The effects, uses and limitations of BDNF (Brain Derived Neurotrophic Factor) production

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Abstract
In December 2012 while we were in Nottingham on a Medlink course we were given the opportunity to write a research project on how the body can affect the brain, mainly through BDNF. After this we started researching around the topic of BDNF, and we soon realized how varied this subject was with all the different possibilities of how this research into BDNF could be used to help people. We decided to focus on how this new research could affect people with dementia, how it could be integrated into schools, possible exercise programs designed to target BDNF production, and a pill form for people who are unable to exercise so that they can also receive the benefits of BDNF as well as any ethics surrounding these issues. In this paper we hope to cover the uses of BDNF and the ethics of how it can be used, why it should be used and in some circumstances why it shouldn’t.

Introduction
It has been long known that exercise can affect the brain by improving the heart rate and circulatory system so that there will be an increased amount of oxygen supplied to the brain. However, it has also been shown more recently how it can show improved memory and learning (while possibly being able to repair or prevent dementia). This is being shown by David J. Bucci and colleagues (2009) in their work on how voluntary physical exercise alters attentional orientation and social behaviour in a rat model of attention-deficit/hyperactivity disorder. It is also demonstrated by MK McGovern “The Effects of exercise on the brain” (2005).

The Brain is a very metabolically active organ and so therefore the brain cells require double the energy of any other cells in your whole body. The brain consists of many cells, which communicate with each other, called neurons. These neurons have a large consumption rate of energy due to them being in a state of metabolic activity all the time, even during sleep. Along with communicating, neurons often use up energy just repairing and rebuilding the worn out structural components or pathways in the brain. They also use up their storage of Adenosine triphosphate (ATP) by doing processes such as manufacturing enzymes or even neurotransmitters. They then must transport these away up to several feet, which again requires more energy. However the most demanding source of a neurons energy consumption is the signals they send to each other which are vital in order for there to be communication throughout the nervous system. These bioelectric signals consume a half of all the brain’s energy. Each neuron has dendrites at one end that receives many inputs from other neurons. They all also have one axon, which carries electrical output signals. They also release chemicals by the electrical signals that trigger this. There are Synaptic clefts between neurons, the electrical signal cannot pass over these gaps and so is converted into a chemical signal in order to cross. These connections are constantly changing, while pathways that aren’t used ‘drop off’, new synapses will form as new information is learnt. Also some pathways can even become reinforced and made more effective as you practice and repeat actions. The power of the brain is all about connectivity. The number of neurons in your brain does not matter; instead it is the number of connections in the brain as well as the strength of these connections that increases brain power and function.
As shown in Figure 1, the neurons do this by causing a burst of neurotransmitters to cross the gap to receptor sites on the dendrites of the other neuron. Once the neurotransmitters reach these receptor sites they all fit into their specific sites in a lock and key form. This then opens up the ion channels, which converts this chemical signal back into an electrical signal to pass down the next neuron. There are two main transmitters responsible for the neuron signals passing through the brain. These are effectively a go transmitter and a stop transmitter. Glutamate acts as the Go transmitter and stirs activity, beginning the signalling between neurons. GABA (gamma-Aminobutyric acid) acts as the stop transmitter and simply stops this activity. Glutamate is the transmitter that is key to learning, the more effective the glutamate is means more signals will be passing between 2 neurons which will cause better connectivity and therefore increase in brain power and functionality. The way of making glutamate more effective is by increasing the numbers of active sites which will in turn increase the brains ability of memory and learning. BDNF (Brain-derived neurotrophic factor) is responsible for the creation of more receptors and so is responsible for the increased effectiveness of glutamate. This is what can be targeted and increased by exercise (aerobic exercise especially). BDNF can also be particularly useful at restricting/preventing the decline of functionality in the brain as well as improving learning. This is because as it makes the glutamate more effective it means more pathways can be reinforced so weak pathways can be made strong again. Lead researcher Sabrina Segal at UC Irvine
centre for neurobiology of learning and memory said ‘we found that a single, short instance of moderately intense exercise particularly improved memory in individuals with memory deficits’. If this is true then it suggest that this increased production of BDNF could be used to prevent memory loss and also decrease the chance of diseases such as dementia.

