of brain health just as is the case at this
time for such diagnostic tests for cardiovascular disease
as blood pressure screening. In other words neuroimag-
ing could be employed in routine medical testing to track
time of ‘mental effort’ over time. Such a forecast,
based on exaggerated elevations with age, could lead to
earlier treatment and preparation for dementia in terms of
carefully planned procurement of assisted living quarters,
arrangement for nursing care, etc.

To determine ameliorative effects of physical activity
on brain activity in those at risk for AD, Deeny et al.
(2008) conducted the first study of physical activity in e4
carriers from a cognitive neuroscience perspective. Their
purpose was to determine if physical activity attenuates
APOE e4-related ‘deficits’ in cortical activation in men
and women (age 50–70 years) during cognitive challenge.
Cortical activation in the physically active e4carriers
during the retrieval phase of a working memory challenge
was similar to that of both groups of noncarriers, who
were undifferentiated, while inactive carriers exhibited
a delayed response relative to noncarriers possibly due
to neurodegeneration. As such, the deficit appeared to be
ameliorated in the active carriers. A prolonged sedentary
lifestyle by e4 carriers may result in earlier decline and
symptoms of dementia. This finding suggests a critical
“window of opportunity” for beneficial effects of exercise
in those genetically vulnerable to pathology to achieve
attenuated decline and delayed onset of AD. In sum, there
is substantial evidence based on animal, epidemiological,
experimental, and clinical studies for the role of aerobic
exercise in the promotion of resilience to dementia, par-
ticularly of the Alzheimer’s type. Certainly there is a need
for definitive evidence, but the scientific literature offers
possibilities for relief of suffering, financial burden, and
stress to potential care-givers for a significant portion of
the U.S. population.

Stroke: A Public Health Problem

In regard to vascular health, stroke is a leading cause of
disability in the United States with approximately
780,000 cases per year, and the number is expected to
double by 2040. Stroke is the third leading cause of
death in the United States and approximately 137,000
man and women die of stroke annually (www.cdc.gov/
stroke). Unfortunately nine out of ten strokes are silent,
meaning that damage is done to the brain without the
awareness of the individual, thus accounting for dementia
rates that are ten-fold higher than in the population at
large. In terms of economic burden the total cost in the
U.S. is estimated at $43 billion per year (i.e., direct and
indirect costs) projected to be approximately $2.2 trillion
by 2050. This magnitude of burden is not sustainable and
the problem is compounded by the accompanying chronic
disease management. For example, persistent deficits in
neural function occur in 75% of patients, fall rates are
at 70% in the first year, impaired glucose tolerance or
diabetes is present in > 75%, fitness levels are typically
compromised, and vascular cognitive impairment with-
out dementia is present in 50% of patients. A promising
area for investigation is the impact of exercise because of
its angiogenic and antihypertensive effects (Black et
al., 1990; Ribeiro et al., 2011). As cited above, animal
studies provide strong evidence that aerobic exercise
training positively influences cerebral blood flow (e.g.,
Issacs, Anderson, Alcantara et al., 1992; Swain et al.,
2003), as well as those studies reported earlier by Rogers
et al. (1990). In addition, the upregulation of IGF-1 is
crucial for exercise-induced neurogenesis (Trejo et al.,
2001) as well as angiogenesis (Lopez-Lopez, LeRoth,
& Torres-Aleman, 2004).

These studies, which are suggestive of benefits for
stroke prevention and recovery, are now joined by a recent
report by Ivey, Ryan, Hafer-Macko, and Macko (2011) of
a clinical trial revealing benefit in the form of improved
cerebral vasomotor reactivity from exercise training
in stroke survivors (>6 months) with mild to moderate
gait deficits. The study employed a randomized design
of treadmill aerobic exercise training compared with a
control condition consisting of nonaerobic stretching.
Blood flow velocity measures of the middle cerebral
artery were conducted before and after a 6-month
intervention period from which the exercise and control
groups showed elevations in peak VO2 of 19% and 4%,
respectively. However, as expected, the results revealed
larger improvements in the exercise group. Of note, the
authors reported that their data “provide the first evidence
to our knowledge of exercise-induced cVMR (cerebral
vasomotor reactivity) improvements in stroke survivors,
implying a protective mechanism against recurrent
stroke and other brain-related disorders” (p. 1994). It is important to note that impaired hemodynamic activity has been linked not only to advancing age, but depression, cognitive decline, and pathogenesis of white matter lesions, as well as risk of stroke. As such, the maintenance or enhancement of brain blood flow through exercise is critical to brain health and may serve both a preventive and rehabilitative role. A related report by Globas et al. (2011) also revealed that chronic stroke survivors benefit from high-intensity aerobic treadmill exercise. This experimental study revealed that three months of progressive high-intensity aerobic treadmill exercise in stroke survivors over the age of 60 years improved aerobic capacity, walking speed, balance, functional leg strength, cognitive function, and quality of life compared to conventional care. Although not measured directly, it may be that the observed improvements were also due to improvements in cerebral hemodynamics as reported by Ivey et al.

