

Exercise: a behavioral intervention to enhance brain health and plasticity

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Extensive research on humans suggests that exercise could have benefits for overall health and cognitive function, particularly in later life. Recent studies using animal models have been directed towards understanding the neurobiological bases of these benefits. It is now clear that voluntary exercise can increase levels of brain-derived neurotrophic factor (BDNF) and other growth factors, stimulate neurogenesis, increase resistance to brain insult and improve learning and mental performance. Recently, high-density oligonucleotide microarray analysis has demonstrated that, in addition to increasing levels of BDNF, exercise mobilizes gene expression profiles that would be predicted to benefit brain plasticity processes. Thus, exercise could provide a simple means to maintain brain function and promote brain plasticity.

In 1890, William James first recognized that one of the most important features of human behavior is the ability to carry out meaningful change [1]. He broadly defined this under the rubric of 'behavioral plasticity'. Since then, this concept of plasticity has been further developed to include structural change in the brain at the cellular, molecular, and system levels, with the convergence of these mechanisms ultimately supporting behavioral plasticity.

Maintaining brain health and plasticity throughout life is an important public health goal, and it is increasingly clear that behavioral stimulation and exercise can help us to achieve it. Such intervention is particularly crucial from middle age onwards, when the brain faces a series of challenges that can include the pathogenesis of neurodegenerative diseases like Alzheimer's disease (AD). Over the past decade, a number of studies on humans have shown the benefits of exercise on brain health and function, particularly in aging populations. Exercise participation has consistently emerged as a key indicator of improved cognitive function [2–5]. Recently, a large, five-year prospective study revealed that physical activity was associated with lower risks of cognitive impairment, AD and dementia in general [6]. Furthermore, a retrospective analysis found that behavioral stimulation and physical activity reduced the risk of developing AD [7]. These data from humans are supported by animal research demonstrating that exercise and/or behavioral enrichment can increase

neuronal survival and resistance to brain insult [8,9], promote brain vascularization [10,11], stimulate neurogenesis [12], enhance learning [12,13] and contribute to maintenance of cognitive function during aging [14].

Exercise and neurotrophic factors

It is possible that some of the beneficial aspects of exercise act directly on the molecular machinery of the brain itself, rather than on general health (as was widely assumed in the early 1990s). To explore this hypothesis, we sought a protocol for an animal study in which exercise would be isolated as the central variable, and that would parallel aspects of human exercise studies. Voluntary wheel-running was selected because it allows rats or mice to choose how much to run (i.e. it avoids confounding variables associated with the stress of forced treadmill running and investigator handling) and it is quantifiable.

Several molecular systems could potentially participate in the benefits of exercise on the brain. Neurotrophic factors have most of the properties that could underlie such beneficial effects. We chose to focus initially on brain-derived neurotrophic factor (BDNF) because it supports the survival and growth of many neuronal subtypes, including glutamatergic neurons [15,16]. Subsequently, as the neurotrophin field evolved, BDNF emerged as a key mediator of synaptic efficacy, neuronal connectivity and use-dependent plasticity [17–20] (Box 1, Fig. 1).

We predicted that a neurotrophin-mediated response to exercise would probably be restricted to motor–sensory systems of the brain, such as the cerebellum, primary cortical areas or basal ganglia. The findings were surprising: several days of voluntary wheel-running increased levels of BDNF mRNA in the hippocampus [21], a highly plastic structure that is normally associated with higher cognitive function rather than motor activity. The changes in mRNA levels were found in neurons, particularly those of the dentate gyrus (DG), hilus and CA3 region. They appeared within days in both male [22] and female [23] rats, were sustained even after several weeks of exercise [24], and were paralleled by increased amounts of BDNF protein (Fig. 2). In addition to the hippocampus, running activity increased levels of BDNF mRNA in the lumbar spinal cord [25], cerebellum and cortex [22], but not in the striatum [22]. Although other trophic factors, including nerve growth factor (NGF) [22] and fibroblast growth factor 2 (FGF-2) [26], were also induced in the hippocampus in response to exercise, their upregulation was transient and less robust than that of BDNF, suggesting that BDNF is a better candidate for mediating the long-term benefits of exercise on the brain.

Research on humans suggests that exercise and behavioral stimulation can maintain or improve

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Box 1. BDNF has neurotrophic and neuroprotective properties and can affect functions that underlie brain plasticity

BDNF is neurotrophic and neuroprotective [a,b]

- BDNF promotes the differentiation, neurite extension and survival of a variety of neuronal populations in culture including hippocampal, cortical, striatal, septal and cerebellar neurons.
- Intraventricular BDNF infusion protects the hippocampus and cortex from ischemic damage and protects septal cholinergic neurons from axotomy-induced loss.

BDNF can enhance brain plasticity [c-f]

- BDNF gene regulation and protein release are activity-dependent.
- BDNF enhances synaptic transmission.
- Mice deficient in BDNF show impaired LTP and present learning deficits that are reversed with BDNF replacement.
- BDNF stimulates synaptophysin and synaptobrevin synthesis.
- Mice deficient in BDNF signaling (trkB mutants) show decreased synaptic innervation and reduced levels of synaptic

vesicle proteins, including synapsin I, synaptophysin and synaptotagmin.

