The effects of exercise on the brain and how it could shape future medicine and change the way GPs treat their patients

Miranda Smith

Pass with Merit

Research Paper based on lectures at the Medlink Conference at Nottingham University in December 2012

March 2013
ABSTRACT
The Brain, weighing about 3lbs and made up of 100 billion nerves cells, it can be the area of the body where many medical issues originate. Research has shown that exercise affects the brain in certain ways. It increases the levels of some neurotransmitters, including BDNF, Serotonin, Dopamine and Endorphins. These increases have been shown to be able to reduce the risks of certain diseases, speed up a person's recovery after they have been ill and improve a persons memory and learning. Research into the effect that exercise has on the brain could greatly change the components of a GPs prescription. Drugs could be designed to create some of the same effects that exercise has on the body. If this did occur it would greatly change the shape of medicine in the future.

INTRODUCTION
Glutamate is one of the major neurotransmitters with widespread uses, found in the brain, it causes signalling between neurons to occur. GABA (Gamma aminobutyric acid) on the other hand is an inhibitory neurotransmitter meaning it slows down/prevents signalling between neurons, by blocking the receptor sites on the neurons. These two neurotransmitters are in balance with each other. GABA prevents every neuron's synapse firing at once by acting as a controller allowing only some messages to be passed on. Robert Winstons, The Human Mind explains how evidence from Rhesus monkeys shows that there may be insufficient supplies of GABA in the brain in old age, which could be the cause of mental deterioration in the elderly. Glutamate becomes more effective when there are more receptor sites on the neuron as the more receptor sites there are, the more two neurons can signal to each other forming what is best described as a beaten track through long grass. This then makes it easier for the same signal to occur again (faster); this process is learning and memory. More receptor sites and neurons are produced by BDNF (Brain-derived neurotrophic factor).

This shows that if we can increase the levels of BDNF in the brain we can increase levels of memory and learning; and therefore intelligence. Exercise in some mammals, including humans, has been proven to increase levels of BDNF in the brain, and not only in the parts of the brain associated with movement as may be expected, but also in the hippocampus, an area linked to memory and learning. This exercise need not be running but can be anything from yoga to swimming.

There is no firm conclusion on why exercise increases the levels of BDNF in the brain, however there are many differing views. M.K. McGovern (2005) suggested that on a cellular level it is possible that low stress levels created during exercise cause an influx of Calcium. This could then affect transcription causing BDNF proteins to be produced in the brain. Work by Ratey highlighted in an article written by Chapa (2011) discusses that this BDNF production could have originated before the evolution of our ancestors. In the past, knowledge and understanding was required to obtain and store food, for survival. Fuel, in the form of food, is needed to learn and knowledge is needed to find fuel. It is therefore suggested that learning and memory evolved alongside motor functions, as together they allowed our ancestors to track down food. This was backed up by a German study (2007), which found that when they put two groups through vocabulary tests, the group that had exercised had higher BDNF levels and were able to learn new vocabulary 20% faster than the other group.

It seems clear to say that endorphins are linked to BDNF. After around 30 minutes of exercise, endorphins are released from the pituitary gland in response to the pain or stress in the body that exercise causes. These endorphins of which there are at least 20 types, interfere with the body's pain impulses to the brain by preventing the release of neurotransmitters. This creates the feeling of well-being you sometimes get after exercise, however it is unknown whether this is caused by the endorphins themselves or by other neurotransmitters such as dopamine becoming more obvious with the presence
of endorphins. Thirty minutes of exercise is needed to feel the full effects of endorphins but after just ten minutes your mood will have improved. In this way, endorphins are said to be linked to BDNF as they reduce the discomfort that arises from exercise, enabling the body to continue to exercise resulting in more BDNF being produced.

With this in mind it is logical to reason that if exercise can increase levels of BDNF in the brain then surely this extra BDNF will create additional neurons where required and produce more receptor sites, allowing more neural connections. Many mental illnesses exist today and cures for some of these, especially ones amongst the elderly, are a main focus of present day research. If it comes to light that exercise could cure many illnesses originating in the brain, in particular Dementia, there could be a huge change in the way GPs treat these illnesses. Therefore research into the advantages of exercise taking into account these conditions is key.

As well as an increase in BDNF, it is believed that exercise can cause an increase in the number of mitochondria in the neurons. An increase in the number of mitochondria allows the brain to work faster and more efficiently. This is the opposite of what normally occurs during ageing when the number of mitochondria in the brain decreases and therefore the brain works more slowly. This tells us more about how exercise could assist in repelling the normal types of mental deterioration that comes with age.

