

Exercise for the brain. Just do it.

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ABSTRACT

Body and mind are not completely separate. Our paper looks at the idea that physical exercise might influence our brains. Firstly there are questions; why should there be such a link, what evidence do we have and how might this knowledge be of benefit? Secondly we look at likely mechanisms of action, in particular IGF-1 and BDNF pathways and consider what could happen in the future. Much of this work has been done in animals but we need answers for humans in whom only observational studies have been done. There are few randomised, controlled trials and none are long enough. Finally, advice; Step 1. Prevent obesity by exercising; Step 2. Get aerobically fit by more intense exercise. The benefits will be improved cognition and memory; and you'll probably have less chance of Alzheimer's disease and other dementias, depression and age-related cognitive decline.

INTRODUCTION

Growth in relative brain size, complexity and associated cognitive development of early members of the genus Homo, was probably triggered by a meat-rich diet around 2.3 million years ago, the start of the paleolithic era.¹ Selection pressures favoured better memory (food sites, hunting techniques, avoidance of predators), cognition (develop new techniques) and performance (physical ability, motivation). By late paleolithic times, our ancestors' genes were finely tuned to a high exercise hunter-gatherer lifestyle.²

Yet today we live sedentary, modern lifestyles but are still genetically programmed for highly physical, stone-age living.

What mechanisms might have evolved to link ability to exercise with better cognition?

In the short term, the fight:flight mechanism of adrenaline and stress hormones enhances energy supply to muscles and brain by improving blood flow and increasing oxygen and glucose supply. Adrenaline improves memory and increases arousal. Cortisol improves neuroplasticity (the ability of the brain to adapt). Together, these hormones increase arousal, enhance vigilance and 'focus' memory processing and attention towards the source of the acute stress.³

In the longer term, growth factors stimulated by exercise, affect both the brain and the body.

All areas of the brain are influenced but especially areas associated with memory and cognition such as the frontal lobes, basal forebrain, hippocampus and entorhinal cortex of the temporal lobe. When we exercise, these areas are protected into old age. Without such exercise, there is an age-related reduction in grey matter volume.⁴