References

- Barde, Y-A. (1994) Neurotrophins: a family of proteins supporting the survival of neurons. *Prog. Clin. Biol. Res.* 390, 45–56
- Lindvall, O. *et al.* (1994) Neurotrophins and brain insults. *Trends Neurosci.* 17, 490–496
- Schinder, A.F. and Poo, M-M. (2000) The neurotrophin hypothesis for synaptic plasticity. *Trends Neurosci.* 23, 639–645
- Lu, B. and Chow, A. (1999) Neurotrophins and hippocampal synaptic transmission and plasticity. *J. Neurosci. Res.* 58, 76–87
- McAllister, A.K. *et al.* (1999) Neurotrophins and synaptic plasticity. *Annu. Rev. Neurosci.* 22, 295–318
- Altar, A. and DiStefano, P.S. (1998) Neurotrophin trafficking by anterograde transport. *Trends Neurosci.* 21, 433–437

brain plasticity. Learning, a high-order of brain plasticity, increases BDNF gene expression [27], and BDNF, in turn, facilitates learning [28]. This predicts that mechanisms that induce BDNF gene expression, such as exercise, can enhance learning. Indeed, running enhances LTP in the DG and improves spatial learning in the water-maze task [12].

Roles of neuronal activity and neurotransmitters
Neuronal activity and neurotransmitter interactions control BDNF gene expression patterns in the hippocampus, with glutamate-mediated signaling being the likely central convergence point. Several modulatory neurotransmitters that converge on glutamatergic neurons, including ACh, GABA and monoamines, could affect BDNF expression.

The medial septum, being a source of cholinergic and GABAergic afferents to the hippocampus, might participate in the upregulation of BDNF in response to exercise. As first reported by Vanderwolf in 1969 [29], voluntary wheel-running activates a persistent firing pattern (known as theta-rhythm) in the rat hippocampus, and this firing pattern is dependent on medial septal cholinergic and GABAergic neurons [29–32]. Extensive literature supports the idea that an ACh-mediated mechanism also regulates BDNF gene expression in the hippocampus, particularly in the basal state [33–35]. This suggests that ACh-mediated activation of the hippocampus could underlie the regulation of BDNF by exercise.

Surprisingly, although septal ACh-mediated input provides tonic regulation of baseline hippocampal BDNF gene expression, it is not a key regulator in the activity-dependent state. Despite causing complete loss of septo-hippocampal cholinergic afferents and a reduction in basal BDNF gene expression, selective lesions of medial septal cholinergic neurons did not impair exercise-induced BDNF gene expression in the hippocampus [36]. By contrast, when partial loss of septal cholinergic afferents was combined with loss of medial septal GABAergic neurons, exercise-dependent BDNF regulation was disrupted, notably in the DG and hilus. Thus, there is a strong involvement of the medial septum in activity-dependent regulation of BDNF gene expression, and it appears to involve either non-ACh-mediated signaling or a combination of neurotransmitter systems [36].

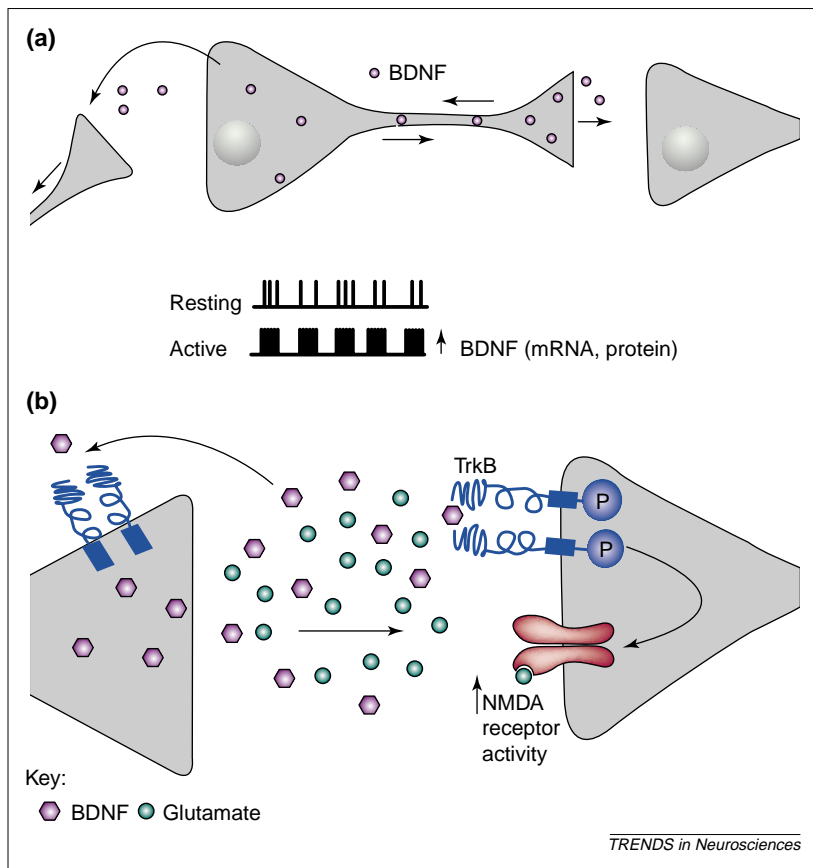


Fig. 1. Characteristics of brain-derived neurotrophic factor (BDNF) that make it a natural candidate to mediate the benefits of exercise on brain health. (a) BDNF is transported retrogradely and anterogradely to synapses, where it potentiates synaptic transmission, participates in gene transcription, modifies synaptic morphology, and enhances neuronal resilience. BDNF mRNA and protein levels increase in an activity-dependent manner. (b) Released BDNF binds to its receptor (TrkB) presynaptically to modify transmitter release and postsynaptically to modify postsynaptic sensitivity, for example, via interaction with NMDA receptors [69,70].

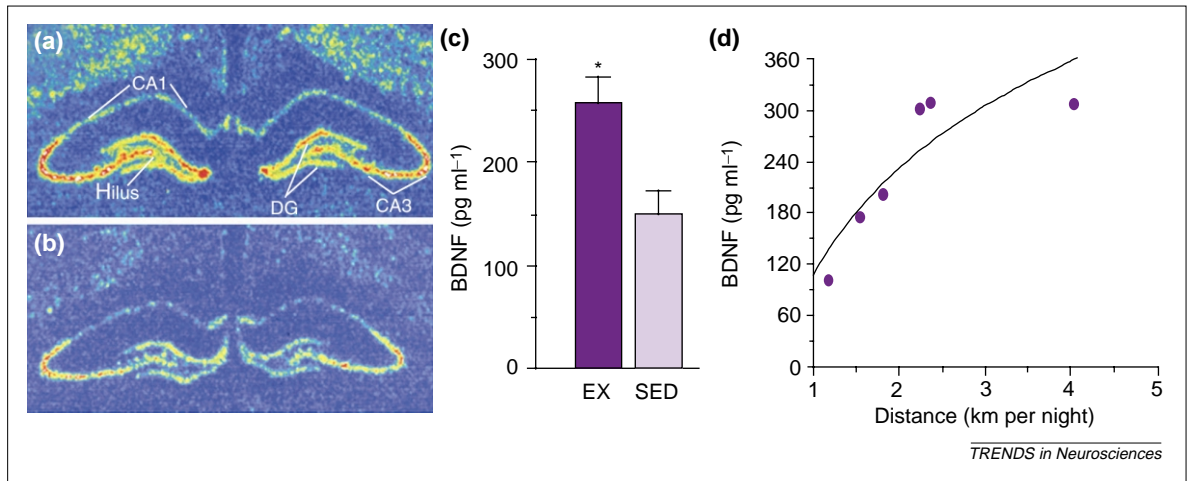


Fig. 2. Effects of exercise on hippocampal brain-derived neurotrophic factor (BDNF) mRNA and protein levels. (a) *In situ* hybridization shows that expression of BDNF mRNA in the rat dentate gyrus (DG), hilus, CA1–CA3 regions and cortex is greater following exercise (seven days of voluntary wheel-running) than in sedentary animals (b). (c) ELISA quantification of hippocampal BDNF protein levels in the hippocampus in sedentary (SED) and exercising (EX) animals, after five days of wheel-running ($*P < 0.05$). (d) Rats and mice acclimate rapidly to the running wheel and progressively increase their extent of daily running, in some cases up to a startling 20 kilometers (~12–13 miles) per night. BDNF protein levels correlate with running distance (average over 14 days running; $R^2 = 0.771$).

Monoamine-mediated signaling also contributes to BDNF gene regulation. Several antidepressants that increase transmission at monoaminergic synapses also increase BDNF gene expression in the hippocampus [37,38]. Interestingly, antidepressant treatment in combination with exercise enhances exercise-dependent BDNF

upregulation in the hippocampus [24].

Noradrenaline-mediated signaling might be particularly important in the modulation of BDNF gene expression by exercise [39].

Regulation by peripheral as well as central mechanisms

Although CNS activity-dependent mechanisms are pivotal in driving exercise-induced changes in levels of BDNF mRNA in the brain, it is now emerging that peripheral mechanisms are also important.

Components contributing to this peripheral control include estrogen, corticosterone and insulin-like growth factor-1 (IGF-1).

Estrogen-dependent upregulation of BDNF gene expression

Steroid hormones such as estrogen influence brain aging, particularly in post-menopausal women. Estrogen replacement (ER) after menopause appears to slow age-related cognitive decline and to delay the onset of AD in human subjects [40]. Conversely, reduced levels of estrogen compromise neuronal function, survival and synaptogenesis in animal models [41], and decrease hippocampal availability of BDNF [23,42].

In females, the benefits of exercise appear to depend on the presence of estrogen [23]. After two months of estrogen-deprivation, exercise no longer increased either BDNF mRNA or protein levels in the female rat hippocampus. By contrast, when exercise was combined with long-term ER, BDNF protein levels showed a greater increase than in response to ER alone (Fig. 3a) [23]. Thus, the presence of estrogen in females might be a permissive factor necessary for exercise-induced regulation of BDNF availability.

Interestingly, levels of voluntary physical activity also depend on estrogen status. Animals were less active in the absence of estrogen, and ER restored activity to normal levels (Fig. 3b) [23]. This effect of estrogen raises the interesting possibility that some of the health benefits associated with hormone replacement in women could be related to increased exercise participation.

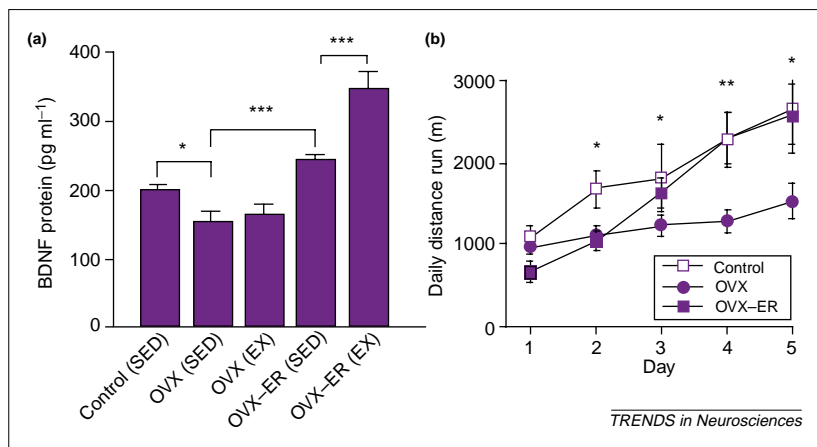


Fig. 3. Effects of estrogen deprivation on exercise-dependent increase in brain-derived neurotrophic factor (BDNF) protein levels and running activity. (a) Exercise and estrogen increase hippocampal BDNF protein levels; however, the effect of exercise is dependent on the presence of estrogen. BDNF levels were lower in sedentary (SED) animals that had experienced eight weeks of estrogen-deprivation (following ovariectomy, OVX) than in intact controls. Four weeks of estrogen-replacement (ER) increased the levels of BDNF protein in OVX (SED) animals. Exercise (five days of voluntary wheel-running, EX) did not significantly increase BDNF levels in OVX animals without ER, but did lead to a significant increase in OVX-ER animals. (b) Estrogen stimulates voluntary running activity. Following three weeks of estrogen deprivation (OVX), running activity was decreased. ER (for five days, concurrent with running-wheel exposure) restored running activity to normal levels. Thus, exercise and estrogen might be part of a positive feedback loop that provides combined benefits to ensure the maintained health and functioning of the brain and body. $*P < 0.05$, $**P < 0.01$, $***P < 0.0001$. For details, see Ref. [23].

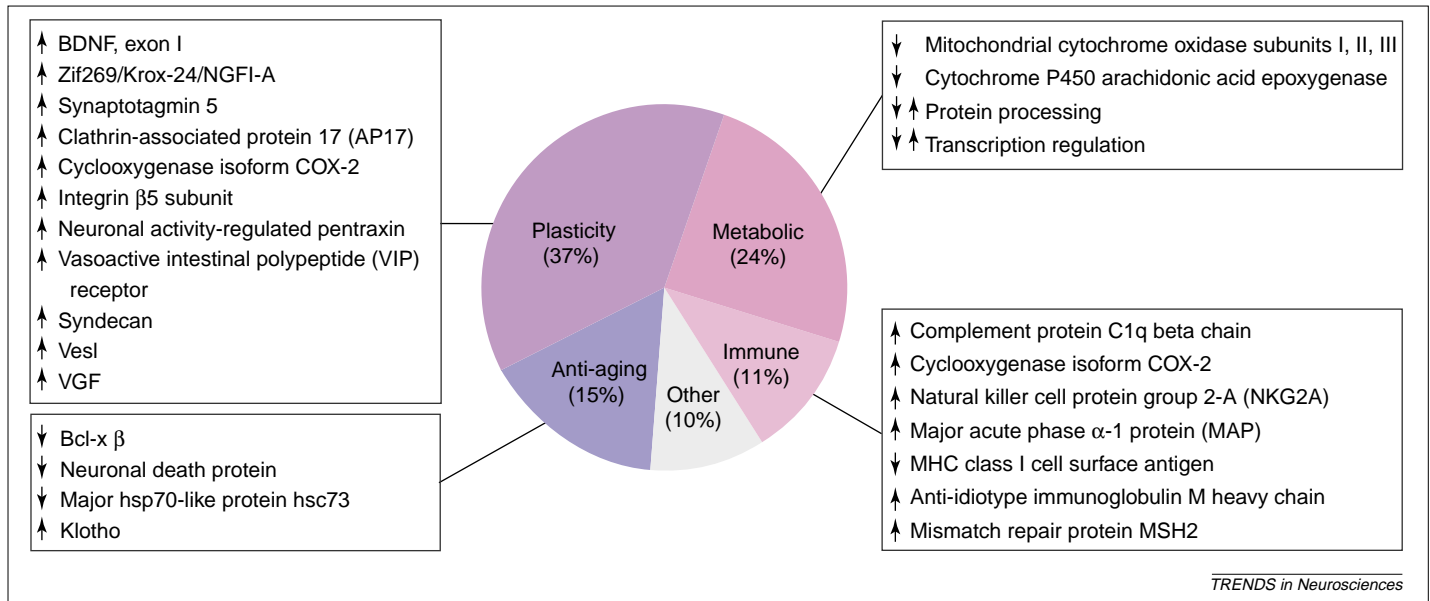


Fig. 4. Effects of exercise on gene transcription. The majority of genes induced by exercise are associated with plasticity and synaptic structure. Other genes regulated by exercise include those associated with immune function, metabolism, anti-aging, protein processing and transcriptional regulation. Abbreviations: BDNF, brain-derived neurotrophic factor; VGF, nerve-growth-factor-inducible growth factor. For details, see Ref. [55].

