Review Article

Nitric Oxide and the Biological Cascades Underlying Increased Neurogenesis, Enhanced Learning Ability, and Academic Ability as an Effect of Increased Bouts of Physical Activity

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ABSTRACT

International Journal of Exercise Science 5(3) : 245-275, 2012. The consummate principle underlying all physiological research is corporeal adaptation at every level of the organism observed. With respect to humans, the body learns to function based on the external stimuli from the environment, beginning in the womb, throughout the developmental stages of life. Nitric Oxide (NO) appears to be the governor of the plasticity of several systems in mammals implicit in their proper development. It is the purpose of this review to describe the physiological pathways that lead to plasticity of not only the vasculature but also of the brain and how physical activity plays a key role in those alterations by initiating the mechanism that triggers NO production. Further, this review hopes to show a connection between these changes and learning, comprising both motor learning and cognitive learning. This review will show how NO plays a significant role in vascularization and neurogenesis, necessary to enhance the mind-body connection and comprehensive physical performance and adaptation. It is our belief that this review effectively demonstrates, using a multidisciplinary approach, the causal mechanisms underlying the increases in neurogenesis as related to improved learning and academic performance as a result of adequate bouts of physical activity of a vigorous nature.

KEY WORDS: Vascularization, exercise, chess, nutrition, environmental enrichment, vascular endothelial growth factor, brain derived neurotrophic factor, relaxation response, long-term potentiation, learning

INTRODUCTION

The positive effects of a physically active lifestyle versus a sedentary lifestyle are common knowledge among health professionals, scientists and the general public. Physical well-being is dependent on a healthy, properly functioning vascular and nervous system that can respond appropriately to increased bouts of physical activity. Once compromised by disease or injury, it is also well known that physical activity tends to be a potent drug for the rehabilitation of nearly every dysfunctional state known to the medical field, whether the disorder is of a physical, mental, or spiritual nature. There are many well-studied biochemical substances known to be of particular importance in the maintenance and rehabilitation of the

cardiovascular system (CVS). Two of the most documented and important substances include Nitric Oxide (NO) and Vascular Endothelial Growth Factor (VEGF). In the sciences concerned with the improvement of physical ability, the brain is often overlooked. However, it goes without saying that any impairment within the brain leads to impairment in physical ability observed as dysfunctional/impaired motor control. Interestingly, recent research has begun to show the biochemical pathways that cause plasticity within the musculature are similar to those necessary to initiate plasticity in the brain (23). Research on this level has very important implications in the fields of education, learning, and developmental psychology, as well as the athletic sciences. It is the purpose of this review to describe the physiological pathways that lead to plasticity of not only the vasculature system but also of the brain, and how physical activity plays a key role in those alterations with the implication that increased physical activity leads to an improved physical and cognitive state of being. Further, this review hopes to show a connection between these changes and learning, comprising both motor learning and cognitive learning. The hypothesis is that learning and/or disability can be objectively linked to these specific physiological changes. This review will show how NO plays a significant role in vascularization and neurogenesis, necessary to enhance the mind-body connection and overall physical performance.

NITRIC OXIDE AND THE HUMAN BODY

Nitric Oxide (NO) and its physiological effects within the cardiovascular system (CVS) have been rigorously explored over the past 25 years. Three known nitric oxide synthase (NOS) isoforms exist: endothelial NOS (eNOS) which is used in the vasculature and brain (27), inducible NOS (iNOS) which is expressed in the brain and immune system (106), and neuronal NOS (nNOS) which is expressed in the brain and central nervous system (CNS). NO is known as a potent vasodilator with antimicrobial properties and acts in some cases as a signaling mechanism (28). It is well-known that aerobic and non-aerobic exercise training induces positive changes in skeletal muscle and CVS. These effects have been positively associated with the direct increase of NO with a wide range of exercise intensities and duration (16, 32, 72, 99, 108, 113,153). The benefits of enhanced NO productivity include increased aerobic capacity, reduced hypertension, increased insulin sensitivity and glucose tolerance, capillarization and angiogenesis, and even long-term potentiation (LTP) and neurogenesis. These effects have been observed in as little as 4 weeks in compromised persons (86) and 10 weeks in healthy persons (32). NO is a byproduct of the conversion of the amino acid L-arginine to L-citrulline by eNOS. NO is quickly broken down into its metabolites nitrate/nitrite (NOx) and researchers commonly test NO productivity by measuring these metabolites in blood, urine or exhaled breath. NO activates guanylyl cyclase which forms the second messenger cyclic GMP (cGMP) which then signals the relaxation of arterial smooth muscle by protein kinase-G (PKG). Although much is known regarding the individual components of this pathway, the

underlying mechanisms responsible for NO activity remain unanswered (72).

There are two common models that have been set forth in attempt to explain the mechanism of NO function in the CVS. One model proposed for stimulation of NO is the shear-stress of the vasculature in response to increased blood flow due to exercise (72, 113, 164). Another model proposed is vascular pulsations (153), as a regulator of basal NO. This is purportedly due to pressure pulses originating in the heart and venous systems. However tenuous these models may be, it is the purpose of this section to take a fresh look at the evidence and research surrounding NO in an attempt to discover a viable alternative hypothesis using an interdisciplinary approach.

Nitric oxide and vascularendothelial growth factor signaling loop induces angiogenesis

It has been shown that NO increases as a result of exercise (16). More importantly, this increase can last for up to 4 weeks after cessation of exercise (108). In addition, Maeda et al., (2001) showed that endothelial-1 (ET-1), a vasoconstrictor implicated in atherosclerosis of sedentary populations, cross-talks with NO forming an inverse relationship. This is very interesting due to structural changes that potentially occur in the vasculature during the same time period as a result of increased NO production due to exercise. Further evidence is provided by a study which showed a decrease in aerobic capacity was correlated to a decrease in post-exercise excretion of nitrate (120). This was shown to be caused by the dysfunction of the endothelial vasodilator mechanism in hypercholesteralemic mice. Due to this there appears to be a significant role for NO in vascular maintenance and potentially in blood vessel formation itself.

Angiogenesis is the process of forming new blood vessels from preexisting vessels which proliferate within tissues. One of the main growth factors necessary for this is Vascular Endothelial Growth Factor (VEGF) which is increased in the bloodstream and organ tissue during hypoxic conditions and is part of a larger system that promotes repair of endothelium to restore blood flow (162) through a process by which VEGF stimulates mitosis in endothelial cells. Sub-maximal exercise has been shown to increase VEGF mRNA after only 1-hour and is attenuated using a NO inhibitor (62). This study concluded that a signaling mechanism exists between VEGF and NO and together promotes angiogenesis (with other factors) post-exercise. Previous to Gavin (2000) the existence of a signaling mechanism between NO and VEGF with respect to angiogenesis has been observed (83,124, 133). However, these studies lack an exercise component to induce NO and VEGF factors and fail to elucidate which factor begins the cascade that leads to tube-like formations. Each study indicates, in vitro, that VEGF stimulates increased production of NO from endothelial cells using NO donors and inhibitors. Another similar and more recent study showed that blocking VEGF or NO attenuated capillary-like tube formation in post-stroke rats (174). Based on the available literature we propose that signaling occurs between NO and VEGF with respect to angiogenesis in healthy and compromised individuals. However, more importantly, it has been suggested that both proliferation and

organization of endothelial cells requiring VEGF is mediated by NO (133). Based on these studies, it is the hypothesis of this review that NO works more specifically as a regulator in a feedback loop with VEGF that switches endothelial progenitor cell (EPC) proliferation to differentiation and formation into new blood vessels.