The mitochondria in cells act as the power house, providing energy that the cells require. As you do more exercise, the amount of mitochondria in the cells making up the muscle increases as the muscle cells require more energy. The same happens with your brain, as during exercise, it is required to work harder in order to keep all the muscles moving and synchronised. J. Mark Davis conducted research on this topic with mice and found that mice that had been exercising on treadmills for two months prior to the testing had more mitochondria in their brain cells than those who had not. Although this experiment was carried out in mice it is believed that the same effect would be found in humans as human muscle reacts in the same way as animal muscle.
DISCUSSION
Taking into account the introduction it makes sense to reason that if exercise can increase levels of BDNF in the brain and mitochondria in the neurons then it can help to reduce the risk of neurodegenerative diseases in some way and also improve memory and learning. The extra BDNF produced during exercise will create extra neurons where required and more receptor sites on them, allowing more neural connections. A deficit of mitochondria in brain cells can lead to some mental illnesses, so a plentiful supply of mitochondria in neurons could reduce the risks of these illnesses and make the cells more resistant to fatigue. Many mental illnesses are around today and finding cures for some of these, especially those in the elderly are a main focus of present day research. If it comes to light that exercise could cure many illnesses originating in the brain, particularly Dementia, then there could be a huge change in the way GPs treat these illnesses.

Not only is BDNF an important neurotransmitter but others such as dopamine and serotonin are important too. All of these are produced during exercise, and as pointed out above, these increased levels can help to reduce the chances of a person contracting a neural originating disease such as Parkinson's and Alzheimer's but they are also the key to learning and memory. This is because as you age (30 +) the brain starts to lose nerve tissue (the primary cause of dementia) and as BDNF causes neurogenesis (the creation of new neurons and therefore nerve tissue) it can prevent this.

Surprisingly, other illnesses such as Depression, Stress and ADHD, which exist amongst younger age groups can also be helped by increased exercise. It has been shown that it is easier to recover from depression when you are physically active as depression is caused by low levels of neurotransmitters such as serotonin and norepinephrine. BDNF increases the production of serotonin, so as you exercise your serotonin levels increase, as well as the production of endorphins, which make you feel good. It has been proven using rats, which displayed depressive symptoms, that exercise along with taking antidepressants resulted in a decrease in depression after two days, however for those rats that only took antidepressants it took two weeks.

Stress levels are also improved with exercise in the same way as it helps depression. When you are stressed about something you think about your problem a lot and so your cognitive functioning increases. Exercise increases the number of mitochondria in neurons, providing energy for the neurons to work, so the brain is able to function more without fatiguing. More supplies for respiration are brought to the brain as an increase in exercise increases blood flow to the brain, bringing more of the glucose and oxygen that is necessary for this increased cognition. The increased blood flow also enables the waste products produced by respiration in the brain to be removed faster. This reduces the foggy feeling in your head, which can occur after you have been thinking intensely. Finally, exercise increases the release of serotonin in the brain as it produces BDNF, which is linked to serotonin production. Serotonin reduces stress levels in the same way that it reduces depression levels.

The behaviour associated with children that have ADHD (attention deficit hyperactivity disorder) can be dampened with exercise as is shown by the work of David Bucci. This is because exercise increases the amount of the neurotransmitter Dopamine, which is associated with attention, something that children with ADHD find very difficult. Dopamine is found in medication given to children with ADHD, however giving young children constant medication is not ideal as other substances in the drugs may be harmful. It would therefore be healthier for children if increased levels of Dopamine could be produced in the brain without the use of drugs.
Only some of the neurodegenerative illnesses that can be combated by exercise are listed above, there are many others. This helps us to see how significant exercise may cure/prevent illness and promote learning. To develop this idea further would not only greatly reduce the amount of money spent on drugs every year as exercise could be prescribed instead of medication but it would have many other benefits to the patient's health.

Exercise affects BDNF levels in people differently and in the work of McGovern (2005) it is explained that the elderly will have lost more neurons than people between 18 and 24 years of age. This means that when people from the two age groups start to do the same amount of exercise the elderly will show significant improvements in their planning and working memory where as the 18 to 24 year olds will not show any significant improvements as they have less room for improvement. A test using mice has also shown that over exercise will not continually increase your BDNF levels, which plateau at a certain point. Mice were over exercised and this resulted in them having an inability to learn, the paper suggests that this could be due to the mice being preoccupied with exercise. Although the mice had elevated BDNF and therefore neurogenesis the levels of BDNF could not be increased beyond a certain level with more exercise.

GPs must therefore realise that when prescribing exercise, the same amount of exercise will have a far greater affect on elderly patients than younger patients. It must also be taken into account that if a patient does too much exercise it is likely that it will not have a positive effect on their overall health. This is important for GPs who may begin to prescribe exercise, as it enables them to see that different amounts of exercise are required for different age groups in a similar way to different doses of drugs being required; the best level must be found for quick improvement.