Exercise and stress: antagonistic regulators of BDNF levels

Prolonged exposure to stress hormones (e.g. corticosteroids) is harmful for neuronal health and survival, particularly in the hippocampus [43]. In response to acute and chronic stress, neurons undergo morphological changes, including dendritic atrophy and spine reduction, which have a negative impact on brain plasticity [44–46]. Exercise is commonly believed to be a behavioral strategy to relieve stress, and can reduce depression and anxiety in humans [47]. Animal studies demonstrate that corticosteroids decrease BDNF availability in the hippocampus [48], although exercise before a stressful event can counteract this downregulation. For example, one week of voluntary wheel-running exercise before forced swimming prevents downregulation of hippocampal BDNF mRNA and improves behavioral measures of stress [49]. The molecular mechanism(s) responsible for the ability of exercise to counteract stress is an exciting field for future research with clear human relevance.

IGF-1 as a mediator of the effects of exercise

IGF-1, a growth factor structurally related to pro-insulin, is a potent survival factor for neurons and oligodendrocytes and participates in neuronal growth and differentiation in the brain [50,51]. In addition, IGF-1 might be an upstream mediator of BDNF gene regulation, neurogenesis and the ability of exercise to protect the brain from injury [9,52]. IGF-1 levels increase in both the periphery [53] and brain [52] after exercise, and at least part of the

increase in the brain reflects increased transport from the periphery across the blood–brain barrier [54]. Interestingly, peripheral IGF-1 appears to participate in the neuroprotective effect of exercise, as peripheral infusion of IGF-1-blocking antibodies before an injury reduces the protection [9]. Because peripheral administration of IGF-1 induces BDNF mRNA in the brain [52], BDNF is potentially a downstream target that mediates some of the protective effects of IGF-1. These data suggest that peripheral IGF-1 initiates growth-factor cascades in the brain that can alter ongoing plasticity mechanisms.

Gene microarray expression patterns that support brain plasticity

In addition to BDNF, a number of other molecular systems that can mediate benefits to the brain are potentially regulated by exercise. To identify other molecular targets, the gene expression profiles of ~5000 genes in the rat hippocampus were examined using high-density oligonucleotide arrays [55]. Three weeks of exercise led to changes – both increases and decreases – in the expression of a number of genes. Many of these genes are involved in synaptic function and plasticity, for example, being associated with membrane and neurotrophic factor trafficking, vesicle recycling or neurite and synaptic growth (Fig. 4). The increased expression of genes encoding several synaptic markers (e.g. synaptotagmin, Vesl and AP17) indicates a direct effect of exercise on synaptic function [55]. It is remarkable that exercise regulates the expression of so many genes in the hippocampus, and the finding underscores the emerging idea that exercise is a powerful effector of brain physiology.

Promotion of neurogenesis

The effect of exercise on genes encoding neurotrophins and other proteins predicts that