A recent study provided evidence that NO is capable of being such a signal switch changing neural progenitor cells (NPC) from proliferation to differentiation in the brain (28). This concept is supported by the following evidence. VEGF is necessary for EPC mobilization which is essential in growth of new blood vessels (1, figure 1). Aicher et al., (2003) showed that eNOS deficient mice have impaired blood vessel growth due to impaired mobilization of stem and progenitor cells from bone marrow.

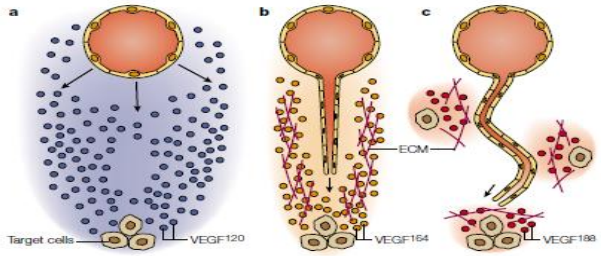

Figure 1. Role of VEGF in vessel formation. VEGF aids EPC's in reaching their target cell through matrix association. **a** In the absence of suitable VEGF isoforms there is insufficient guidance for EPC's to cause vessel branching and results in vessel expansion rather than branching. **b** A specific form of VEGF allows for the formation of a matrix and attraction to EPC's allowing log sprouts to extend to the target. ECM, extracellular matrix. **c** If only a single isoform of VEGF is present EPC's become misguided taking wrong turns. Source: (23).

We suggest that a lack of the switching signal NO can reduce the need for increased EPC in circulation. This can concurrently reduce the expression of VEGF. Even in mice that had effective VEGF mobilization of EPC's (tested through eNOS bone marrow cell injection in wild-type mice) there remained a significant impairment of vascularization; presumably due to inhibited NO production, specifically linked to eNOS deficiency. This may indicate that a lack of adequate NO in the blood stream can lead to the impairment of neovascularization. This concept is also suggested by Benest et al.,(2008) who concluded, based on previous literature, that vessel growth and remodeling are dependent on increased blood flow.

It is well known that daily exercise increases capillarization in muscle tissue due to the repetitive nature of muscle contractions, and that hypoxic condition developed from vigorous, repeated usage, in turn, stimulates the increased development of tube-like formations (89). Based on the present literature we conclude that NO plays a vital role in that process during muscular activity. We propose that the roles of VEGF and NO for vessel formation during neovascularization occurring in skeletal muscle are responsible for vascular remodeling in the brain as well (15, 87, 158). Swain et al., (2003) established that neural activation is increased in response to increased physical activity that led to changes in cerebral blood flow. Taken together, we propose the following mechanistic process of action:

1. Increased physical activity increases VEGF in the blood stream (62).
2. VEGF mobilizes EPC's in the blood stream and increases mitosis of EPC's (1, 100).

3. Increased physical activity simultaneously increases NO in the blood stream(16)
4. NO works in conjunction with VEGF to switch EPC's from proliferation to differentiation and mobilization into tube-like formations (23, 133).
5. As observed, in areas of hypoxic need, capillary-like tube formations appear in muscle and/or brain tissue in response to increased physical activity and blood flow (15, 89).

Nitric oxide and the brain

The brain is the site of the highest NO activity in the human body (61). Cheng et al., (2003) identified a novel mechanism to describe the regulatory process of neurogenesis in adult and developing brains. The researchers discovered that a feedback loop exists between brain derived neurotrophic factor (BDNF) and NO. BDNF actually stimulated nNOS (which leads to production of NO in the brain) and that NO produced by the proliferating cells then signaled proliferating NPC's to begin differentiating into neural cell phenotypes. This action was blocked by NO inhibitor (L-NAME) and increased by NO donor (nitroprusside). The study by Jacoby et al. (2001) demonstrated that NO was required for long-term potentiation (LTP). The spread of this potentiation extended to synapses 168 μm away from the stimulated purkinje cells. They show that this spread is dependent upon the NO produced by the cell that is receiving the raised frequency stimulation (RFS) of 8 Hz. This RFS is what exercises neurons, and LTP is the strengthening of the synapses in response to such stimulations with other neurons making the brain 'stronger'. Interestingly, in conjunction with NO, VEGF plays an important role in neurogenesis as well (52), along with a role in neurotrophin activity, axonal outgrowth, Schwann cell proliferation, and cell survival (152). Increased bouts of repetitive physical activity and/or motor learning increase these stimulations (15, 87). Similarly, the same mechanisms and messengers that regulate physiological responses to exercise in the vasculature and muscle tissue are the same processes occurring in completely different tissue in the brain as a simultaneous response to the same exercise bout (88). This stimulation affecting brain performance has been recently reproduced by an external stimulation in humans (29). In this study the researchers used direct transcranial stimulation to the anterior lobes (L-R+ and L+R-) and subjected control and experimental groups to a set of cognitive tasks involving arithmetic statements. It was that those subjects who had inhibited left-brain stimulation and increased right-brain stimulation (L-R+) had a three-fold increase in problem solving ability.

Another important role NO plays in the brain is on the hypothalamus-pituitary-adrenal axis (HPA) in response to stress (18, 20,154). The HPA axis plays a master role in blood pressure and fluid retention, reproductive and hormonal function, mood, and energy levels, thru the release of corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol. This leads to the fight/flight response as coritsol stimulates norepinephrine/adrenalin. The Hypothalamus-cerebellar connection is important to note with regulation of many responses including HR and respiration (25). Chronic elevation of cortisol is known

to lead to a host of physiological and psychological disease states (Table 1). According to the review by Calabrese et al., (2007) NO actively stimulates some parts of the HPA axis in response to stress, specifically CRH, which is released by the hypothalamus. In another review by Stern (2004) a mechanism of action is set forth as to how NO plays a centrally inhibitory role once an imbalance is reached, restoring balance by acting as a braking mechanism to decrease sympathetic responses of the autonomic nervous system. Voluntary physical activity in rats has been reported to cause significant changes in hormonal secretory rates and structural changes in HPA axis physiology (42). The thymuses were lighter and adrenal glands grew larger in exercising mice versus control groups after 4 weeks. Baseline levels of ACTH in exercising mice were decreased. More importantly, in the paraventricular nucleus (PVN) of the hypothalamus, CRH levels were decreased confirming the conclusion of Stern (2004). Intriguingly, and underscoring the dual nature of NO in neovascularization and neurogenesis; playing shogi, a Japanese form of chess, has been shown to boost testosterone production (80). Together, these results would suggest that NO in the brain plays an important signaling role in the effect of the HPA axis and the response to stress. As a side note, post-traumatic stress disorder patients (PTSD) who suffer from both cerebral perfusion abnormalities (31) and brain atrophy (17) have found relief of symptoms through exercise (116).

Based on the previous literature, we theorize that a single molecule, NO, is responsible for cascading reaction systems in both the neural and vasculature systems, and the communication between the neural and the vascular. There exists such a model that describes the mechanism of vascular-neural signaling (59, figure 2).