Beyond the hemodynamic effects of exercise, an earlier report by Luft et al. (2008) revealed that treadmill exercise also activates subcortical neural networks and improves walking after stroke in survivors. Specifically, Luft and colleagues employed a RCT consisting of six months of treadmill exercise resulting in an increase in cardiovascular fitness, improved velocity of walking, and enhanced activation of cerebellar and midbrain circuitry as revealed by fMRI. The investigators noted that walking is a complex neuromotor activity that is mediated by cortical, subcortical, and spinal control mechanisms and that the neurobiological benefits of exercise may act on all these levels of the CNS and they maintained that such functional mobility is critical to the preservation of strength, weight management, balance, and overall quality of life. In this manner, there is a critical link between the ability to walk and a host of other health benefits.

In addition to such essential exercise-induced change in the central nervous system, a number of investigations have revealed benefits to stroke survivors in terms of improved peripheral circulation in the lower extremities (Ivey, Hafer-Macko, Ryan, & Macko, 2010) as well as improved glucose tolerance and insulin sensitivity (Ivey, Ryan, Hafer-Macko, Goldberg, & Macko, 2007). Collectively, the reports by Luft, Ivey, Globas, and colleagues demonstrate that exercise shows great promise in the rehabilitation of stroke via both angiogenic and neurotrophic effects on brain plasticity and, importantly, one can deduce that such adaptations in men and women who have not suffered a stroke could offer some protection (i.e., resilience) against the occurrence or severity of occurrence depending upon the specific nature of the mishap.

Traumatic Brain Injury (TBI)

TBI, also known as intracranial injury, occurs when an external force traumatically injures the brain. TBI can be classified based on severity, mechanism (closed or penetrating head injury), or other features (e.g., occurring in a specific location or over a widespread area). According to the Centers for Disease Control (www.cdc.gov/TraumaticBrainInjury), each year an estimated 1.7 million people sustain a TBI. Of them, it is estimated to involve 52,000 deaths, 275,000 hospitalizations, 1,365,000 emergency room visits, and countless others receiving other medical care or no care (undiagnosed/untreated). It is reasonable to speculate that exercise would offer relief in light of the neurobiological benefits discussed earlier (Mossberg, Amonette, & Masel, 2010). Although no direct studies of exercise treatments in humans have been reported to date animal studies have been conducted that provide promise of a rehabilitative effect. Of primary relevance is the increase of neurotrophins, which can serve as activity-dependent modulators of synaptic transmission and, in turn, of synaptic plasticity (Schinder & Muming, 2000). More specifically, Molteni and colleagues (2004) conducted a study in animals and observed that voluntary exercise increased axonal regeneration in sensory neurons. Specifically, the investigators provided evidence of activity-dependent neural plasticity such that neurite outgrowth in neurons located in the dorsal root ganglia was increased in rats when cultured from the animals that had undergone exercise training for just three or seven days, and the effect (i.e., length) was directly correlated with the distance that the animal had run! In addition, axonal regeneration after experimentally-induced nerve crush was revealed in the exercised animals. Sensory ganglia showed elevations in brain-derived neurotrophic factor (BDNF; i.e., as indicated by messenger ribonucleic acid—mRNA levels) relative to that observed in sedentary animals. In addition, a report by Griesbach et al. (2004), also conducted in animals, revealed upregulation of brain-derived neurotrophic factor and recovery of function in terms of water-maze performance from engagement in voluntary exercise following traumatic brain injury. Importantly, the timing of the exercise intervention was a critical factor in the outcome of the study as acute exercise intervention within six days of an experimentally-induced trauma (i.e., fluid percussion injury—FPI) was ineffective for benefit while delayed exercise intervention yielded benefit. The investigators posited that the energy substrate used for recovery was not available during the early stage after trauma and was only able to be employed after reasonable passage of time. These studies are highly relevant to the justifica- tion for exercise intervention studies with the returning warriors to the United States from the current conflicts in the Middle East. It is estimated that 20% of the 1.64 million veterans from the war in Iraq and Afghanistan suffer from TBI; this represents approximately 320,000 men and women.