**Exercise routines targeting BDNF production**

There are many short and long term effects of exercise with different exercises targeting different effects. Short-term effects to the brain involve increased oxygenation where there is an increase of blood vessels, which bring the oxygen, enriched blood to the brain regions, which are involved, in cognitive functioning. It has also been shown that it can make people feel happy due to the production of endorphins. However the main long-term effect focused on in this paper is this increase in production of BDNF. Research has shown that engaging in moderate, high intensity aerobic exercise (for example going for a run or cycling) will stimulate a greater expression of BDNF than going to the gym to do weights. Animal studies where mice have been forced to run on a treadmill have shown much greater concentration of BDNF. What affects the production is the increased heart rate. This suggests that a more aerobic type of exercise where the heart rate is raised has a more beneficial effect on BDNF production. This allows for the opportunity for leisure centres or gyms to start an aerobic exercise specifically targeted at BDNF production by using heart rate levels. Due to the fact that heart rate depends on the individual, the exercise does not have to be at the same intensity for all in order to have the same effect. This allows very unfit people to try this exercise for better memory or learning ability. This is especially useful considering that a large proportion of people using this will be older people who may not be as fit as younger people. A good exercise for heart rate would be to run as fast as you can for 60 seconds, slow down to a brisk walk for two minutes and then repeat the pattern. If you wore a watch measuring your heart rate you could make sure your heart rate was staying high. Sports centres could run these sessions as intelligence/memory boost sessions for old people and young people if they want. It would even be possible to do memory tests after the exercise to show the improvements in order to get more people involved in this new type of exercise. Or even perform a before and after text on the BDNF protein expression levels by using Enzyme-linked immunosorbent assay, an immunological technique that makes use of an enzyme that is bonded to a particular antigen. This would be beneficial to the centres as it would bring in a wider range of people but it could
also be especially useful for older people who are beginning to have problems with their memory and also want to stay fit as it would target both at the same time. In an experiment testing this out participants were given a memory test one hour after exercising using this method of high intensity aerobic exercise. The test showed a noticeable improvement between those who exercised and those who had not even after just short a period of doing this exercise program. This effect was apparent in all volunteers, the healthy volunteers as well as the cognitively impaired ones. This shows how the exercise can be incredibly beneficial to all people for increased learning and memory when this exercise is targeted solely to get an increased, sustained heart rate in order to improve BDNF production.

**Integration into the school system**

If there were to be a causal link between exercise and BDNF production then there would be something to be said about integrating this knowledge into the school system, i.e. as in the Naperville, Illinois School District 203, where some students take part in Zero Hour PE, which is exercising prior to classes. What they found was that this improves mood, comprehension and reading. The ultimate benefit being that their learning is enhanced. The Naperville program is 17 years old and in this time it has been tested on students at schools from various socioeconomic and less affluent backgrounds and has found the same results every time.

It has been shown that these benefits are due to the improvement in BDNF production; this means that any imbalances in the ratios of glutamate and GABA are remedied, and also helps support existing neurons and the differentiation of new neurons.

BDNF has also been found to be key to the development of the brain and sensory nervous system; this was shown when mice born without the ability to produce BDNF suffered from defects of those areas, as there was no development there, and in most cases died soon after birth.

If BDNF is so important in neural development then surely it should be compulsory for schools to do whatever they can to stimulate BDNF production, however would it be ethical to force children to exercise on a regular basis? They probably wouldn’t understand why they had to, and this would have one of two outcomes:

1. The child would not understand, even when it is explained, that if they don’t exercise, they will miss out on the benefits whilst other children are
getting them, placing the child at a disadvantage in their education, however if forced to continue then they will come to resent the exercise, and/or the people who they see as to blame, (be that teachers and/or parents) this could lead to emotional discomfort in a negative environment and as per Bowlbys Continuity hypothesis this may lead to later life psychological damage.

2. The child understands, enjoys the benefits of both mental and physical health and has great potential to grow up to be an intelligent, fit and healthy member of society.