The area for research now is in how varying amounts of exercise affect people of different ages and with different conditions. It is possible that in the near future GPs could start to prescribe exercise instead of some drugs but for this to occur much planning is required into the prescription of exercise in order for it to be used to maximum effect.

However, in an ever more sedentary world, many people would not be capable or willing to do exercise in order to improve their health and well-being. This poses the question, could a drug be designed which could act as a supplement of BDNF? A further question that should be asked and could act as a mid way point; could a drug be produced which could increase the levels of endorphins in the brain, making exercise a more enjoyable experience from the start (not from 30 minutes in)?

It has been shown that many compounds are associated with increasing the levels of BDNF, but none have been proved to increase the levels directly. Some of the compounds only have affect in certain parts of the brain but others work throughout the organ. Memantine, Olanzapine, Sertraline and Zinc are some of many compounds that seem to be able to increase BDNF production. Another point to mention is that BDNF need not be produced in the brain and therefore can be produced elsewhere in the body before being transported to the brain.

Research by Jonathon Kipnis (2010) shows the immune system affects the functioning of a healthy brain. This opens many more possible avenues for research to discover a safe way to produce BDNF without doing exercise. The route taken in his paper tells us how learning produces a slight stress in the brain and by a process starts the production of IL-4. The IL-4 decreases the stress in the brain and also
starts a process for BDNF production, which then goes on to increase learning and memory and prevent a number of neural diseases.

The way forward for researchers in this field is to establish what compounds in particular increase the production of BDNF in the body. Using this knowledge they could then design a drug specifically to increase these BDNF levels. If this was to be created it is highly likely that the number of cases of dementia, depression, stress and other illness that BDNF can combat will decrease. A possible serious disadvantage of a drug like this is that it may cause the already low levels of exercise of many people today to drop. As exercise not only affects BDNF levels this could lead to other problems including increasing obesity, therefore it would be best if the drug is issued only to those who really need it. Although BDNF can increase learning and memory I do not think that, if a drug were to be developed, it should be used to increase the academic potential of people as this could lead to addiction and when not necessary it is unhealthy for a person to take a drug. Healthy living through exercise should still be heavily encouraged.

Increasing the levels of endorphins in the brain via a drug it does not need to be so complicated. It has been shown that eating foods like chocolate and chilli peppers (the hotter the chilli, the better) lead to the secretion of endorphins in the body. Acupuncture, massage therapy, sex and meditation have also been shown to increase the levels of endorphins produced by the body. The easiest way to increase your endorphin levels ever so slightly is by smiling or petting an animal. Without even exercising to produce BDNF these endorphins can make you feel a lot better about yourself and so reduce depression levels. These endorphins will on the other hand also hide the discomfort of exercising and even mask pain making a little exercise a lot easier, meaning BDNF production through exercise is not such a mental battle. Not only would this enable BDNF to be produced but it would allow more mitochondria to form in the neurons meaning the brain would not fatigue as easily. If you have already high endorphin levels then you will feel good about yourself. It makes sense then to suggest that this already pleasant feeling will make exercising easier before your body starts to release endorphins due to the stress/pain of exercise. If this were to be the case then instead of prescribing a drug to boost BDNF levels, GPs could simply advise people on how to change their lifestyle to increase endorphin levels as well as prescribing exercise. This would be a more favourable alternative to patients being prescribed a drug to artificially increase the synthesis of BDNF in the body as it would be healthier and would definitely mean that more mitochondria are produced in the neurons.

This calls for research in this area as to if, and how, endorphins produced prior to exercise can make exercise easier and therefore more enjoyable; even though it is fairly certain that this does occur. If so, it would be worthwhile discovering which of the over 20 endorphins are best for masking the discomfort of exercise and how they are produced. If this were to be discovered GPs could refine their recommendations to patients as to how to increase endorphin levels, making exercise easier. This is because they could then emphasise the use of certain methods such as eating chocolate to increase endorphin levels for the main reason of making exercise easier and therefore the likelihood of patients undertaking exercise would increase.