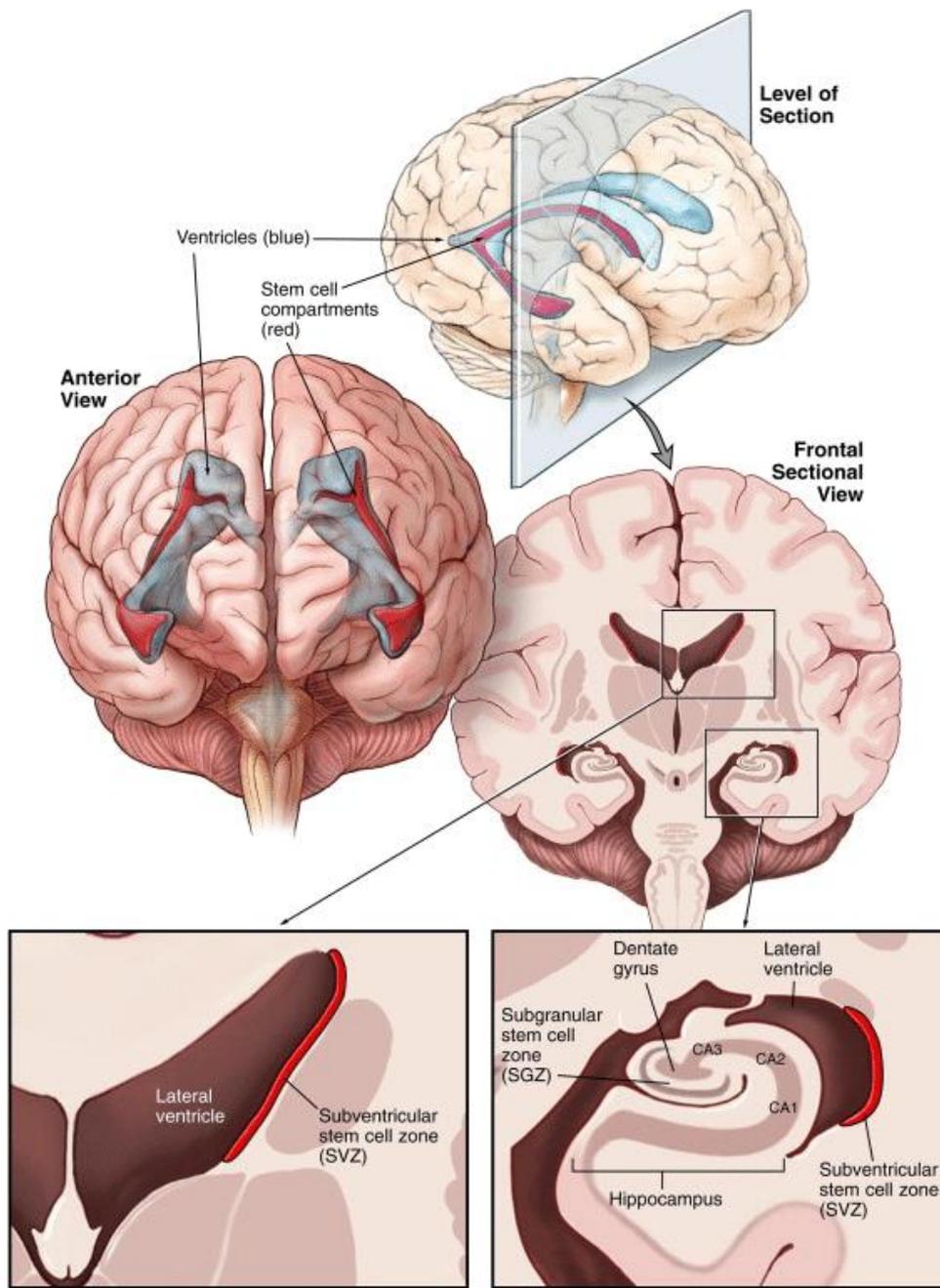


Figure 1.

Exercise maintains mental acuity by increasing levels of brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF-2). Neurogenesis (new neurones), angiogenesis (new blood supply) and long-term potentiation (LTP) are all increased.⁵ Put simply, “use it or lose it”.

IGF-1 is produced in the liver and the brain. With growth hormone, it promotes growth of organs and other tissues such as bone and muscle. 80% of BDNF is produced in the brain but it is also found in the retina (improved vision might be beneficial when moving faster),

kidney (perhaps improved excretion of metabolic products after exercise) and motor nerves (increased muscle mass and control).⁶

Exercise stimulates uptake of IGF-1 into the brain. IGF-1 stimulates BDNF production in the hippocampus and BDNF and IGF-1 act together to mediate the effects of exercise. VEGF works with IGF-1 to mediate vascular effects and FGF-2 increases neurogenesis in the hippocampus (Cotman et al, 2007).⁷ All these factors decrease with age and we know that IGF-1 levels correlate with cognitive performance.⁸ Importantly, the effect of exercise on neurogenesis is blocked by preventing IGF-1 uptake.⁹

So in the long term, physical activity stimulates production of growth factors to maintain and increase physical and mental ‘power’ as needed. In the brain, this is mediated by increasing levels of BDNF in areas concerned with memory, attention, processing and executive functioning.

So why might these effects on memory, learning and motivation be relevant to us now?

Dementia; the most common type is Alzheimer’s disease (AD) which has devastating effects on memory and cognitive ability. Current drugs have limited benefit. AD is arguably the most serious medical condition faced by our society.¹⁰

Psychiatric conditions; each year 6% of adults will suffer symptoms of depression and overall 15% will suffer depression at some time in their lives. The World Health Organisation (WHO) predicts that by 2020, depression will be the most common disease in developed countries.

Cognitive enhancement; Stimulants such as methylphenidate (Ritalin), cholinesterase inhibitors such as Donepezil and neurotransmitter reuptake inhibitors such as Modafinil, are increasingly being used without prescription.¹¹ Maher reports in a 2008 article in Nature that 7% of US students regularly use drugs to aid studying, with up to 25% admitting to their use in the last year.¹² All these drugs have side effects and some are addictive. Long term toxicity is unknown.

Other relevant conditions; brain injury, learning difficulties, age-related cognitive decline, epilepsy and drug dependency.

What exactly is BDNF?

BDNF is a polypeptide growth factor belonging to the neurotrophin family. Neurotrophins are involved with embryological development and adult functioning of the brain. BDNF promotes; a) production of new neurones, b) enhancement of existing neurones by increasing branching of dendrites and axons and c) increased synaptic activity. These changes enhance neuroplasticity, the brain’s ability to adapt, by promoting LTP and therefore strengthening synaptic signals between neurones.¹³ BDNF was best described by Dr. John Ratey, Harvard Medical School as “Miracle-Gro for the brain”.

BDNF acts via two receptors, Trk and p75NTR. Trk stimulation triggers a cascade of factors which trigger neurogenesis and increase nerve survival. P75NTR stimulation acts to limit and balance the Trk effects, so limiting excessive neuronal growth and causing

apoptosis. This balance is necessary because over-stimulation can be neurotoxic and may even trigger an epileptic fit.

Does BDNF improve cognition?

Direct evidence of cognitive improvement has been shown in rats in many studies, where BDNF is injected into their brains. Neurogenesis was seen in the dentate gyrus of normal adult rats who received a hippocampal infusion of BDNF for two weeks. Importantly, lack of BDNF in knock-out rats has been associated with early mortality, abnormal brain development and learning difficulties (Murray and Holmes, 2012 review article).¹³

It's not possible to do this type of work in humans. However, a similar effect in humans is strongly suggested. Low BDNF levels were significantly associated with poor cognitive tests in elderly women but not men.¹⁴ Griffin et al, 2011, investigated the effects of acute vs chronic exercise in young adult men. After 5 weeks of aerobic training they saw improved fitness, cognitive function and increased serum BDNF concentrations.¹⁵

Does exercise increase BDNF levels?

Yes. Many studies have shown that hippocampal BDNF mRNA and/or BDNF protein are increased after exercise in rats of all ages. Rasmussen et al, 2009, showed that in humans, the brain contributes 70% to 80% of circulating BDNF and that BDNF concentration increases 2-3 fold during exercise.¹⁶

Does exercise improve cognition?

Yes. Exercise of varying intensity, both short and long term have been shown to improve performance of memory tasks and executive functioning in humans and rats.

Smith et al, 2011 published a meta-analysis review of randomised controlled trials investigating the impact of activity on cognition.¹⁷ Aerobic exercise was defined as brisk walking or cycling with / without jogging for at least 4 weeks. Cognitive improvement (attention and processing speed, executive functioning and memory) was seen but the effects were very small; Hodges $g < 0.2$ in each case. Unfortunately, if pre-existing mild cognitive impairment was present, the effect on executive functioning was even less.

Regular exercise does however reduce the risk, if started beforehand, of mild cognitive impairment due to ageing and dementia. Chang and Etnier, 2009, described a dose-response relationship between the amount of exercise and cognitive benefit.¹⁸ They also showed that the type of exercise determines the type of benefit. High intensity exercise increased speed of information processing whereas moderate intensity exercise improved executive performance. It has been shown that aerobic fitness positively correlates with memory and executive control (Colcombe and Kramer, 2003),¹⁹ which in turn correlate with brain volume, cerebral blood volume and hippocampal size, in particular neurogenesis in the dentate gyrus.

Exercise has immediate benefit but importantly, regular exercise early in adult life improves cognitive function in older age.²⁰ It's never too late though, even for lifelong couch potatoes. Van Praag et al, 2005, reported exercise-induced neurogenesis in elderly

mice that were previously sedentary.²¹ Children also benefit; Sibley and Etnier, 2003, showed cognitive improvement with physical activity.²²

DISCUSSION

Recent work has focused on a group of related risk factors for Alzheimer's disease; high blood pressure, obesity, hyperlipidaemia and type 2 diabetes, collectively called the metabolic syndrome. The two most important risk factors for metabolic syndrome are central obesity and insulin resistance. There is growing evidence that controlling factors leading to insulin resistance, reduces the risk of AD. Some scientists have suggested that AD might actually be renamed type 3 diabetes.²³ We know that exercise reduces all these risk factors, so perhaps exercise works by simply preventing these risk factors as shown with AD. Certainly vascular dementia could also be reduced, simply by improving cardiovascular health. It's also possible that the beneficial effects of exercise on age-related cognitive decline might be simply due to improvement in cerebral blood flow dependent upon cardiovascular health.