Another issue is that everyone is different. In order to stimulate BDNF production exercise must be performed at quite a high intensity in order to create a high heart rate. However, what this high intensity may be varies from person to person, and this might be misconstrued as to mean the fitter you are the smarter you’ll get. This could lead to schools/parents/children who want to achieve highly, turning to substance abuse like steroids to increase physical performance under the impression they will become smarter. It is important to note that the level of fitness does not matter; the benefit of this exercise is that only the heart rate matters. Therefore, children of varying sporting abilities can do different levels of intensity in sport to get the same neural benefits. Indeed, some children do not need the BDNF boost to perform well, and to force them to exercise would just be a waste of time.

**Using production of BDNF in a pill form**

An alternative to using exercise to provide people with BDNF would be if it were possible to either manufacture a consumable form (e.g. a pill), or use a substitute like oestrogen treatment [Sohrabji F,][Singh M]. This pill could potentially have many beneficial effects for the general population, though it would come with a few possible side effects/limitations.

Its main limitation would probably be manufacture and later on there would be ethical concerns of distribution if (as is likely) mass production cannot be achieved. Manufacturing problems could include efficiency, cost, and sustainability; all of these things could impact the pills existence. Also if mass production weren’t possible, then it could mean that the privileged are the only ones able to get access to the pill, leading to an elitist group of people who have effectively paid their way to being smart (though not necessarily intelligent).

However, trying not to be pessimistic, there is a lot of promise for a BDNF pill. For instance, if successful, it could mean entire generations filled with smarter people, which could ultimately mean entire world problems solved by some innovative
ideas (though this would have to be taken with a pinch of salt, as an enhanced ability to learn does not mean more intelligence. Nor does it mean that someone would have a more creative mind.) Also, if it is in a consumable form then it will enable people who might not be able to exercise enough to stimulate production i.e. the old and infirm. This means the pill could just be restricted to people who are unable to exercise and so removing the issue of the privileged group being the ones to buy the pill.

**Links with curing dementia**

Dementia is classed as an umbrella term for the symptoms that occur when the brain is affected by a disease or condition. The type of dementia we are referring to here is Alzheimer’s disease. There was a famous procedure on Henry Gustav Molaison in 1953 by a brain surgeon called Bill Scoville who tried to cure this patients’ debilitating epilepsy using an experimental procedure, which involved sucking up part of his brain through a silver straw. This case has been used for many years as a psychological study. The Hippocampus was removed in order to prevent seizures. It did lessen the severity and made the seizures more rare but it also caused severe memory loss. This case made it clear that the hippocampus is involved in forming new (episodic and semantic) long-term memory. The major role of the hippocampus seems to be forming, sorting and storing new memories. The inability of forming new memories while keeping the old memories is a very common symptom of dementia. Exercise is already proven to cause neurogenesis (the development of new tissues) in the hippocampus. This occurs particularly in the Dentate Gyrus part of the hippocampus, which is one of the few regions in the brain where adult neurogenesis has been confirmed. It may play an important role in translating neural codes for creating memories. This means if the hippocampus can be improved or repaired using this BDNF produced by aerobic activity during exercise then older people suffering from dementia may be able to start forming new long term memories (ones that last years rather than days) once more due to more neurons with better connections (as BDNF is also known to increase connections due to making Glutamate more effective).

This could be made even more effective if made in pill form that just stimulates production of BDNF to begin neurogenesis in the Dentate Gyrus part of the hippocampus without the need of exercise that may be more difficult to achieve in older people, especially those who are suffering from dementia or memory problems.

**BDNF Links with Disease**
There are numerous links with BDNF to diseases, but what are they and how reliable are the links?

Vascular dementia is caused by cerebrovascular lesions such as long-term chronic cerebral ischemia, which damages brain cells. Two of the ways it is shown is as learning and cognitive disorders. BDNF plays an important role in the survival, differentiation and growth of neurones it does this by promoting neuronal regeneration, maintaining the nervous system. BDNF also promotes both early and late-phase long-term potentiation (increases strength of nerve impulses along previously used pathways), and promotes dendritic protein synthesis, and dendritic spine formation (Bramham et al.). For these reasons alone it is only logical to infer that BDNF could be used as a form of treatment for vascular dementia and/or Alzheimer's disease.