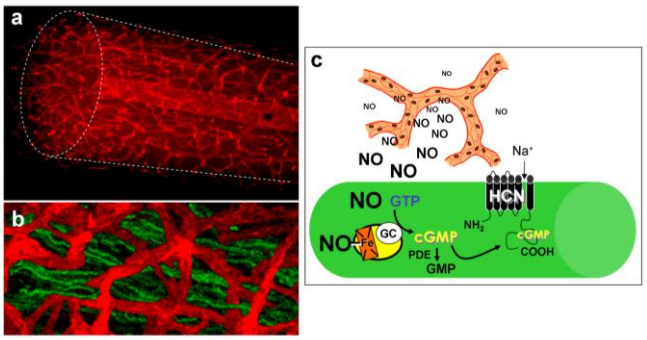

Figure 2. Signaling from blood vessels to axons in the optic nerve. **a** A whole mount preparation of rat optic nerve, immunostained for eNOS. The shape of the nerve is represented by the dotted line. **b** Composite graph of the relationship between axons (green) and capillaries (red). **c** A schematic of the proposed mechanism by which the NO production in the circulation depolarizes axons by raising cGMP levels which activates hyperpolarization-activated cyclic nucleotide-regulated (HCN) channels. Source: (60).

In that review, endogenous NO from the microvasculature depolarizes optic nerve axons, by engaging hyperpolarization-activated cyclic nucleotide-regulated (HCN) channels. A common factor leading to this membrane depolarization is raised cGMP levels which not only causes depolarization, but also signals PKG to cause vasorelaxation. The characteristic rise in cGMP from increased NO levels has been observed not only in the optic nerve but in the olfactory bulb as well (84). The olfactory bulb and optic nerve relay signals that are associated with sight and sound. As NO increases cGMP levels which trigger the action of PKG to cause vasorelaxation; that vessel dilation generates RFS in neural tissue increasing vascular-neural signaling. That raised RFS leads to increases in LTP

and neurogenesis. Noting all the parallels we have described herein, it would seem logical that a similar vascular-neural signaling is taking place in potentially all sensory inputs into the brain. To support this hypothesis, Fessenden and Schacht (1998) detail how NO and cGMP regulate the physiology of the hearing system.

The olfactory bulb is part of the limbic system (along with the hypothalamus) and relays signals to the olfactory tract. Importantly, with respect to our memory of certain odors, the hypothalamus, amygdala, and the hippocampus all play a role in the memory associated with specific odors and their sympathetic/parasympathetic response to those stimuli. This has important evolutionary implications with characteristic behavioral responses of predator, prey, or mate and the complex systems underlying the properly induced responses. According to Garthwaite et al.,(2006) the same applies to vision. Arguably, based on the foregoing evidence, the one molecule responsible for the properly mediated response of both the cephalic and somatic physiology to specific environmental stimuli is NO. In sum, as one increases inspiration across the sinus, we propose that a subsequent increase in microvascular-neural signaling is taking place, governed by NO, through the olfactory bulb and cascading into various signaling mechanisms of multiple other systems regulating homeostasis and sympathetic/parasympathetic responses to stimuli. All of these processes are dependent on the initial signaling mechanism, the paracrine messenger, NO.

Nitric oxide and the sinus

This review has provided only summary information with respect to how NO is involved in many pathologies within the human body. The intricate mechanisms for each subsystem are included in many of the reviews cited. However, this review has attempted to show an underlying cascade of events of gross anatomy occurring during an increased bout of physical activity; exercise itself being an acute form of stress. In this review, NO, apluripotent, ubiquitous, paracrine messenger has been shown to mediate seemingly all physiological processes recruited in response to exogenous stimuli. All that remains is to describe the causal mechanism that produces the physiological effects mediated by NO in response to stress and at the same time governs the basal maintenance of homeostasis. The mechanism for this is inspiration across the nasal sinus cavity.

Ambient oxygen (O_2), as it passes through the sinuses diffuses across the nasal epithelieum and can be used by the cell to produce NO (17). As the sinus produces NO and air is continually inhaled, NO reaches the lung and is diffused into the capillaries surrounding alveoli expanding vessels and increasing O_2/CO_2 exchange. NO is also generated in the lung in proportion to inspired O_2 concentration until reaching an equilibrium between production and consumption (47). This process begins in the paranasal sinus and while some will reach the lungs, some will be absorbed in the sinus itself. Rates of absorption range from 17 $ml \cdot min^{-1}$ at resting breathing rates, to 24 $ml \cdot min^{-1}$ at increased breathing rates (44). Odorant molecules diffuse across the mucus of the sinus cavity and stimulate sensory neurons

binding to receptors on the cilia. This signal is passed along the olfactory nerve sending a stimulus to the olfactory bulb. This stimulus is passed on to many structures in and around the olfactory bulb, specifically the HPA axis through the hypothalamus-cerebellar (HC) circuit and the hippocampus (39, figure 3).

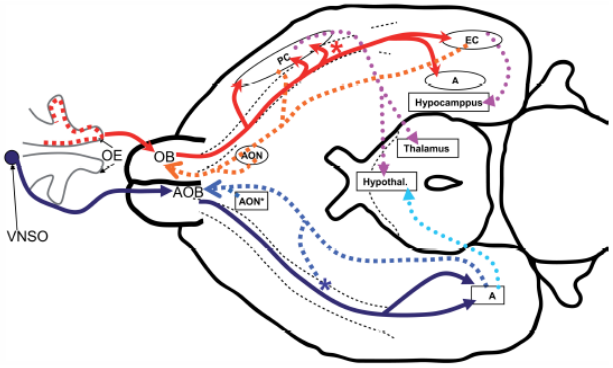

Figure 3. General schematic of the mammalian olfactory system and accessory olfactory system. Olfactory sensory neurons (red dots) project into the olfactory bulb (OB) forming the olfactory nerve. These axons project into the olfactory cortex and connect to the anterior olfactory nucleus (AON), the amygdaline complex (A), and the entorhinal complex (EC). The black dotted lines ventral and dorsal are the lateral olfactory tracts. Source: (40).

Substantiating our hypothesis that inhalation is the mechanism underlying the production of NO throughout the body, and not vascular pulsations (153) or laminar shear stress (164), is the study by Dusek et al., (2006) on relaxation response (RR). RR focuses heavily on intentional breathing practice and is characterized by reduced HR, BP, and breathing rate. The purpose of this study was to determine if the RR was mediated by NO. This was qualified by measuring VO_2 slope and fractional exhaled NO (F_eNO). Prior to intervention there was no association of VO_2 slope and percent change in F_eNO in either control or experimental groups. However, post-training, there was an inverse relationship between percent change in F_eNO and VO_2 slope after 8 weeks in the experimental group. There was no change in the control group. In conjunction, another study on Zen meditation and effects on serum NO showed similar results (95, 132). Zen meditation also focuses attention and emphasizes breathing technique to elicit a RR. To measure NO activity serum NOx was measured in the blood. The experimental group practiced Zen meditation for 10 weeks, while controls practiced no form of stress management. Post-training results showed a significantly increased serum NOx level over controls demonstrating increased NO activity. Taken together these two studies show us two things,

1. NO activity can be altered by focused breathing technique.
2. Basal NO levels appear to be controlled by proper breathing technique thru the nasal cavity.

From these findings, we can see how NO, through nasal breathing at rest begins a cascading effect of vasostimulation of blood vessels from the nose, to the lungs, to the heart, to the periphery, to increase O_2 uptake and regulate basal vessel diameter by cross talking with ET-1. Simultaneously, NO, through nasal breathing at rest, 1) dilates the capillaries of the sinus, which stimulates neurons directly thru a neurovascular communication mechanism (simultaneously occurring with optic, auditory, tactile, gustatory senses); and 2) increase stimulation along the olfactory nerve and potentially pass to the HC axis, the HPA axis, and other interneural loops that regulate autonomic functions like HR,

respiration, blood pressure, digestion etc., along with mood, sleep cycle, fluid balance, and reproduction. One can understand then that during altered homeostasis, including reaction to a sense of danger, voluntary exercise, or increased arousal, the same cascade is initiated to a degree proportional to the perceived necessary reaction level by an immediate increased initial inspiration.

One can further hypothesize that NO and its impaired function (including oral breathing which potentially reduces intake/production/stimulation of NO mechanism), since it is so intimately associated with so many axes and interneural regional loops throughout the brain and connecting to the body, potentially leads to 1) decreased perfusion and 2) brain atrophy; and plays a significant role in mental health (51, table 1 and 2). It is unknown whether mental health disorders lead to atrophy or if atrophy leads to mental health disorders. However, regular exercise may help to ensure normal mental health functioning by increasing neural stimulation and acting as a potent treatment for mental health disorders (77, 156).

Diseases associated with aging are well known. In addition, as we age, levels of physical activity tend to decline. Therefore, if NO, a vasodilator whose levels increase with exercise, decreases with a decrease in physical activity associated with aging; and if ET-1, a vasoconstrictor associated with atherosclerotic disease, increases as NO decreases; then aging itself may be associated with a decline in NO and concurrent rise in ET-1. It appears mindfulness (meditation), which centers on breathing, can mediate the effects of aging which are related to vascular disorders (78, 126, 132). According to a review by Epel (2009) meditation can potentially slow aging by affecting the level of stress arousal, and biological markers of aging (figure 4).

Table 1. Mental Disorders and their associated regions of brain atrophy.

Study	Mental Disorder	Atrophied Region(s) of Brain
(107)	Borderline personality disorder	Frontal lobe
(17)	PTSD	Hippocampus, Medial PFC
(174)	ADHD	Basal ganglia, Corpus collosum
(121)	ADHD	Right sided fronto-parietal grey matter, bilateral white matter
(64)	Cushing's Disease	Diffuse
(38)	Depression	Prefrontal cortex & Hippocampus
(57)	Depression	Anterior cingulate, Prefrontal cortex, Basal ganglia, Cerebellum
(25)	Alzheimer's Disease	Global, medial temporal lobe
(148)	Alzheimer's Disease	Temporal lobe, Medial parietal lobe, Frontal lobe
(9)	Autism	Limbic system, Cerebellum

Table 2. Mental disorders and their associated region of decreased perfusion.

Study	Mental Disorder	Decreased Regional Cerebral Blood Flow (rCBF)
(69)	Borderline personality disorder	Temporal cortex, Prefrontal cortex
(31)	PTSD	Limbic regions, Frontal and Temporal cortex, diffuse
(94)	ADHD	Prefrontal & Frontal cortices, Cerebellar cortices
(11)	Depression	Prefrontal cortex, Anterior Cingulate cortex
(10)	Depression	Prefrontal regions, Limbic areas
(2)	Alzheimer's Disease	Temporal, Parietal, Frontal, Posterior cingulate cortices
(75)	Autism	Prefrontal & frontal regions, generalized hypoperfusion
(63)	Autism	Global

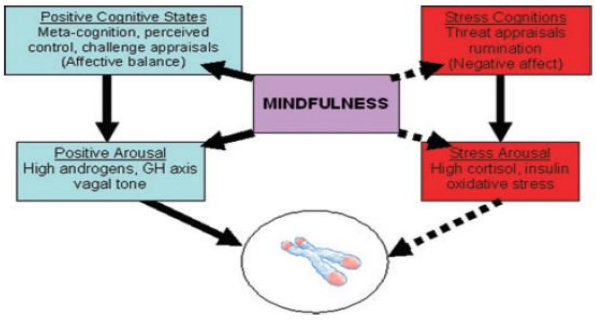

Figure 4: A model for the effect of meditation on biological markers between positive and stressful states of cognition. Inverse relationships are represented with dotted lines. In this model positive cognitive states are linked to increase positive affect and lower negative affect while stress cognitions represents the inverse of this. Non-stress states promote a healthier HPA axis on homeostasis leading to positive arousal. These two pathways seem to counter-regulate each other producing opposite effects on telomere length. Source: (48)

NO, through proper breathing technique and adequate amounts of physical activity, is ubiquitous in its ability to properly maintain the human mind and body (42).

NITRIC OXIDE AND LONG-TERM POTENTIATION WITH ANALOGY TO EXERCISE SCIENCE

As we have shown throughout, NO is an essential component of neuronal function including, differentiation of progenitor cells (28, 133), signaling (60, 83, 124), neurotransmitter release and LTP (see next section). Exercise science is the study of how the human body physiologically reacts to environmental stress and increased workload. Much of the inquiry of Exercise Science deals with studies surrounding the insertion of the neuron at the neuromuscular junction and less on its corresponding origin in the brain and the plasticity activated in response to increased physical activity and new motor learning. The neuron pathway has its point of origin in the brain and a point of insertion in the body. Similar to a muscle fiber, a neuron can gain and lose strength as well. Practically every cell in the body has a corresponding neuron that is connected to a pathway that leads to some focal point in the brain.

The overarching concept of exercise science is the principle of overloading. Briefly, overloading simply involves forcing a

muscle group to perform at a higher level than normally accustomed. Continual progressive overloading leads to increases in size, strength, and endurance. This is also true for pulmonary efficiency and heart health. What is less accounted for is that this same principle is also true for brain health and neuron efficiency as well (as described in the previous section). As neurons receive increased electrical stimulation they potentiate more robust synapses (endurance), increase dendritic spine growth (strength), and arborization (size) (161).

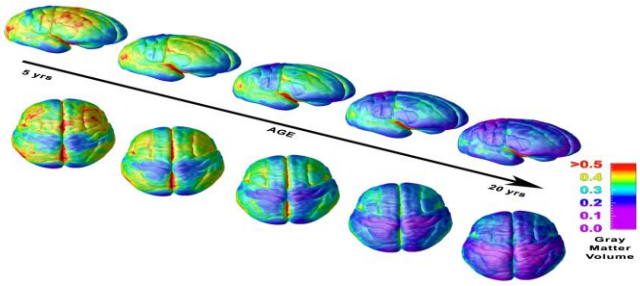

Figure 5. Development of the human brain from childhood to early adulthood. Yellows and reds represent the grey matter mass, and blue, purple and green represent the transition to white matter mass. Grey matter is associated with basic functions and white matter is associated with higher-order cognitive thinking. Source: (71).

One theory behind strength gain and increased reaction time is that due to overloading there will be a potentiation of new neuromuscular junctions having more neuronal connections with a greater number of muscle cells via end bulb and endplate connectivity across the neuromuscular cleft. This provides increased stimulation to an increased number of muscle fibers for increased contraction speed and power. What is left unconsidered is the plasticity correspondingly occurring at the origin of the nerve pathway associated with specific movements and/or activities. In addition, consideration should be given to what is not happening at the point of origin in the CNS in those individuals who are not overloading the muscles with increased physical activity.

Long-term potentiation

Long-term potentiation (LTP) can be described as the increased efficiency of synaptic transmission in excitatory pathways throughout the brain as a response to high frequency stimulation (RFS). RFS bursts occur during normal thinking processes along mossy fiber pathways and increase dendritic spine number and synaptic strength (109, 130,163). RFS happens not only along existing pathways but actually causes the outgrowth of new structures from dendrites, literally morphing the neurons and their networks (114, 134). Neuroscientists are discovering that these effects are not localized in the brain only, but throughout the CNS (172). LTP is also associative and does not only affect the synapse in which the excitation occurs but also other active synapses adjacent to it and can last for days and hours with positive effects on neural circuitry (115). Logically, increases in RFS would play an important role in neural development from formation in the womb throughout the lifespan (figure 5).