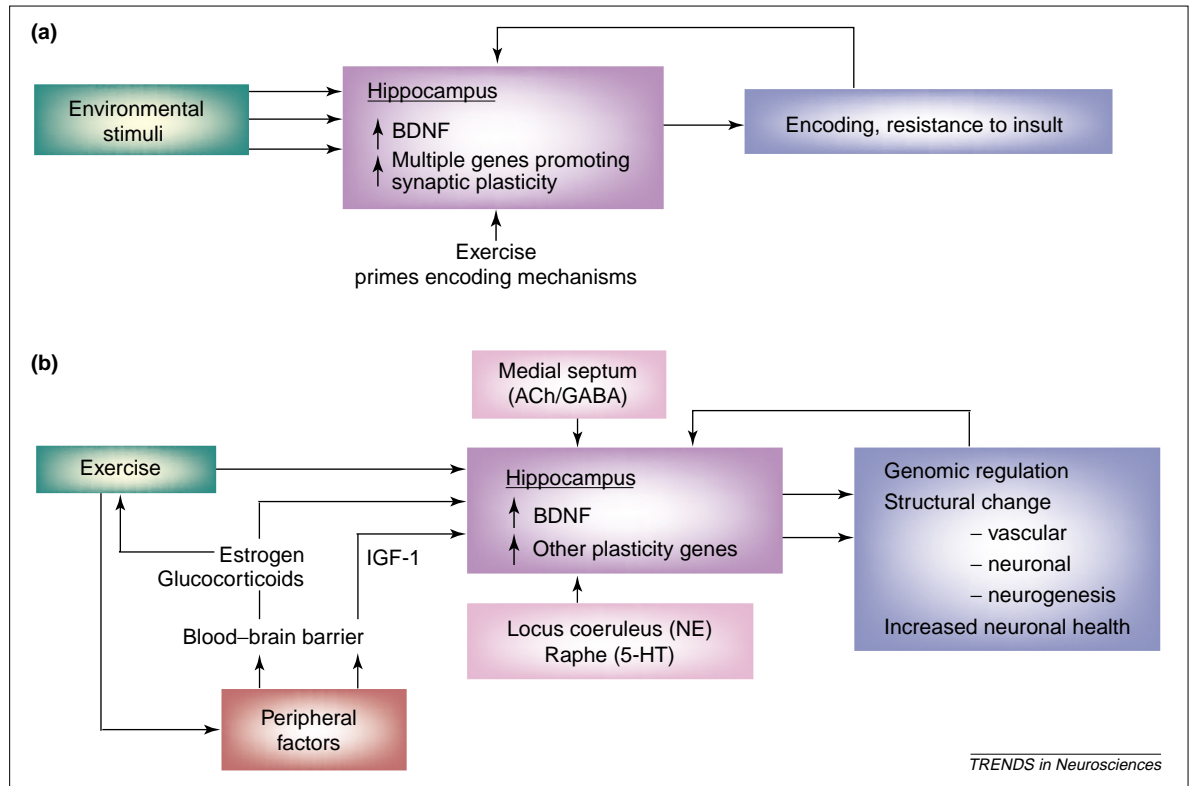


Fig. 5. Mechanisms by which voluntary running primes the brain to encode meaningful information from the environment. (a) Exercise might act as a gate that primes the hippocampus to respond to environmental stimulation, while simultaneously ensuring the viability of neurons to resist insult. These responses, in turn, feed back to strengthen the brain in a use-dependent fashion. (b) Exercise-mediated enhancement of the encoding of information and neural resistance could involve factors such as brain-derived neurotrophic factor (BDNF), a prototypical candidate molecule that can help us to understand how exercise benefits the brain. Multiple factors control BDNF expression in the hippocampus. BDNF is expressed in glutamatergic neurons and its levels are modulated by neural activity and neurotransmitter input from the medial septum, raphe and locus coeruleus. Exercise-dependent BDNF gene changes are modulated by combined septal ACh and GABA inputs, noradrenaline (NE) and peripheral factors. BDNF gene expression is also dependent on steroid hormone (estrogen and corticosterone) status and peripheral entry of insulin-like growth factor 1 (IGF-1) into brain (which is itself modulated by exercise).

exercise could regulate downstream anatomical changes that support brain plasticity. Recently, it has been demonstrated that exercise increases the number of new neurons in the DG of adult animals [56]. Trophic factors, such as BDNF, IGF-1 and FGF-2, might mediate this effect. Exercise increases levels of BDNF in the DG (the progenitor-cell layer of the hippocampus) and BDNF promotes the survival of newly differentiated neurons [50]. Support for the idea that BDNF is a key variable comes from the observation that estrogen [57], corticosteroids [58,59] and neuronal activity [60] each regulate both BDNF gene expression and neurogenesis. Exercise increases brain uptake of circulating IGF-1, a factor that promotes neuronal differentiation of progenitor cells [50,61] and increases hippocampal BDNF gene expression [52]. In addition, levels of FGF-2, a

molecule that stimulates proliferation and differentiation of hippocampal neuroprogenitor cells [62,63], are increased in hippocampal astrocytes after exercise. Finally, microarray analysis reveals increased expression of additional neurogenesis-related genes (e.g. those encoding Krox-24 and VGF) [55] that are likely to act in concert with IGF-1, BDNF and FGF-2 to modulate neurogenesis. Thus, exercise activates a number of factors that converge on neurogenesis.

Common mechanisms underlying plasticity induced by exercise, behavioral enrichment and learning

A robust literature documents that experience and behavior activate brain plasticity mechanisms and remodel neuronal circuitry in the brain. Exercise and behavioral enrichment paradigms, such as environmental enrichment [64], rehabilitation training [65,66] and learning [67,68], affect common endpoints in the brain, including regulation of growth factors, neurogenesis and structural changes. The similarities between the effects of exercise and these well-established paradigms support the hypothesis that there are common mechanisms regulating behavioral plasticity.

Conclusion

Exercise is a simple and widely practised behavior that activates molecular and cellular cascades that support and maintain brain plasticity. It induces expression of genes associated with plasticity, such as that encoding BDNF, and in addition promotes brain vascularization, neurogenesis, functional changes in neuronal structure and neuronal

resistance to injury. Significantly, these effects occur in the hippocampus, a brain region central to learning and memory. BDNF availability could be crucial for these mechanisms. Exercise-driven increases in the level of hippocampal BDNF are controlled by neuronal activity, neurotransmitters and interactions with peripheral factors that include estrogen, corticosterone and possibly IGF-1. The peripheral influence illustrates how exercise can relate overall body status to brain function. Exercise recruits use-dependent plasticity mechanisms that prepare the brain to encode meaningful information

from the environment and, at the same time, activates mechanisms that protect the brain from damage (Fig. 5). By inducing BDNF and other molecules, exercise strengthens neuronal structure and facilitates synaptic transmission, thus, priming activated cells for encoding.

The clinical literature has recognized for years that exercise affects overall health and brain function. Scientific studies are now strengthening the premise that exercise can benefit brain function and are encouraging additional clinical research in this area.