In The Cardiovascular Health Study,⁴ Erickson et al, 2010, showed that an exercise regime spared the expected age-related loss of grey matter volume seen on MRI (magnetic-resonance-imaging) scan after 9 years. In particular, the entorhinal cortex and hippocampal regions were larger compared with a control group and the risk of cognitive impairment was halved after 13 years. The LADIS study²⁴ was started in 2001 and investigated 631 people using clinical scoring and MRI scans annually. It showed that small blood vessel disease was associated with cognitive impairment and risk of depression at the start, and was predictive for future events. Small blood vessel disease is another consequence of poor cardiovascular health and hence should be reduced by exercise.

In rats, blocking BDNF prevents exercise-related benefit in memory and learning,⁹ so clearly peptide growth factors are involved. They are increased after exercise in local areas, such as the dentate gyrus and larger areas of the brain, such as the frontal lobes. Angiogenesis, neurogenesis and neuroplasticity, controlled by growth factors may well be a 'final common pathway' for cognitive benefit.¹³ If so, further research might provide drugs that work with or without exercise!

Mood is also improved by release of endorphins from the pituitary gland within 30 minutes of starting exercise. Endorphins act on opioid receptors to reduce pain impulses to the brain and have a euphoriant effect which is linked to increased concentrations of serotonin and dopamine. Both of these neurotransmitters are increased with antidepressants. Therefore, might exercise-related serotonin increase help to prevent depression? Alternatively, could exercise be used to treat depression?

Interestingly, reduced hippocampal volume and hippocampal BDNF expression are implicated in chronic stress and depression.²⁵ Antidepressants reverse these effects and also increase neurotransmitters such as noradrenaline, serotonin and dopamine. BDNF promotes the survival and differentiation of serotonin neurones and antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) increase BDNF and serotonin levels.²⁶ Perhaps SSRIs work via effects on BDNF. If so, other drugs that alter BDNF concentrations

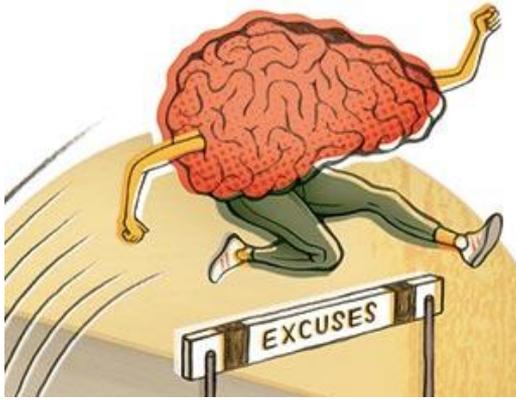
might be used for depression. Equally, drugs similar to SSRIs might be useful to prevent age-related cognitive decline.

Considering exercise to prevent depression, there are very few longitudinal studies. One however, Paffenbarger et al, 1994, followed 10,201 Harvard alumni for 23 to 27 years.²⁷ Depression rates were lower amongst physically active people and sports players. However, although there's a link, it does not prove cause. It may be that people predisposed to depression are less likely to be active. Paffenbarger et al also showed that depression rates were higher with personality traits such as insomnia, exhaustion, cyclothymia, and self-consciousness. Perhaps those personality types were less likely to exercise anyway?

The evidence that exercise can be used to treat depression is also unclear. In 2012, a Cochrane database review of 31 trials reported a moderate clinical effect but many of these trials were of poor quality and only 4 trials were considered satisfactory.²⁸ When these were considered alone, the benefit was much smaller. In general practice, Chalder et al, 2012 followed up 361 adults for 12 months and concluded that "The addition of a facilitated physical activity intervention to usual care did not improve depression outcome or reduce use of antidepressants compared with usual care alone".²⁹ A systematic review of 8 studies by Eriksson and Gard in 2011 concluded that physical exercise can be an effective treatment against depression though there were conflicting results in some studies.³⁰ In summary, exercise might have a role in treating or preventing mood disorder but the evidence is poor. The Cochrane review suggests caution in recommending exercise for treatment of depression, however exercise should be recommended as part of a healthy lifestyle because of its other proven benefits.