This data suggests that LTP innervated by activity in the brain, caused by the induction of bioelectric activity through afferent information received by the five senses, literally changes the shape (134) and ability of the brain to process and store information as memory; in turn, enhancing

the brains ability to send efferent signals to the body for improved reaction to stimuli causing amplification in motor, enteric, pulmonary, and neuronal development. The importance of understanding this process in relation to exercise, mental health, and neural development throughout the life-cycle cannot be overstated. What is actually occurring during exercise and new motor learning is simultaneous potentiation of the neuron pathway from the origin in the brain to muscles and other systems at the neuronal insertion in the body. This specialization leads to increased reaction speed and signal transfer from the brain to the body in coordination with the five senses whose associated neuronal templates are being potentiated (exercised) in concert. These are the processes that morphologically increase the density of the brain into adulthood through normal development. Lastly, there is a failure to appreciate that the brain is actually a 5-dimensional organ with regard to five sensory inputs. With every stimulus from any sensory perception, it is all being received in concert with stimuli from four other senses. Simultaneously, these concerts of neurons, coordinated from specific brain regions, form templates (figure 6). Each sense forms a template of neurons stimulating different parts of the brain. This is happening in 5 completely different pathways at every instance simultaneously!

The increased strength of the brain-body connection and its efficiency come from continual exercise and physical activity throughout an organism's lifespan. The foundation for optimized development is dependent on the mother during fetal evolution (96, 105), and then on through the developmental stages into adulthood and throughout the lifespan.

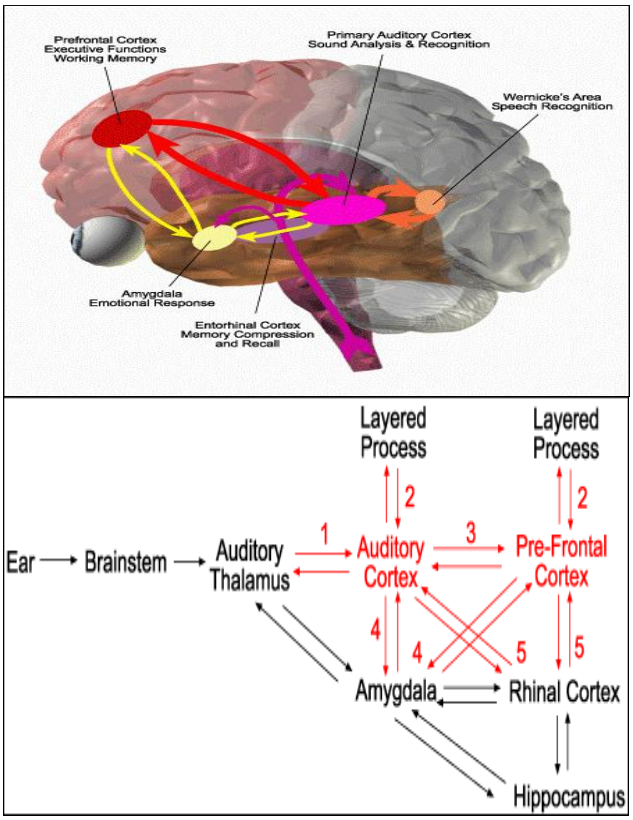

Figure 6. A brain and flat schematic of the template of neurons associated with the sense of hearing. Source: (92).

It goes without saying that the increased exercise of the neural template will create proficiency, the result being seen in the musculoskeletal and cardiopulmonary system and measurable as increased strength, coordination, intelligence, and VO_2 max. Alternately, if an organism does not overload the neurons with stimulation through exercise and physical activity, then, just like unused muscle tissue, the brain will experience atrophy in various regions. This atrophy can potentially lead to physical manifestations as seen in disorders such as Parkinson's (166). Further, if some form of physical activity is not prescribed,

Table 3. Correlates of exercise and fitness on neuroanatomy and cognitive function

Study	Activity	Duration	Outcome
Exercise and brain volume			
(32)	Aerobic vs. stretch/toning	6 mo	Significant increase in brain volume
(46)	Peak VO_2	Acute	Increased fitness is associated with increased hippocampal volume and is associated with increased spatial memory performance
Exercise and neurogenesis			
(19)	Graded treadmill test	Acute	VO_2 peak was associated with decreased brain atrophy in ALZ patients
(112)	Estimated VO_{2max}	Acute	Increased aerobic fitness is associated with an increased white matter integrity in pre-frontal brain region
Exercise and cognitive function in older adults			
(96)	(Aerobic) P.A. intervention	6 mo	Modest cognitive improvement
(8)	3x graded treadmill test	6 yrs	Cardiorespiratory fitness predicted preserved cognitive function and performance over 6 years.
(49)	Aerobic training vs. mental training vs. combined group	2 mo	Combined training group increased cognitive function better than aerobic or mental only groups. Aerobic training group showed significant improvement over controls.

then it is well known that disease and increased mortality can result.

There are several types of potentiation: long-term potentiation (LTP), short-term potentiation (STP), and postactivation potentiation (PAP) that increase neurogenesis not only in the brain, but throughout the CNS (171, 172). The opposite of potentiation is depression (LTD). Growth, throughout the life cycle, is nothing more than potentiation of physical attributes when needed and depression of attributes when they are not needed. The repeated encounterance to certain stimuli leads one to proficiency of movement in response to that stimulus, thus developing expertise. Cognitive functioning adapts much the same way. Adaptation by potentiation not only occurs for neurons (to which it applies), but similar processes occur for other cellular structures throughout the body. This, in turn, leads to improved motor learning that enhances cardio-respiratory and skeletal muscle systems' efficiency. This plasticity leads to increased physical performance. Increased physical activity leads to greater sensory perception, proprioception, and reception by the CNS. The increase in afferent information received by the CNS leads to improved cognitive function (90,161, Table 3) through the development and strengthening of motor and cognitive networks (122). We can deduce then that exercise and physical activity drives LTP throughout the CNS which is dependent upon the increased intake of NO across the sinus and into the lungs. CNS potentiation and neurogenesis then, as a direct consequence of increased NO and due to increasingly efficient efferent signal transfer leading to increased recruitment of motor units, leads to increases in sport performance (145, 146) and learning proficiency (See next section for review).

NITRIC OXIDE, ENRICHMENT, AND LEARNING

Up to this point, we have shown the relation of NO as a switching mechanism

used to initiate vascularization and LTP and how various intensities and durations of exercise can contribute to increasing systemic volume of NO. In this section we will parallel these increases to how proper levels of physical activity (as a type of enrichment along with nutrition and chess) also increase LTP and how that neurological enhancement is correlated with improvements in learning. Much of the research conducted on how diet, exercise, and enrichment affect learning, memory, and neurogenesis involve rodents and other non-human mammals. The correlates to human learning are implied because of the similarity of the rodent brain to humans as well as many other cost-effective and ethical considerations. The similarities on brain behavior have been experimentally verified (137). However novel and profound the implications are, and whatever mountain of research exists substantiating the premise that exercise, as an aspect of enrichment, induces neurogenesis, LTP, and a host of other positive effects on cognitive functionality and social behaviors; the fact remains that the majority of tests are on rodents and not humans. When trying to develop what neurologists have learned over the past 25 years and adapting that to human biological development and learning, the transfer becomes infinitely more complex. In fact, there are at least 80 teaching-learning models (91) and developmental psychologists are continually attempting to add to this rich diversity (39). This is mind-boggling, and anyone taking a wide-angle view can understand how this could actually be pushing human learning in the opposite direction of its intended purpose. In fact, a perspective by Daniel and Poole (2009) state, "It is clear that the sheer complexity of the environments we are creating for students may pose a serious threat to their motivation to engage in learning" (p.94). The article goes on to state that while a certain teacher may have been trained to teach in one model to a varied group of students in one class, another teacher was taught another model to teach another group of varied students in the next class, and so forth. The problem becomes that for students exposed to these models some will excel and some will be harmed by that method of teaching. In Exercise Science all of the research can be neatly shown to relate to one over-arching, easily defined principle; overloading (ibid.). However, no matter what field you are in, whether it is psychology, education, sociology, or even motor learning, it appears the reason there are so many models for learning is due to the fact that learning, in a human biological context, remains undefined (30, 169). According to White (1996), the majority of teachers have been equipped, not with understanding the brain and its plasticity, but with "how you do it teaching manuals", and this is largely inadequate for teaching one lesson plan to a classroom full of individuals. Building a foundation from the studies on rodents, defining an interdisciplinary principle for human learning, and describing a process that accelerates cognitive ability will be the keys to solving the education crisis.