In response to this public health issue for wounded warriors, the Department of Defense (aided by funding from the Fallen Heroes Fund and by Mr. Arnold Fisher who is a primary benefactor) recently opened the National Intrepid Center of Excellence (NICoE) on June 24, 2010 in Bethesda, Maryland on the grounds of the National Naval Medical Center. A number of Defense Centers
of Excellence were initiated recently in response to the negative conditions surrounding the medical treatment of wounded soldiers at Walter Reed Army Hospital in Washington, DC. The NICoE is specifically charged with the treatment of TBI and posttraumatic stress disorder (PTSD; described below), which have been termed the “invisible wounds of war.” The Center offers a comprehensive approach to clinical treatment and research of these debilitating brain injuries in those men and women from around the country who present the most challenging cases. In light of the discussion above, it does seem timely to explore the prophylactic effects of exercise as an element of treatment to help alleviate this problem in the military and general populations.

**Post-Traumatic Stress Disorder**

In many cases, those suffering from TBI also suffer from Posttraumatic stress disorder (also known as posttraumatic stress disorder or PTSD), which presents as a severe anxiety disorder that can develop after exposure to any event that causes psychological trauma. However, it is possible that TBI and PTSD can also occur independently. Approximately 300,000 veterans currently suffer from PTSD and the financial burden to the country is estimated at $6.2 billion (http://www.Washingtonpost.com/article/2008/04/17/AR2008041701749). Although the processes underlying PTSD are not fully understood, it is reasonable to assume that the exaggerated response of the amygdala to certain stimuli is a central manifestation of the disorder. Pessoa (2010) posited a model in which the amygdala influences the forebrain and is connected in a manner analogous to a hub or center with connectivity to the cerebral cortex analogous to the spokes of a wheel. It is also noteworthy that several contemporary models of emotion regulation posit the primary role of the frontal lobes in the management of the amygdalar response (Ochsner & Gross, 2008). That is, those with frontal control over the amygdala effectively manage stress and anxiety likely due to an inhibitory influence of the frontal region on the limbic structure mediated by the anterior cingulate cortex. In this regard, it is interesting to note that the frontal region of the brain, and associated executive functions appear to benefit remarkably from exercise participation in older men and women and in children (Kramer et al., 1999) and it may be that any exercise–induced neurobiological benefits to the frontal region facilitate the efficacy of this inhibitory process.

**Physical Activity in Children: Building Resilience to Brain Disorders**

However, what may be most important to building resilience to brain disorders is the physical activity that occurs in early life—childhood and adolescence. Although the study of exercise and the brain has typically focused on older men and women, several studies reported recently (i.e., during the last six years) have been conducted on the effect of physical activity and fitness on the neurocognitive processes of children. In addition to behavioral studies, Hillman, Castelli, and Buck (2005) published the seminal study conducted to determine whether a high level of fitness was associated with enhanced cognitive performance and a superior neuroelectric profile on a visual discrimination task in preadolescent children. Collectively, the results are remarkably consistent in terms of positive findings, but virtually all of these investigations employed correlational designs thus preventing conclusions of causal influence. The notable exceptions to this rule are two papers reporting the results of RCTs that have been published by Davis et al. (2007; 2011) who found robust support for such influence on multiple levels of measurement (i.e., behavioral and neuroimaging). Specifically, they reported a study conducted in overweight children (age 7–11 years old, ≥85th percentile BMI), who were randomized into low-dose (20 min/day exercise), high-dose (40 min/day exercise), or a nonexercise control condition. The primary dependent measure, assessed at the end of the 15-week intervention, was the Cognitive Assessment System (CAS), which includes four scales: Planning, Attention, Simultaneous, and Successive. Only the Planning scale score, a measure of executive function, was higher for the high-dose group, as compared with the control condition, which supports a selective benefit to executive function in children. Furthermore, a dose-response benefit of the aerobic training on executive function and mathematics achievement was observed, but not for reading achievement. It is reasonable to assume that mathematical ability is essentially related to executive function in light of the dependence on working memory (Diamond, 2011). In addition, the exercise group exhibited increased bilateral prefrontal cortex activity and decreased activity in bilateral posterior parietal cortex compared with controls. Such a finding implies heightened involvement of the executive processes due to exercise and relative efficiency in the brain regions that are involved in nonexecutive attentional processes. Although a potential criticism of the study is the focus on overweight children, limiting generalizability, this profile is becoming more characteristic of American children over time.