References

- James, W. (1890) *The Principles of Psychology*, Holt, New York
- Berkman, L.F. *et al.* (1993) High, usual and impaired functioning in community-dwelling older men and women: findings from the MacArthur Foundation Research Network on Successful Aging. *J. Clin. Epidemiol.* 46, 1129–1140
- Blomquist, K.B. and Danner, F. (1987) Effects of physical conditioning on information-processing efficiency. *Percept. Mot. Skills* 65, 175–186
- Rogers, R.L. *et al.* (1990) After reaching retirement age physical activity sustains cerebral perfusion and cognition. *J. Am. Geriatr. Soc.* 38, 123–128
- Hill, R.D. *et al.* (1993) The impact of long-term exercise training on psychological function in older adults. *J. Gerontol.* 48, P12–P17
- Laurin, D. *et al.* (2001) Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch. Neurol.* 58, 498–504
- Friedland, R.P. *et al.* (2001) Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3440–3445
- Stummer, W. *et al.* (1994) Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. *Stroke* 25, 1862–1869
- Carro, E. *et al.* (2001) Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *J. Neurosci.* 21, 5678–5684
- Black, J.E. *et al.* (1990) Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc. Natl. Acad. Sci. U. S. A.* 87, 5568–5572
- Isaacs, K.R. *et al.* (1992) Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. *J. Cereb. Blood Flow Metab.* 12, 110–119
- van Praag, H. *et al.* (1999) Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. U. S. A.* 96, 13427–13431
- Young, D. *et al.* (1999) Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nat. Med.* 5, 448–453
- Escorihuela, R.M. *et al.* (1995) Environmental enrichment and postnatal handling prevent spatial learning deficits in aged hypoemotional (Roman high-avoidance) and hyperemotional (Roman low-avoidance) rats. *Learn. Mem.* 2, 40–48
- Barde, Y.A. (1994) Neurotrophins: a family of proteins supporting the survival of neurons. *Prog. Clin. Biol. Res.* 390, 45–56
- Lindvall, O. *et al.* (1994) Neurotrophins and brain insults. *Trends Neurosci.* 17, 490–496
- Schinder, A.F. and Poo, M.-M. (2000) The neurotrophin hypothesis for synaptic plasticity. *Trends Neurosci.* 23, 639–645
- Lu, B. and Chow, A. (1999) Neurotrophins and hippocampal synaptic transmission and plasticity. *J. Neurosci. Res.* 58, 76–87
- McAllister, A.K. *et al.* (1999) Neurotrophins and synaptic plasticity. *Annu. Rev. Neurosci.* 22, 295–318
- Altar, A. and DiStefano, P.S. (1998) Neurotrophin trafficking by anterograde transport. *Trends Neurosci.* 21, 433–437
- Neeper, S.A. *et al.* (1995) Exercise and brain neurotrophins. *Nature* 373, 109
- Neeper, S.A. *et al.* (1996) Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res.* 726, 49–56
- Berchtold, N.C. *et al.* (2001) Estrogen and exercise interact to regulate brain-derived neurotrophic factor mRNA and protein expression in the hippocampus. *Eur. J. Neurosci.* 14, 1992–2002
- Russo-Neustadt, A. *et al.* (1999) Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. *Neuropsychopharmacology* 21, 679–682
- Gomez-Pinilla, F. *et al.* (2001) Differential regulation by exercise of BDNF and NT-3 in rat spinal cord and skeletal muscle. *Eur. J. Neurosci.* 13, 1078–1084
- Gomez-Pinilla, F. *et al.* (1997) Physical exercise induces FGF-2 and its mRNA in the hippocampus. *Brain Res.* 764, 1–8
- Kesslak, J.P. *et al.* (1998) Learning upregulates BDNF mRNA: a mechanism to facilitate encoding and circuit maintenance? *Behav. Neurosci.* 112, 1012–1019
- Tokuyama, W. *et al.* (2000) BDNF upregulation during declarative memory formation in monkey inferior temporal cortex. *Nat. Neurosci.* 3, 1134–1142
- Vanderwolf, C.H. (1969) Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr. Clin. Neurophysiol.* 26, 407–418
- Lawson, V.H. and Bland, B.H. (1993) The role of the septohippocampal pathway in the regulation of hippocampal field activity and behavior: analysis by the intraseptal microinfusion of carbachol, atropine, and procaine. *Exp. Neurol.* 120, 132–144
- Lee, M.G. *et al.* (1994) Hippocampal theta activity following selective lesion of the septal cholinergic system. *Neuroscience* 62, 1033–1047
- Buzsaki, G. *et al.* (1985) Depth profiles of hippocampal rhythmic slow activity ('theta rhythm') depend on behaviour. *Electroencephalogr. Clin. Neurophysiol.* 61, 77–88
- Knipper, M. *et al.* (1994) Positive feedback between acetylcholine and the neurotrophins nerve growth factor and brain-derived neurotrophic factor in the rat hippocampus. *Eur. J. Neurosci.* 6, 668–671
- Lapchak, P.A. *et al.* (1993) Cholinergic regulation of hippocampal brain-derived neurotrophic factor mRNA expression: evidence from lesion and chronic cholinergic drug treatment studies. *Neuroscience* 52, 575–585
- Ferencz, I. *et al.* (1997) Effects of cholinergic denervation on seizure development and neurotrophin messenger RNA regulation in rapid hippocampal kindling. *Neuroscience* 80, 389–399
- Berchtold, N.C. *et al.* Hippocampal BDNF is regulated by exercise and the medial septum. *J. Neurosci. Res.* (in press)
- Nibuya, M. *et al.* (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J. Neurosci.* 15, 7539–7547
- Fujimaki, K. *et al.* (2000) Administration of a cAMP phosphodiesterase 4 inhibitor enhances antidepressant-induction of BDNF mRNA in rat hippocampus. *Neuropsychopharmacology* 22, 42–51
- Ivy, A.S. *et al.* (2001) The effects of NE and 5-HT receptor antagonists on the regulation of BDNF expression during physical activity. *Soc. Neurosci. Abstr.* 25.213
- Garcia-Segura, L.M. *et al.* (2001) Neuroprotection by estradiol. *Prog. Neurobiol.* 63, 29–60
- Wise, P.M. *et al.* (2001) Estrogens: trophic and protective factors in the adult brain. *Front. Neuroendocrinol.* 22, 33–66
- Singh, M. *et al.* (1995) The effect of ovariectomy and estradiol replacement on brain-derived neurotrophic factor messenger ribonucleic acid expression in cortical and hippocampal brain regions of female Sprague-Dawley rats. *Endocrinology* 136, 2320–2324
- Sapolsky, R.M. (1996) Why stress is bad for your brain. *Science* 273, 749–750

- 44 Woolley, C.S. *et al.* (1990) Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res.* 531, 225–231
- 45 Gould, E. *et al.* (1990) Short-term glucocorticoid manipulations affect neuronal morphology and survival in the adult dentate gyrus. *Neuroscience* 37, 367–375
- 46 Watanabe, Y. *et al.* (1992) Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Res.* 588, 341–345
- 47 Byrne, A. and Byrne, D.G. (1993) The effect of exercise on depression, anxiety and other mood states: a review. *J. Psychosom. Res.* 37, 565–574
- 48 Schaefer, M.J. *et al.* (2000) Corticosterone effects on BDNF expression in the hippocampus. Implications for memory formation. *Stress* 3, 201–208
- 49 Russo-Neustadt, A. *et al.* (2001) Physical activity–antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. *Behav. Brain Res.* 120, 87–95
- 50 Arsenijevic, Y. and Weiss, S. (1998) Insulin-like growth factor-I is a differentiation factor for postmitotic CNS stem cell-derived neuronal precursors: distinct actions from those of brain-derived neurotrophic factor. *J. Neurosci.* 18, 2118–2128
- 51 Markowska, A.L. *et al.* (1998) Insulin-like growth factor-1 ameliorates age-related behavioral deficits. *Neuroscience* 87, 559–569
- 52 Carro, E. *et al.* (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J. Neurosci.* 20, 2926–2933
- 53 Schwarz, A.J. *et al.* (1996) Acute effect of brief low- and high-intensity exercise on circulating insulin-like growth factor (IGF) I, II, and IGF-binding protein-3 and its proteolysis in young healthy men. *J. Clin. Endocrinol. Metab.* 81, 3492–3497
- 54 Reinhardt, R.R. and Bondy, C.A. (1994) Insulin-like growth factors cross the blood–brain barrier. *Endocrinology* 135, 1753–1761
- 55 Tong, L. *et al.* (2001) Effects of exercise on gene-expression profile in the rat hippocampus. *Neurobiol. Dis.* 8, 1046–1056
- 56 van Praag, H. *et al.* (1999) Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat. Neurosci.* 2, 266–270
- 57 Tanapat, P. *et al.* (1999) Estrogen stimulates a transient increase in the number of new neurons in the dentate gyrus of the adult female rat. *J. Neurosci.* 19, 5792–5801
- 58 Gould, E. *et al.* (1992) Adrenal hormones suppress cell division in the adult rat dentate gyrus. *J. Neurosci.* 12, 3642–3650
- 59 Cameron, H.A. and Gould, E. (1994) Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience* 61, 203–209
- 60 Cameron, H.A. *et al.* (1995) Regulation of adult neurogenesis by excitatory input and NMDA receptor activation in the dentate gyrus. *J. Neurosci.* 15, 4687–4692
- 61 Aberg, M.A. *et al.* (2000) Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. *J. Neurosci.* 20, 2896–2903
- 62 Palmer, T.D. *et al.* (1999) Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. *J. Neurosci.* 19, 8487–8497
- 63 Yoshimura, S. *et al.* (2001) FGF-2 regulation of neurogenesis in adult hippocampus after brain injury. *Proc. Natl. Acad. Sci. U. S. A.* 98, 5874–5879
- 64 van Praag, H. *et al.* (2000) Neural consequences of environmental enrichment. *Nat. Rev. Neurosci.* 1, 191–198
- 65 Biernaskie, J. and Corbett, D. (2001) Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *J. Neurosci.* 21, 5272–5280
- 66 Tillerson, J.L. *et al.* (2001) Forced limb-use effects on the behavioral and neurochemical effects of 6-hydroxydopamine. *J. Neurosci.* 21, 4427–4435
- 67 Rampon, C. and Tsien, J.Z. (2000) Genetic analysis of learning behavior-induced structural plasticity. *Hippocampus* 10, 605–609
- 68 Geinisman, Y. (2000) Structural synaptic modifications associated with hippocampal LTP and behavioral learning. *Cereb. Cortex* 10, 952–962
- 69 Black, I.B. (1999) Trophic regulation of synaptic plasticity. *J. Neurobiol.* 41, 108–118
- 70 Kohara, K. *et al.* (2001) Activity-dependent transfer of brain-derived neurotrophic factor to postsynaptic neurons. *Science* 291, 2419–2423

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