There is also research that has shown that whilst gender, age, level of education, blood-glucose or history of smoking and drinking shows no significant differences between normal people and those with vascular dementia, levels of BDNF do show that people with vascular dementia are slightly lacking in BDNF when compared to those without. Though there is not enough evidence to show a causal link.

BDNF also has the ability to alter a mature central nervous system's structure and function. This is why it has been linked to diseases such as epilepsy, which could involve abnormal cortical development or modified brain structure and function after maturity of the brain. Studies have shown that seizures are proportional to greatly increased expression of BDNF in parts of the brain that are involved in limpid seizures (Isackson PJ,) and also in hippocampal pyramidal cells, along with other areas of the brain susceptible to temporal lobe epilepsy. However, the relationship between epilepsy and BDNF is not that simple, because there seem to be endogenous controls that limit BDNF's ability to increase excitability (cells responsiveness to stimuli). One example is the fact that BDNF induces neuropeptide Y expression, which seems to potently depress synaptic transmission at as many synapses as BDNF potentiates. (Vezzani A,) Another is that trkB decreases whilst under the same conditions which BDNF has thrived on, though in some cases, an elevation of BDNF does not mean a fall in trkB. (Xu B,) Transgenic mice have also been used to show how mice with BDNF overexpression, were afflicted with increased seizure susceptibility and high in vitro hyperexcitability. (Croll SD,)

Finally, the link between drug addiction (cocaine) and BDNF. The main property of BDNF expression in relation to drug addiction is its association with synaptic plasticity. A part of the neurological side to drug addiction, is that drug-induced long-term neuroadaptations that include changes to molecular components at the synapses. BDNF may be able to regulate these neuroadaptations along with changes in gene expression and behavioural output.
After repeated administrations of psychostimulants such as cocaine, amphetamine or alcohol, the expression of bdnf mRNA and BDNF protein are temporarily increased in the forebrain structures (Fumagalli et al., 2007). This could be a base for psychostimulant-induced altered neurotransmission. An infusion of BDNF to the ventral midbrain could lead to cocaine withdrawal symptoms after a long period of abstinence (Lu L.). This could mean that past drug addicts who exercise simply to get fit could start getting withdrawal symptoms even after a long time, due to the increase in BDNF expression as a result of the exercise. These kinds of findings have lead some investigators to conclude that BDNF is negative in terms of drug addiction. However, these are based on what happens when BDNF acts on the subcortical regions of the brain, and do not even consider the possible effects of BDNF on other regions of the brain.

For example, in depression, when BDNF is infused into the hippocampus, it has an anti-depressant effect, but has a pro-depressant effect when infused into the VTA (ventral tegmental area). [Shirayama Y,] [Eisch A]. Similarly, BDNF has pro-drug seeking effects when infused with subcortical regions of the brain, but suppresses drug-seeking effects when infused into the dorsomedial prefrontal cortex. Therefore, dependent on the distribution of BDNF, it could have either negative or positive effects on the brain.

**Conclusion**

They’re clearly many beneficial uses of BDNF with the possibilities ranging from better exam results to helping combat the symptoms of dementia. There are issues considering BDNF as it could be used to give only an elitist group of people an increased amount of intelligence for tests and exams. This would become even more likely if it was used in pill form because as it is a new idea with new technology it will be expensive, limiting the possible buyers to only those who can afford it as a luxury. This will need to be stopped by
possible funding by the government in order to make it more widely available or simply restricting it to people with illnesses such as dementia.

There are also clearly some health risks with using this BDNF production. If this link between BDNF and drug addiction was proved to be true then targeting this production could cause massive effects to people, especially young children exposed to an environment fraught with peer pressure, and since it has been shown children are far more easily addicted than adults. The link between BDNF and long-term susceptibility to drug addiction, will have to be thoroughly researched in order to find out how reliable it is before any widespread use of targeting BDNF production.

The idea of BDNF is to help strengthen everyone’s memory by simple exercise that anyone can do. This makes it a simple way of increasing brainpower that does not require people to pay for programs or treatments. The new research into this topic area is especially exciting for older people as it can change many individuals’ lives drastically just by doing a simple exercise such as a jog every day. Quite possible the best part of this research is as it is just exercise it is free and achievable by anyone who is physically able and for those who aren’t it can be supplemented in a pill form.

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