As such, the impact of exercise on the brain development of children may be profound during this critical developmental period as Gogtay et al. (2004) recorded anatomic brain scans of healthy children to report the dynamic anatomical sequence of human cortical gray matter development between the ages of 4–21 years. Those parts of the brain associated with more basic functions matured early: motor and sensory brain areas matured first, followed by areas involved in spatial orientation, speed and language development (upper and lower parietal lobes). Areas involved in executive function, attention, and motor coordination (frontal lobes) were later to mature. Therefore, higher-order association areas, such as the prefrontal cortex (PFC) are the last to mature. In addition, ongoing myelination, synaptic pruning, and strengthening of existing neural connections occur with
and unintended side effects that compromise learning pharmacological treatment of ADHD may have negative performance. The implications of the study are important as a beneficial effect of physical activity on executive performance impairment. The findings support the possibility of exercise to facilitate the development of neural integrity particularly in the frontal areas, resulting in enhanced executive functions, such as response inhibition. Further, these benefits may endure into adulthood via the notion of increasing cognitive reserve. Cognitive reserve indicates that experiences as a child, such as physical activity and exercise, can cause long-term benefits, such that those who were more physically active and fit as a child exhibit higher levels of cognitive functioning as an adult via the capacity to withstand structural and functional neurodegenerative processes (Stern, 2002).

Beyond the implications for normal children, it appears promising to speculate that exercise may be beneficial to those children afflicted by attention deficit and hyperactivity disorder (ADHD), which is characterized by a pervasive pattern of developmentally inappropriate inattentive, impulsive and hyperactive behaviors that typically begin during the preschool years and often persist into adulthood. According to the Centers for Disease Control (www.cdc.gov/ncbddd/adhd/data) recent data from surveys of parents indicate that approximately 9.5% or 5.4 million children 4–17 years of age have ever been diagnosed with ADHD, as of 2007. Furthermore, the percentage of children with a parent-reported ADHD diagnosis increased by 22% between 2003 and 2007. Rates of ADHD diagnosis increased an average of 3% per year from 1997 to 2006 and an average of 5.5% per year from 2003 to 2007, revealing an increasing occurrence, and the financial burden to the nation is estimated at $31.6 billion.

Studies of physical activity on ADHD are just beginning to appear in the literature. Recently, Kim et al. (2011) conducted a study with spontaneously hypertensive rats (that display major symptoms of ADHD such as inattention, hyperactivity and impulsiveness) and observed exercise-induced elevations in BDNF and tyrosine hydroxylase, the rate-limiting enzyme for the synthesis of dopamine as well as alleviation of their spatial learning impairment. The findings support the possibility of exercise as an effective therapeutic intervention. In addition, Gapin and Etier (2010) recently conducted a study with children diagnosed for ADHD and observed a beneficial effect of physical activity on executive performance. The implications of the study are important as pharmacological treatment of ADHD may have negative and unintended side effects that compromise learning and attention. In light of this concern, Halperin and Healy (2011) state that it would be highly beneficial to demonstrate the influence of environmental factors on brain development and functioning. They proposed an approach based on directed play and physical exercise to promote brain growth, particularly in the frontal region, which would provide more enduring treatments for the disorder without problematic side-effects.