GPs could then begin to prescribe exercise to many people in order to reduce the chances of certain diseases. If exercise was too difficult, even with increased endorphins, for the patient and if research was developed enough, drugs to increase the production of BDNF could be produced. There are however risks associated with this route as many people might want to take these drugs instead of doing exercise.
It is known that if BDNF production is increased in people, it will reduce their chances of contracting many neurodegenerative diseases such as dementia and/or decrease the effects of existing illnesses while benefitting their memory and learning capabilities. This leads on to the suggestion that GPs could start to prescribe exercise instead of drugs to patients. For this to be effective, research should be carried out on what level of exercise suits which situation best. Some patients however will not be willing to or capable of doing exercise and therefore it should be part of future research to work on a drug that could increase your body's BDNF production artificially. The dangers of this is that people could become addicted to these drugs, using them as a substitute for exercise (which would mean the other positive effects of exercise are not reached) or request them from their GP simply to enhance their academic potential (helping memory and learning). A balance between the two may well be the best solution. So looking at an increase in the level of endorphins in the body prior to exercise would make exercise easier, and therefore natural BDNF production more accessible to anybody.
CONCLUSION
It has been proven that exercise causes the production of many neurotransmitters including BDNF, Serotonin, Endorphins and Dopamine. In particular BDNF has been found to be very useful in combating many neurodegenerative illnesses, particularly those that cause the loss of nerve tissue in the brain, such as Dementia. BDNF has also been found to benefit your memory and ability to learn. BDNF increases neurogenesis, which also increases the amount of receptor sites on neurons. It therefore helps to improve our memory and learning. There are no differing views that BDNF is good for us and it has been proved that the level of BDNF in our brains is increased with exercise. However there are debates as to why exercise causes this increase, one hypothesis tells us that it is due to our ancestors. On a more cellular level this production of BDNF is caused by Calcium (the influx caused by the stress of exercise), which is believed to affect transcription.

The production of endorphins is said to be linked to BDNF. Endorphins are what mask the discomfort of exercise after 30 minutes or so of it. They are not only produced by exercise and make you feel happy so can be very useful in reducing the chances of depression. Serotonin and Dopamine are also vital as a deficit of these neurotransmitters can lead to depression. The levels of all these neurotransmitters is increased during exercise however BDNF seems to be the most important of these as the production of both Endorphins and Serotonin is linked to BDNF.

If GPs began to prescribe exercise as a substitution for drugs it would be far healthier for the patient. This would require research into what exercise works best for a range of people. As many of the patients will be unable to do the exercise suggested by their GP a more advanced solution could be the creation of a drug that could cause the synthesis of BDNF, without exercise. A caution to be taken, should a drug like this be developed, would be that some people may become addicted to the drug. On the contrary, if the production of endorphins could be increased in the body, prior to patients undertaking the exercise prescribed by their GP then this would make the exercise far less discomforting and therefore more achievable by any of these patients.

If this research was to occur and GPs began to prescribe exercise with or without increasing patients endorphin levels and/or drugs to increase synthesis of BDNF in the body then medicine as a whole could greatly change. Further developments could then lead to prevention of many neurodegenerative diseases in the first place. This has only touched on some of the known benefits of BDNF, however exercise itself has other benefits and it is likely that there are other diseases that BDNF can cure or help. GPs using a combination of drugs and exercise to increase BDNF is not necessarily going to happen but what seems certain is that BDNF will be at the front of medical research for a long time to come and with it exercise.
REFERENCES


Gretchen Reynolds in The New York Times, 28th September 2011, article on how exercise can strengthen the brain:

Gretchen Reynolds in the New York Times, 30th November 2011, article on how exercise benefits the brain:

Joaquin Chapa, Axon sports, report on how exercise affects cognitive health:

Longecity, list of substances that increase BDNF:
   http://www.longecity.org/forum/topic/58707-big-list-of-substances-that-increase-bdnf/

Mind tools site, report on managing stress with regular exercise:

MK McGovern (Spring 2005), report on the effects of exercise on the brain:
   http://serendip.brynmawr.edu/bb/neuro/neuro05/web2/mmcgovern.html

National Register of Personal Trainers, report on how short bursts of exercise improve memory:
   http://www.nrpt.co.uk/articles/burst-exercise-improves-memory.htm

Noel Derecki, Amber Cardani, Chun Hui Yang, Kayla Quinnes, Anastasia Crihfield, Kevin Lynch and Jonathon Kipnis (May 2010), research on regulation of learning and memory by meningeal immunity: a key role for IL-4:
   http://jem.rupress.org/content/207/5/1067.full

Petra Rattue, Medical news today, Exercise and its effects on the brain:
   http://www.medicalnewstoday.com/articles/245751.php

Stephani Sutherland, Scientific American, report on how exercise affects the brain:
   http://www.scientificamerican.com/article.cfm?id=how-exercise-jogs-the-brain

The Dana Review, The Dana Foundation 2007 on the DNA Learning Center site:
http://www.dnalc.org/view/848-Exercise-induced-Neurogenesis.html

The Power Platform, how does exercise affect the brain, with reference to Carl W. Cotman, PhD: