Exercise and BDNF: Effect on Memory and Potential Treatment of Degenerative Memory Diseases

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DISTINCTION

"Memory is a way of holding onto the things you love, the things you are, the things you never want to lose." – The Wonder Years (Television Show)

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ABSTRACT

The myth that our brains stop growing when we are adults has been known to be false for a long time. However, it is only recently that scientists are beginning to understand that neurogenesis is due to levels of brain-derived neurotrophic factor (BDNF) in the blood. This chemical is produced mainly during and after exercise. This paper firstly looks at its current uses in mental conditions such as depression, and also in other conditions such as diabetes. We then concentrate on the research surrounding exercise, BDNF and memory. One important aspect of this is its use to treat degenerative disease such as dementia. We conclude that there is clearly a link between increased exercise and BDNF levels, with falling rates of dementia. We believe there is a promising chance that exercise will hold a prevention or a cure for these conditions in the future.

INTRODUCTION

The brain is a remarkable thing. Without it we would be unable to do all of the things that make us human. We would be incapable of using our senses or responding to our surroundings, which is crucial for our survival. Although we may feel things with our fingers ultimately it is the activity of the brain that enables us to make sense of what we touch. The brain is able to do this by sending electrical and chemical impulses along neurons and neurotransmitters. One type of neuron is the nerve cell, which sends and receives messages.

The protein BDNF (Brain-derived neurotrophic factor) has the ability to help support the survival of existing neurons, and encourage the growth and differentiation of new neurons and synapses. It is an active protein in the hippocampus, cortex, and basal forebrain of the brain, which are areas vital to learning, memory, and higher thinking. BDNF therefore plays an important role in capability of the brain to do neurogenesis. This consequently is how it transmits and receives electrical impulses, since every process that the brain is capable of is a result of neurons.

Scientists are increasingly recognizing the capacity of physical activity to maintain and compensate for the deterioration of nerve cells. A recent study[1] conducted by Carl Cotman at Columbia University using mice demonstrated that mice that exercised displayed higher levels of BDNF as well as a direct relationship between the amount of running that the mice did and BDNF levels in their brains. Although this study was carried out on mice this and other similar research suggest that the increase in levels of BDNF induced by exercise may play a particular role in improving memory even in humans.

Currently research into BDNF have shown possible links between this protein and medical conditions such as depression, schizophrenia, obsessive-compulsive disorder, Alzheimer's disease, Huntington's disease, Rett syndrome, dementia as well as anorexia nervosa and bulimia nervosa. From the extent of the current research it can clearly be seen that BDNF is an essential protein, which could bring about astounding medical discoveries into potential treatments for these conditions.

Medical Treatment of the 21st century acknowledges the effectiveness of exercise to treat chronic diseases and illness. For instance, at present medical conditions such as high blood pressure can be treated by regular cardiovascular exercise. Similarly Cholesterol, Type II Diabetes, Depression, Anxiety, Arthritis and Osteoporosis can all be treated more effectively by means of regular exercise than medication. Even Heart Disease can be prevented by undertaking regular cardiovascular exercise.

Anxiety and Depression are both conditions linked to the Brain and there has been research done to suggest that exercising helps to reduce the symptoms of these conditions. In a study

carried out by the University of Texas in 2005 they found that thirty minutes of moderately intense exercise five days a week reduced symptoms of depression by nearly half after twelve weeks. From this study it is evident that exercise can be used in the medical treatment of conditions to do with the brain. This is significant as this paper will also examine the possible treatment of the degenerative disease Alzheimer's and Dementia, which are involved in the brain's processing of memory.

Memory is arguably the most important aspect of a human; it makes us who we are, it shapes our personalities and our future. Without memory, even the smallest things in life would be impossible – holding a conversation, taking a bath, or reading a book. However, it has only been for the last hundred or so years that humanity has really started to investigate how memory works, and there are still many questions to be answered. There are three kinds of memory: sensory, short-term, and long-term.

Sensory memory is the ability of our brain to retain information that comes from our senses, for just a few moments. Johann Segner, a scientist in the 18th-century discovered this. He realised that if glowing coal is spun round at a high speed, then it just looks like one wheel of light, instead of just one piece of coal, which is what it was. This is how we can trace letters by using sparklers, or recall information if something is held briefly in front of our eyes, and is called 'iconic' memory. One can also recall sounds for several seconds after we hear them – this is called 'echoic' memory. Sensory memory works by storing electrical activities in the sensory areas of the brain. When the electrical activities disappear, so does the memory.

Short-term memory retains roughly seven items of information for 15-20 seconds. It is created when the mind chooses to extract pieces of information from the sensory memory. Verbal or visuospatial information can be stored, but in different areas of the brain. Working memory is closely linked with short-term memory, as it involves processing and manipulating the information. For example, entering a phone number after memorising it. This memory seems to be held in the prefrontal cortex of the brain.

Long-term memory is more complicated as it has many different forms. They are stored by their meaning; when asked to recall information one can often not repeat the exact wording, but rather the meaning. The first type of long-term memory is semantic memories, which concern one's knowledge of facts. It is used to recall one's date of birth, mother's maiden name, or the capital of Germany. A second type, episodic memories, are used to recall particular important events in someone's life, such as their wedding day.

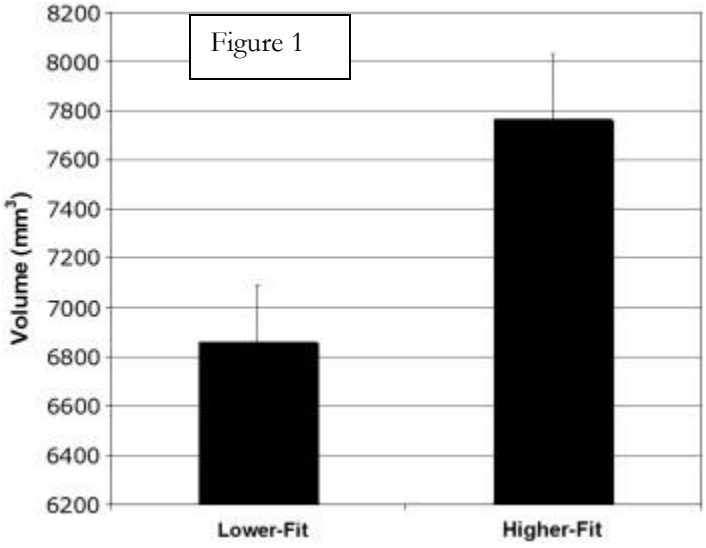
The process of creating, storing and encoding memories involves many areas of the brain. The first step is the situation when the memory is formed. One is far more likely to recall memories if they have to manipulate the information they are given when they first see it. Also, if the events affect someone's life in an important way, such as meeting their partner, then it will also be more likely to be recalled accurately. Memories are made by neurons strengthening their connections, called synapses. Scientists have shown that if an electrical impulse is given to a pair of neurons, the two will communicate more easily in the future. This process is known as long-term potentiation, and is especially obvious in the hippocampus. Memories are sent up from senses to the cortex, and then to the areas surrounding the hippocampus, which 'binds' the information together. The memories are then sent into the hippocampus, where information and context or location is stored.

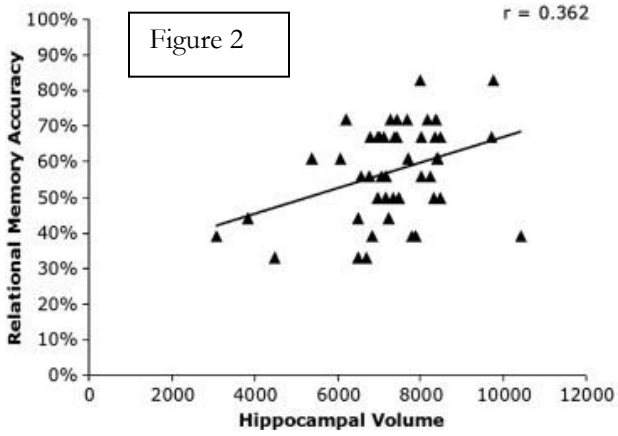
As memory is so important in our lives, losing our memory can be devastating. This is called amnesia, can occur as a result of head injury, surgery, or disease, such as Alzheimer's disease. It

can be temporary or permanent, and can affect the storing of new memories or the retrieving of old ones. Damage to brain structures that form the limbic system, the hippocampus and thalamus, or the diencephalon can lead to amnesia. One of the most common forms of amnesia, dementia is an ever rising problem. As many as 1 in 20 people will develop some form of dementia by 65 years of age - a figure that rises to 1 in 5 in the over-80s[2]. In dementia, neurons in the brain are damaged and die faster than they normally do. This is why researching the field of how exercise may create more neurons is so important. This paper will examine how exercise might affect the production of BDNF, which in turn could improve memory and the onset of dementia.

DISCUSSION

The issue of whether exercise affects memory has been widely researched in recent times. One piece of research [1] was led by Art Kramer of the University of Illinois. Using brain imaging, it was demonstrated that even modest increases in fitness can lead to moderate, 15 to 20 percent, improvements in memory. These benefits are not just restricted to adults; as Kramer and his colleagues also found [2] that memory was affected in a similar way in pre-adolescent children. One can see from figure 1 that the children who had a higher fitness had a comparatively larger hippocampal volume than those with a lower fitness. The study the tested whether the children with a larger hippocampal volume were better at performing a relation memory task. The results are illustrated in the graph of figure 2 where a positive correlation can be seen between the bilateral hippocampal volume and relational memory accuracy. Unfortunately one limitation of this study, was that it did not show the link between BDNF production and memory.





A second study [3] carried out by scientists in Ireland on a group of sedentary male college students compared two groups; one doing exercise, and the other relaxing. They also took blood samples throughout the experiment. These offered a biological explanation for the improvement in memory, since immediately after the strenuous activity, the cyclists had significantly higher levels of the protein BDNF, compared to the other non-exercising group, and they also performed better in memory tests.

Even though all of these studies show the link between exercise and increased BDNF which correlates to increased memory, they do not suggest how this could be implicated for a medical

use. Research carried out in Germany [4] in 2007 investigated the effectiveness of different types of exercise on BDNF production and consequent improvements in memory. They split the participants into three groups; one relaxing, another doing 40 minutes of low impact running and the other doing two, three minute sprints. They measured the lactate levels in the blood and found that those doing intense exercise (sprints) had 10mmol compared to 2mmol in those doing moderate running (low impact exercise). This showed that high intensity running were doing more anaerobic exercise which is illustrated by the higher lactate levels.

The first step was to take a blood sample immediately after exercise. The intense exercise group saw the strongest increase in BDNF levels as well as other chemicals called catecholamine whose importance wasn't discussed further in the study. Then the participants underwent a session where they learnt novel vocabulary from an artificial language. Immediately after, they had a test on their retention. Those who did intense exercise did 20% better than the others in this test. A second retention test was done after 1 week to see the effect on intermediate memory, and then a third test after 8 months to see the effect on long term memory. For all the tests, those who did intense physical exercise performed better.

One flaw of this experiment was that it was not clear which chemicals contributed to the increase in memory. It states that BDNF was more involved in the immediate retention, whereas the catecholamine chemicals were involved in the long-term retention. However it is not known whether these chemicals are complementary, and therefore rely on each other to work. If exercise will be used to improve memory in the medical setting in the future, then it must be clear which chemicals are contributing factors. Therefore it could be suggested that this is an area of future research.

This research all suggests the direct correlation between the amount of physical activity done and the ability to remember things. This knowledge has been used to try and discover possible medical treatments for tragic and ever increasing degenerative diseases like Alzheimer's, which result in a loss in memory. One study produced by Fred Gage and his colleagues at the Salk Institute in California studied 15 young and 18 old mice - the latter about the equivalent of a 70-year-old human. The study involved half of each group of mice having running wheels in their cages whilst the remaining went without. After a period of about a month the mice were all subjected to several days of cognitive tests. This included the Morris Water Maze which required the animals to remember the location of a submerged platform beneath milky water. Old wheel-runners were about as quick to find the platform as the young mice. But old non-runners took twice as long. This was not due to swimming speed - all the old mice swam a bit more slowly - but rather due to a better memory for where the platform was.

The researchers also examined the animal's brains since prior to the experiment the mice had been injected with bromodeoxyuridine or retrovirus to label newborn cells. It was found that the old mice that had been running had reactivated neurogenesis, whereas virtually none was taking place in the brains of their aged inactive peers. It was also discovered that the structure of the new neurons in the aged mice, in terms of spine density, and dendritic length and branching appeared to be similar to those produced in young mice. One limitation of this study however is that it does not clearly indicate that this increased memory performance is due to the protein BDNF. The only way to be certain is to block the ability of ageing animals to generate new neurons while they run, and see if the cognitive effects disappear as well - not an easy task.

A second piece of research however, did try to prove just this by taking a different approach. The research team led by Mark Tuszynski at the University of California [6] injected BDNF

into the entorhinal cortex and the hippocampi of animals, the parts of the brain where memories are formed and consolidated and where Alzheimer's strikes first.

After the injections, all the animals, which included mice with a version of Alzheimer's, elderly rats and monkeys with natural degeneration, and rats and monkeys given brain lesions similar to those of Alzheimer's, improved their performance on memory and learning tests. The injections also reduced the rate of brain cell death and increased by 25 per cent the number of connections between neurons, a crucial aspect of memory formation. Interestingly, these benefits arose even in animals whose brains had developed the protein plaques typical of Alzheimer's and often blamed for its symptoms. The deposits of these plaques clog up the brains of elderly people, and cause neurons to become abnormal, or even destroys them. Therefore this suggests that BDNF can not only act as a prevention for Alzheimer's but also a cure. Another discovery from this experiment was that although some animals received BDNF directly, the best results were in those injected with a harmless virus carrying the BDNF gene, which continued to make the protein. This could be an extremely important area for future research.

Although all of these studies show a clear link between an increase in exercise and improved memory it is difficult to see whether the same results be true on humans. A study [7] was carried out over a period of six years on 1740 people aged 65 and over on people without normal mental function, which was determined by a screening examination. This provided evidence to support the research previously discussed and illustrate the effects of doing exercise and the result on memory in humans. The participants were monitored over a time period of six years during which 158 of the 1740 developed dementia. The researchers defined "regular exercisers" as those who reported exercising at least 3 days per week. They then evaluated participants every 2 years to determine if they had developed dementia by using a standard set of examinations done by physicians, nurses, and a neuropsychologist. On the whole people who exercised at least 3 times per week were less likely to develop dementia than those who were less active. Over the 6.2 years in which the research took place, the rate of dementia was 13.0 per 1000 person-years in those who took part in regular exercise and 19.7 per 1000 person-years in those who exercised less than 3 times per week.

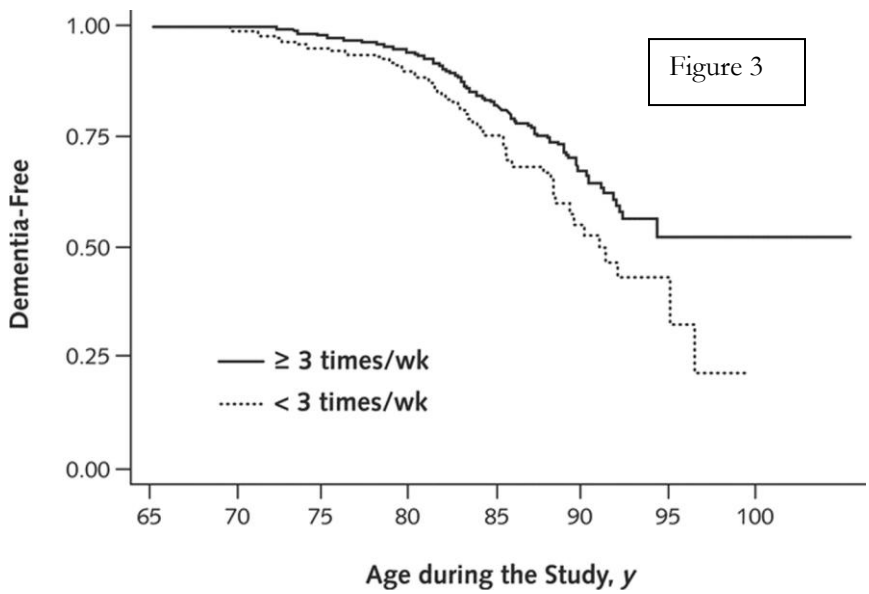


Figure 3

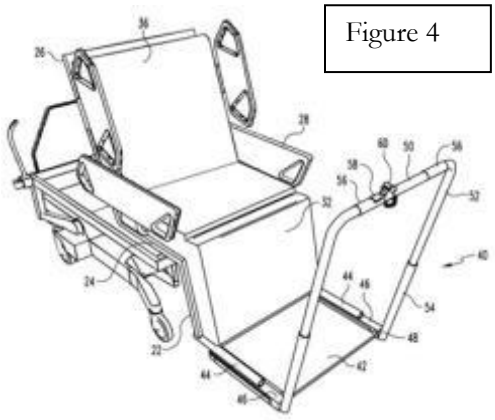
Figure 3 shows that those who took part in regular exercise had a much higher chance of not developing dementia than those who did not.

Although this study supports the idea that exercising regularly helps to reduce the risk of developing dementia it does have some limitations which need to be taken into account. Firstly the exercise was self-reported and was only reported at the

beginning of the study. Secondly the study sample was mostly white and well educated, and all had health insurance. The association between exercise and dementia might be different in less advantaged populations. In addition, the study suggests but cannot prove that exercising delays the onset of dementia.

Even though there is much research which has been conducted to support the theory that exercise could be used as medical treatment for conditions like dementia which result in memory loss there is still a long way to go. For one, suggesting exercise is a simple task in itself but enforcing it becomes more difficult. Another thing to consider is the individual capabilities of people particularly those who are older and perhaps more frail. Charles Filipi, [8] a surgeon at Creighton University in Nebraska has suggested the idea of building a treadmill into the hospital bed (see Figure 4). This allows exercise to be easily accessible to a patient with minimal assistance from others.

Figure 4



Another issue to consider is what type of exercise would be most beneficial. Previously in this research paper it has been discussed that short intense burst of physical activity stimulate a higher rate of BDNF production than prolonged moderate exercise. Again however the ability of the participant has to be considered as it may cause other health issues and safety implications.

Finally in terms of ethical issues are methods like artificially injecting BDNF into the brain. This could be seen on the same level as creating designer babies, where the chemicals can be used to improve memory in a healthy person who does not suffer from diseases like dementia. In addition to this, whose responsibility is it to promote and enforce the idea of people doing exercise in order to encourage neurogenesis. Is it the government's or perhaps even employers?

CONCLUSION

Fact: Regular physical activity can reduce the risk of developing Alzheimer's by up to 40% [1]. Even though we have known this for a considerable amount of time, it is only just becoming clear why: BDNF and other chemicals such as catecholamine in the brain. This paper has not only shown the effect of BDNF on memory in general, but also specifically on degenerative memory diseases. We believe that we are now closer than ever to finding a cure, or prevention for Alzheimer's, as the current research looks very promising. As mentioned in our discussion, we think that future research needs to concentrate more on how BDNF can be effectively extracted and injected, and whether this does indeed improve the memory of humans with dementia.

However, we understand that research on this level takes many years to complete, and many lives and memories could be lost by then. It is also difficult to determine whether this relationship is because exercise actually prevents dementia or because people with early dementia become less active. Therefore we believe that at the same time that the research is happening, the government should be encouraging more people to exercise. Everybody accepts that children nowadays at least do some exercise in school, but very little emphasis is

put on the importance of exercise is middle-aged and elderly life. Many people see the main or only benefit of exercise as losing weight. If more people were educated on its other numerous benefits, then they may be more encouraged to exercise more

Working together is always the best way to solve problems, and this one is no exception. If researchers, governments, and individual people and families do, then we could, we will, one day live in a world free from this life-destroying condition.

REFERENCES

Introduction:

[1] Study on BDNF levels in mice, Carl Cotman, Columbia University
http://www.axonpotential.com/exercise-and-cognitive-health/

Discussion:

[1] Study showing how exercise increasing hippocampus size and memory, Fred Gage
http://www.pnas.org/content/108/7/3017

[2] Study showing improvements of hippocampal volume in preadolescent children, Arthur Kramer
http://www.sciencedirect.com/science/article/pii/S0006899310018317

[3] Exercise increases BDNF production in young males, SA Warmington
http://www.ncbi.nlm.nih.gov/pubmed/21722657

[4] High impact running improves memory, Bernward Winter
http://www.sciencedirect.com/science/article/pii/S1074742706001596

[5] Exercise enhances hippocampal neurogenesis in aged mice, Henriette van Praag
http://www.jneurosci.org/content/25/38/8680.long

[6] Injected BDNF in aged animals increases memory, Mark Tuszynski
http://www.nature.com/nm/journal/v15/n3/full/nm.1912.html

[7] Long term Study of dementia is elderly people, Walter Kukull
https://annals.org/article.aspx?articleid=719427

[8] Patent for exercise bed, Charles Filipi
http://patentscope.wipo.int/search/en/WO2008052220

Conclusion:

[1] Fact about Alzheimer's
http://exerciseismedicine.org/documents/EIMFactSheet2012_all.pdf