Environmental Enrichment

Environmental enrichment, through controlled experiments with mice, involves groups of animals engaging in social stimulation while interacting with a variety of objects including, running wheels, tubes, platforms, etc. Similarly in humans, enrichment involves the addition of many

toy-like items (168). However, and more applicable for all children in a group and across ages, enrichment may also involve physical education, music/dance (as a form of motor learning), chess, and nutrition. The effect of this kind of enrichment versus social isolation in rodents is profound, including reductions of the stress response to social anxiety (12, 123, 149), a sort of epidemic in human children in an educational setting.

In a very telling experiment, Praag et al. (1999) showed that increased neuronal cell proliferation was observed only in rats that had voluntary access to a running wheel (See Nitric Oxide and the Human Body section: NO is a switching mechanism for cells to go from proliferation to differentiation into tube-like formations and neurites/LTP/neurogenesis). As well, new cell survival was doubled in the enrichment and voluntary exercise group. Rats that were forced to learn a water maze or forced swimmers (while wearing a yoke) experienced no change in cell numbers (Figure 7). This confirms the results of an earlier study from Bernstein (1975). Bernstein concluded that rather than wheel running, the important variable was the free access to environmental enrichment. This demonstrates that restraint stress and/or forced learning (which increases cortisol and stress) leads to impaired neural development while free, voluntary access to physical and visual enrichment lead to enhanced neurogenesis and improved learning. This is also complicit with the observation that tonic/background dopamine, the neurotransmitter known to regulate emotional response to stimuli, is necessary to assist the induction of LTP (strengthening of the synapse).

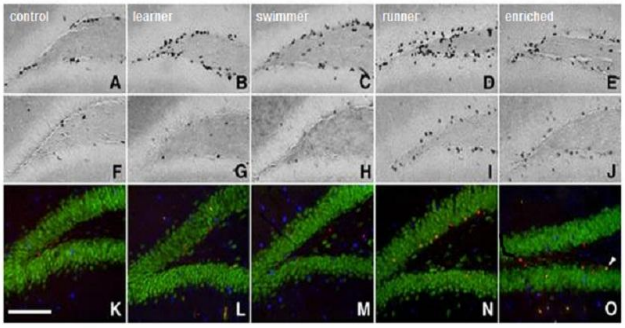

Figure 7. Proliferation and neurogenesis in rodent dentate gyrus. BrdU-positive photomicrograph images (a-j) show cell proliferation and survival in rodent dentate gyrus between first day (a-e) and after 4 weeks of intervention (f-j). Confocal images (k-o) show immunoflourescent images of differentiation into neuronal phenotype (green) and glial phenotype (blue). Arrow in (o) shows BrdU-labeled neurons. Scale bar 100 µm. Source: (140).

Relating these ideas back to human models, a study of 100 preschool children at 3 years old were placed in a two year enrichment program and 100 controls matched for age, gender, and ethnicity were placed in a two year program in a normal preschool setting. All subjects were tested for skin conductance and electrical activity of the brain (EEG) prior to the study and 8 years later at 11 years old. Enrichment consisted of field trips and gardening, conversation sessions, nutrition and hygiene, free play, educational games, and music. At 11 years old, the enrichment group had better skin conductance measures and decreased slow-wave EEG measures. There is a significant trend here to notice: forced learning has minimal measurable outcome and early enrichment prior to entering kindergarten has lasting effects on a child's brain activity. Voluntary exercise, associated with tonic/background dopamine levels, leads to enhanced neurogenesis and increased electrical activity in the brain of humans

and rats. In addition, exposure to enriched environments has also lead to increases in BDNF in the cerebellum (4) and NOS which lead to improved behavioral and cognitive performance in prepubertal rats (104).

Physical education and appropriate exercise leads to improved cognitive performance and academic achievement

Those who wish to expand learning in students have more emphasis on inculcating with facts and memorization than enhancing actual cognitive ability. Learning naturally and easily flows from those children whose minds are ready and capable of handling the social stimulation and rigor of a classroom setting with information loading. Those who are not enriched prior to entering the school systems will quickly fall behind and become isolated and tend toward deviant behaviors (27). Substantiating this is a study by Coe, et al., (2006), comparing moderate and vigorous physical education on academic achievement of sixth-grade students. They found that students in the vigorous group, who met Healthy People 2010 guidelines (having 60 min of physical activity per day), were associated with higher grades. More importantly, the decreased classroom time of the groups did not translate into lower academic performance. In another study a system of play, titled PRIDE for PLAY, was used to test social-emotional learning (SEL) outcomes and academic achievement after a 10-week intervention. SEL was measured by a self-report questionnaire and students showed significant behavioral improvements. However, there was no difference reported on academic testing scores. There are two reasons why this might be. As noted by Coe et al., (2006), the activities might not have been of a vigorous enough nature to show a benefit, and the students may not have been involved in any activities that required heightened attention or awareness adequate enough to stimulate LTP and/or neurogenesis. This sentiment is echoed in a review article by Sattelmair and Ratey (2009) who suggest that physical education needs to be modernized and to become more focused on an approach that brings students greater experience with a variety of sports that involve activity of a strenuous nature. The effect of the attentional focus from exposure to new motor programs, which physical education curricula requires, is clearly shown to cause LTP and neurogenesis in imaging studies on aerobic/non-aerobic physical activity and motor learning (90, table 3).

Exercise has been shown to increase scholastic performance (25, 74, 79, 165), cognitive ability (34, 81), and improved behavior (6, 7). The research by Hillman, Castelli, and Buck (2005) is significant for two reasons: 1) high-fit children (classified according to FITNESSGRAM normative data for age group)were shown to recruit larger populations of neurons than low-fit children and low/high fit adults (also classified according to FITNESSGRAM category for age)indicating that high-fit children have a greater propensity and are better adapted cognitively for new learning; and changes in 2) the neurocognitive processing ability of both high-fit children and adults was faster than that of low-fit children and adults. This is supported with the observation that increased cerebral blood volume (CBV) and increased capillarization of the brain are induced by exercise (15,138). The results of Castelli et

al., (2007) also indicated better academic achievement being associated with lower BMI and higher aerobic fitness regardless of age, gender, or school.

As was shown previously above the initial benefit of vigorous activity during a properly designed physical education course is the increased breathing through the nasal sinus which stimulates brain blood flow and increased NO production, both essential components of what we will define as true learning. Learning is simply the adaptation of the sum of the neural networks within the brain and CNS. This is applicable across all domains. If there is not a corresponding strengthening of the synapse or template of which that synapse is a part, then no learning has occurred, no new synapses will be developed, no new cells will be created, and test scores will remain unimproved. As a result, learning capacity and academic achievement will decline over time as students grow older.