In this manner, it seems that physical activity may benefit the child, whether normal or ADHD, with enhancement of their executive skills such that they are poised to benefit from the educational environment. Of course, one must exercise caution in their conclusions in light of the predominant cross-sectional nature of the literature and the paucity of investigations with children with ADHD. Furthermore, the translation of any such benefit to basic neural processes to improved academic performance would likely occur only in the context of high-quality teaching as well as parental influence that is conducive to the valuation of education. In that sense, a complex set of relationships, including the amount and nature of physical activity, must be considered to clearly determine the influence of exercise on academic performance.

However, there may be benefits to the brain and mind beyond those of short-term neurocognitive or academic performance. We know the importance of early-life brain health to gracious brain aging based on the work of Riley, Snowdon, Desrosiers, and Markesbery (2005) with participants in the Religious Orders studies. Those studies, conducted on factors influencing cognitive aging in nuns and priests, offered great opportunity to determine influential factors in light of the relative homogeneity of lifestyles. That is, significant differences in diet, physical activity, sleep, education, and cognitive stimulation were more likely to reveal in light of similarity in lifestyle. One of the notable findings in their research was that early-life linguistic ability (brain integrity) was robustly related to late-life cognitive health. More specifically, evaluation of autobiographies written at a mean age of 22 years was undertaken to determine “idea density”—a measure of linguistic ability that likely was related to neurocognitive integrity. Interestingly, the early-life idea density was positively related to brain weight and inversely related to cerebral atrophy at death approximately 60 to 70 years later! They hypothesized that low linguistic ability in early life may reflect suboptimal neurological and cognitive development. In addition, the presence of AD was minimal in those who had high ideational density while much higher in those who did not.

Such a temporal relationship between early-life status and the quality of health and cognitive function in later life is captured by the investment hypothesis. Support for such a notion in the case of physical activity was provided by Andel et al. (2008) who conducted a large-scale epidemiological study of twins and observed that exercise at midlife may reduce the odds of dementia in older adulthood, suggesting that exercise interventions should be explored as a potential strategy for...
delaying disease onset. They found that participants who engaged in light regular exercise exhibited reduced odds of dementia and AD approximately 31 years later! The relevance of this work to that with children is that a physically active lifestyle, by its contribution to neural integrity, may have far-reaching implications for the quality of physical and, particularly brain health, much later in life. Such an effect would imply that the investment in exercise and activity may yield great benefit at a later stage when degenerative processes due to age and pathology are present. Such a notion implies long-term benefit and resilience in addition to any short-term benefits and holds significant implications for the role and valuation of Physical Education.

Summary

In summary, participation in physical activity shows great promise for the alleviation of a great number of afflictions involving the brain, mood, and cognition that are facing our population. It appears to hold promise for benefit across the lifespan and physical activity in early life may significantly influence brain health later in life. These benefits may be particularly important for those who are at genetic risk for accelerated aging and characterized by increased susceptibility to dementia and the impact of trauma. Importantly, participation in physical activity offers the possibility of a cost-effective treatment for health conditions that pose a staggering financial burden on the country as well as significant stress to those afflicted as well as their care-givers. Government and private agencies are cognizant of these benefits as evidenced by broad initiatives such as the National Physical Activity Plan. It has been 15 years since the last report of the Surgeon General on physical activity and health (U.S. Department of Health and Human Services, 1996), but a recent report on the adequacy of evidence for physical activity was released by the Institute of Medicine of the National Academies in 2007. I believe that the future will hold a summary of the evidence for the brain disorders described herein particularly as the tools of neuroimaging are increasingly employed along with well designed clinical trials that effectively gauge the ‘medicine’ of exercise and physical activity in their various forms such as dance, play, sports, cardiovascular and resistance training on the health and disease of the human brain. The translation of the research to clinical practice in the future will be guided by the results of high-quality experimental studies and definitive evidence from clinical trials with patient populations, but it may be that one of the most important outcomes of this effort is the hope that it provides to parents, children, middle-aged, and older adults that they can indeed manage their mental health and quality of life through the adoption of a physically active lifestyle. It appears that the wisdom of the ancient cultures, captured in the Latin motto ‘Mens Sana in Corpore Sano,’ was good advice to guide our present society.

References

Davis, C.L., Tomporowski, P.D., McDowell, J.E., Austin, B.P., Miller, P.H., Yanasak, N.E., et al. (2011). Exercise improves executive function and achievement and alters