Benefit from exercise on mood and depression is related to polymorphism of the BDNF gene due to one substitution of Valine (Val) by Methionine (Met), resulting in Val:Val, Val:Met or Met:Met alleles. Carriers of the Met-allele have lower expression of BDNF and higher risk of mood disorders.³¹ Gene frequency is approximately 60% Val:Val, 37% Val:Met and 3% Met:Met but varies between populations. Interestingly the variants predict differing responses to exercise. Bryan et al, 2007, showed that compared with Val:Val homozygotes, Met-carriers showed a small but significant improvement in mood response and much less self-reported fatigue.³² This effect influences depressive symptoms longer term as well. Mata et al, 2010, looked at exercise-related benefit on depression in 82 healthy adolescent girls.³¹ They found that exercise was protective for depression in girls with the Met-allele but not those with Val:Val.

According to The Health Survey for England 2006, 60% of the population don't exercise enough as defined by 150 minutes per week of moderate exercise such as walking and cycling. Such behaviours are difficult to change but why do some people seem to love exercising and others hate it?



Some of us get immediate benefit from exercise, therefore finding it attractive and hence do it willingly.

Others don't get the same short-term effect and hence aren't motivated.

Might the 60% of the population who are sedentary be similar to the 60% of the population who are Val:Val homozygous?

Motivating the sedentary 60% to exercise won't be easy. As this group aren't rewarded physiologically, perhaps other types of reward might help, such as financial incentives like discount coupons or competitions with prizes or lottery tickets. Targeting this group with education about long-term benefits might also help. Recent advice from the Department of Health, 'Let's get moving' encourages GPs to prescribe exercise.³³ However, the impact of exercise referral schemes was assessed by Pavey et al, 2011.³⁴ They report "considerable uncertainty" about the benefit on activity, fitness or other health indicators and question whether they are an efficient use of resources.

In the workplace, exercise regimes are recommended as a priority to improve worker health and business performance. Unfortunately, Pronk and Kottke, 2009, recommend such regimes to businesses, while stating that effects of physical activity on performance indicators are inconclusive.³⁵ Exercise-related benefit is reported mainly from observational cross-sectional studies. Proper et al, 2006, reported that workers who exercise vigorously three times a week, had less sick-leave.³⁶ A Finnish study of military personnel showed that cardiovascular fitness was associated with less sick-leave.³⁷ Unfortunately, randomised controlled trials do not confirm these findings. Strijk et al, 2013, concluded that there were no significant differences in vitality, work engagement, productivity, and sick leave between the intervention and control group workers after 6 and 12 months follow up.³⁸ Clearly, fit workers will take less sick-leave and their health insurance costs will be less. Again, exercise is associated with beneficial outcomes but randomised controlled trials have failed to show cause.

Conclusion.

"The body and the mind exist as facets of the same being, with the mind being simply one of the body's functions". Aristotle 4th century BC.

Our society suffers the truth of Aristotle's insight. An increasingly sedentary lifestyle causes many physical problems which in turn cause many brain problems. We don't know if exercise benefits the brain simply because it maintains cardiovascular health to peak performance, or whether further cognitive benefit can be expected, even in otherwise fit people.

Concerning cardiovascular fitness, the evidence is overwhelming. As prevention is better than cure, we as a society need to exercise much more. The Department of Health's

recommendations are a minimum and it's likely that more benefit is possible. Avoiding obesity will benefit joint, respiratory, metabolic and cardiovascular problems as well as mental health.

However, change won't be possible for everyone. For those who can't or won't exercise and remain unfit, might drugs that work via IGF-1 and BDNF pathways help? Unfortunately, the physical problems would remain.

Perhaps such drugs might be used in other ways. Some students already take cognitive enhancers, though the risks are unknown.³⁹ In examinations, taking drugs is like doping in sport, it's simply unfair. However, you could argue that caffeine has been used for years as an enhancer. Also, why should those who can exercise have a cognitive benefit over a physically disabled person? Furthermore, in jobs where alertness is needed for long periods or speed of response is critical, drugs might be useful and acceptable.

Medically, gene therapy might in the future, be used for carriers of the BDNF Met-allele to reduce the risk of depression. Also, drugs acting on the BDNF system might be used for sufferers of dementia.

Finally, when we understand the BDNF system, would this knowledge be used to enhance everyone or just certain individuals? If so, would it be ethical if only the rich or privileged could afford it?

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