Chess as a method of mental enrichment

Chess is an effective tool for improving cognitive and academic performance and demonstrating intelligence (58, 65, 82, 85, 117, 151). The same processes shown to be important to chess: pattern recognition, search processes, and memory are applicable and similar across many career domains where specific recall under pressure is important and in some cases life-dependent (66). Chess play shows major differences in imaging studies on the regions where electrical activity of the brain occurs between novices and experts (3, 5, 22, 127, 129). Chess provides the increase in electrical stimulation necessary to initiate increases in neurogenesis/ LTP as governed by NO even when the body is at rest or incapable of physical activity (refer to section 3.1 and 3.2). New learning appears to activate specific regions of the brain in chess that are different from the already associated 'chunks' of familiar positions that experts recall from long-term memory (LTM) (67). This is confirmed by a study on verbal reasoning skills which showed that different brain circuits were used during naïve or practiced performance (141). These studies would suggest, confirming Jeuptner et al., (1997) which as one begins to learn any new information it will be associated and encoded as a template in memory (134). As one gains experience with the exercise of that template over many hours of practice, then one becomes an expert due to the plasticity taking place. If it is the 'overloading' principle that drives potentiation for generation of new dendritic morphology so the mind and body can adapt to new stimuli, then the sheer volume of new spatial patterns in chess, stimulating activation in a broad spectrum of brain regions to induce LTP (103), could be deduced to be the mechanism for the improvement of chess players' cognitive performance over controls.

Nutrition as an essential component of normal development and any enrichment program

The importance of nutrition, as including both diet and supplementation, cannot be overstated in the process of neurogenesis and LTP throughout the lifespan. Conventional knowledge tells us that without proper nutrition, the system breaks down due to the fact that the essential chemical elements for every cascade in any biological process are gained through external sources, i.e. food. The following isolated food elements demonstrate how

important chemical substrates are for aiding and enhancing the role and proper function of NO for increasing brain perfusion and LTP. Simply stated, eating a quality breakfast on a daily basis is shown to improve scholastic performance (37,142). Of particular importance are the Omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) due to their relevance to cognitive function and anatomy (118, 131). In order to build new neural networks by way of potentiation; the proper nutrients are going to be essential materials for the formulation of those networks. Deficiencies in DHA and EPA have been implicated in the psychopathologies of developmental disorders and schizophrenia (112, 135, 136, 143), autism (170), cognitive aging (167), learning (63, 160), and Alzheimer's disease (98). Remarkably, all of these deficiencies are reversible due to the fact that the body only produces these substances on a limited basis and they must be gained through diet and supplementation (110). Further, since EPA and DHA are linked to LTP and dopamine transmission, then this would make a strong link to the developmental disorders and the possible intervention of strategies that would increase supplementation to support LTP as treatment of these disorders. Similar neurological outcomes can be seen with supplementation of vinpocetine/ vincamine for dementia (55), increasing cerebral blood flow (rCBF) and enhancing memory (76, 111, 159), and increasing motility of dendritic spine morphology, showing the pathophysiology between LTP and cognitive function (101). Many of these same effects are also beneficial for healthy populations after only 3 days of supplementation (157). Gingko biloba, a plant extract (GbE), has shown positive results on working memory and executive processing (155), and general intelligence and cognitive performance (92, 139, 144). As we can see, many substances, taken for centuries by many cultures, show us how nutritional elements are essential for brain development and restructuring. A simple balanced breakfast and obtaining the essential fatty acids EPA and DHA in proper amounts through diet can provide an incredible boost to children's developing minds. On the other hand, the absence of these components gives us clues as to why children are falling behind in educational settings.

Exercise, Chess, and Nutrition: a synergistic effect on development and mental health?

Due to the emergent technologies of Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT), studies on visualization of brain activation during learning of new motor programs through exercise, playing chess, and nutrition; it appears that the effects these activities have on learning ability is more than corollary and probably causal (table 4). LTP has been induced by exercise such as vigorous physical activity, and nutrition such as maintaining proper levels of fatty acids. Although it is impossible to teach any other mammal how to play chess, there are studies on rats linking experiments that induce LTP to human chess ability, since both can be exposed to spatial novelty (5, 103). Chess is a continuous flow of differing spatial novelties of two possible variations (41) in a single game; let alone what one would encounter through a lifetime of playing chess. The implication here is that

Table 4. Imaging Studies that Reflect the Role of Exercise, Nutrition, and Chess on LTP and Brain Activation

Exercise		**Effect**	**Brain Region**	**Function of brain region**
fMRI	(137)	Rats& Hum: exercise increases CBV and correlates with neuro- genesis, cognition and fitness level	Dentate gyrus and hippocampus	Encoding and analysis of new information, memory.
PET	(56)	A) Specific rCBF increase indicating synaptic change and adaptation, B) increased activation	B) Primary somatosensory cortex, primary motor cortex, cerebellar cortex, premotor cortex	Motor skills of a repetitious and patterned nature.
PET	(90)	Brain regions activated during NEW were not activated during ATT	Dorsal prefrontal cortex, Dorsal anterior cingulate cortex	Executive functions and social thinking, rational functions and decision making.
PET	(150)	Decrease of rCBF of Hippocampal-complex, limbic, and para-limbic structures as learning increased	A) Basal ganglia, Motor areas, cerebellum, red nucleus; B) Right hemisphereC) Motor areas	Motor skills of a repetitious and patterned nature.
PET	(81)	Improved reading achievement	Fronto-central, central, and parietal regions	Executive functions, integrating sensory information
Nutrition				
SPECT	(144)	Increased cognitive function; Reduced blood viscosity; increased CBF increased mental control; increased general intelligence; all after T and follow-up	L/R hemispheres: frontal and parietal regions.	Executive functions and social thinking, rational functions and decision making; sensory integration and navigation.
PET	(159)	Increased rCBF in stroke region, with marked increases in flow in non-affected regions	Basal ganglia, pons, mesencephalon, occipital and frontal cortex, thalamus	Motor control, learning, visual, executive functions, sensory relay.
EEG	(160)	learning disability was reversed in DHA deficient rats after supplementation w/DHA	Cerebral cortex, hippocampus, striatum	All higher order thinking, sensory, association, and motor; memory; attention
EEG	(73)	Improved learning deficits in rats with DHA deficiency	CNS	Afferent/Efferent signal transfer
2PM	(81)	Significant increase in dendritic motility, morphology	Dendritic spines in neocortical layer 2/3 pyramidal cells	All higher order thinking, sensory, association, and motor function, imagination
Chess				
MEG	(3)	Marked differences in the focal brain activity of novice and expert	N: medial temporal lobe, hippocampus; E: neocortex	N: Encoding and analysis of new information; E: expert memory
PET	(127)	Increased activation	premotor cortex, occipital lobe temporal lobe, hippocampus, cerebellum, prefrontal cortex	Indentifying objects, perceiving spatial relations, spatial vision and attention; memory and cognitive processing; managerial knowledge, planning, executive functions.
SPECT	(13)	Localized brain activation of non-dominant hemisphere; rCBF significantly increased during observation (obs).	RH: r-prefrontal cortex & r-temporal cortex;LH: l-prefrontal cortex & l-temporal cortex	Executive functions and social thinking, rational functions and decision making; auditory processing, semantics and LTM.
fMRI	(5)	Bilateral activation; left hemisphere (Lh) more active than right hemisphere (Rh)	BA 7, 19, 39, 40; Lh only: BA 6, 8, 9	Perceiving spatial relations, spatial vision and attention, speech; Motor skills, eye movement, working memory.
fMRI	(22)	Experts brain activation pattern different from novices.	Novices: temporal areas, frontal, cerebellum, post. cingulate cortex	Auditory process, semantics and LTM; coordination, sensory perception, learning, motor control; episodic memory, cognitive function.

Box 1. Exercise oxygen consumption as analogy of learning ability.

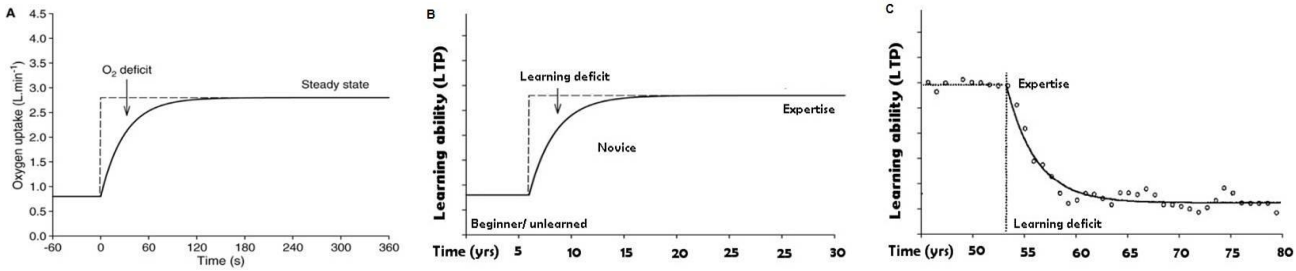

Figure 5. A) At the onset of acute exercise the body's need for oxygen increases. This results in an O_2 deficit resulting in rapid breathing to supply the need for O_2 as the body reaches steady state. In an untrained individual the time to reach steady state is longer than in a trained individual. Also, the body uses two different systems to produce energy: anaerobic, at the onset, becomes increasingly more aerobic as steady state is reached. B) A similar type of event could be described for learning. As the brain processes new stimuli, a 'learning deficit' occurs. Instead of increasing breathing, the brain increases LTP. Just as exercise uses two different systems to produce energy from one state to the next, the brain alters the neural net in response to new learning and expertise. C) As one progresses to the level of expert, or learning steady state, LTP sharply declines returning to the new learning levels of the beginner. This graph does not indicate a decreased ability for new learning or an inability to induce LTP with new learning in aged populations. All graphs are relevant with respect to acute or long-term exercise. Important: The time to reach expertise for the beginner/ unlearned might be able to be reduced with training, just like the time to reach steady state can be reduced in athletes who practice by performing aerobic exercise. Source: Figure A (19).

chess, even after the body is beyond ability for extraneous physical activity, is capable of continuing to induce neural growth and morphology regardless of age or physical ability (36).

Chess studies are particularly important in conjunction with LTP and exercise and nutrition. Interestingly, with respect to the above cases on the differences between novices and experts, the same process is also at work in the acquisition of new motor skills (150). As well, increased rCBF through supplementation of GbE, was correlated to improvements in executive processing, speed of processing, and working memory; processes that are strongly correlated with chess skill (22, 49, 68). Contextual exercise, in any domain, of newly learned concepts leads to experience. Repetitive experience in many contexts with alternate variations leads to expertise. Learning, physiologically speaking, yields synaptogenesis in the CNS, and repetition does not (15). There appears to be a direct relationship between LTP and learning ability (figure 8).

Supporting this idea is the evidence that LTP can be linked to cerebral blood volume (CBV) and CBV has been positively correlated to aerobic fitness and improved cognition (137). This can be corroborated with research that shows spatial learning tasks, in collusion with increasing levels of physical activity, have been shown to increase fibroblast and neurotrophic growth factor levels in the brain (5, 71) and increased cerebral blood volume, specifically in the Hippocampal/ encoding region of the brain. BDNF and VEGF are essential biomarkers not only of the LTP process (97), but that learning is actually occurring over time (figure 5, Box 1). These

studies are further elucidated by the fact that long-term supplementation of GbE shows no benefit to memory performance (138), indicating that GbE may only be useful for increasing rCBF during new learning and creation of newly developing synapses and neural networks and that the effect of GbE is lost on expertise. LTP is not an affect of expertise, but of new learning and/or encoding of new templates as they, and the body, receive exercise. Engineering a method that would accelerate LTP at the right age of development should have profound and lasting effects on improved cognitive and physical performance in children and adults. Combined, these articles describe a cause and effect relationship between enrichment involving physical education, chess, and nutrition and learning.

SUMMARY AND PERSPECTIVE

The purpose of this review has been to describe the underlying mechanism of NO production and how that molecule acts as a switch with VEGF and BDNF to trigger progenitor cells to go from proliferation to differentiation. This pluripotent, paracrine messenger is the initiator of vascular and cognitive plasticity that results in the enhancement of physical and cognitive performance. This review has also shown how the plasticity of these systems directly cause developmental, social, learning, and behavioral improvements by over-viewing their biological pathways as linked to LTP and neurogenesis occurring as a result of enrichment. As a method of essential enrichment for whole brain improvements and rehabilitation, this review focused on physical education, chess, and nutrition as individual processes that increase neural stimulation through exercise/motor learning, focused attention, and increased cerebral blood flow.

In sum, it has been shown that the basis for general intelligence and physical performance is strictly neurologically based. Duncan (2000) makes a similar claim, stating that, "general intelligence derives from a specific frontal system important in control of diverse forms of behavior." It is the optimal development of this amazing apparatus that effectively separates humans from lower primates and all other mammals and species. In future studies, it would be very interesting to develop research focusing on synergistic effects of these foundational types of enrichment activities and their impact on development and rehabilitation. The first question that comes to mind is, "at what age and duration is optimal to begin such a program?" Two studies also support this question. First, Olson et al. (2006) published a similar review combining voluntary exercise and environmental enrichment. Although by distinct pathways, they concluded that enrichment and voluntary exercise both "massively" increase neurogenesis. However, testing needs to be conducted to see if a combined approach offers more benefits and to what extent it benefits enhanced cognitive performance. Secondly, research showed that increases in NO and cognitive performance after exposure to environmental enrichment was age-dependant (104). To discover the optimal age-range and duration to expose children to these types of enrichment to boost cognitive performance will require several future longitudinal studies to be conducted. In addition, with the advancement of imaging technology and

practice over the past 15 years all of these research opportunities should include such a component to test the definition of learning offered herein.

It is our belief that this review effectively demonstrates the causal mechanisms underlying the increases in neurogenesis as related to improved learning and academic performance as a result of adequate bouts of physical activity of a vigorous nature. Thus, we conclude that the consummate principle underlying all physiological research is corporeal adaptation at every level of the organism observed. With respect to humans, the body learns to function based on the external stimuli from the environment, beginning in the womb, and continuing throughout the developmental stages of life. The unknown potential, met with increased resistance, becomes the kinetics of purposeful plasticity within the vascular and central nervous systems. This plasticity is the observable process of learning. Simply, learning is the acquisition of knowledge or skill. There is only one universal method to objectively demonstrate learning has occurred and that is by the associated plasticity occurring as a result of LTP and neurogenesis. Cognitive learning involves the adaptation of the sum of the neural networks at their origin in the CNS to their peripheral insertion. Motor learning involves the adaptation of the cardiovascular and skeletal muscle systems. These two systems operate reciprocally and synchronously to encompass all human knowledge and skill acquisition. Their adaptation mechanisms, as governed by the interactions: NO-VEGF and NO-BDNF, initialized by the increased inhalation across the sinus, can be summed as learning potentiation.

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