How can exercise improve the health of the brain?

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ABSTRACT
In this paper we show and explain the effects of exercise on the brain. We discuss how exercise can affect the mental health of a person and how it can be used as a treatment for a number of conditions such as depression and the treatment of neurodegenerative diseases. We also discuss recent progress in the area of exercise and the brain and further advancements which may be made in the subject area. Finally, we discuss the benefits of exercise as a treatment in comparison with more traditional drugs and treatments.

INTRODUCTION
It was widely accepted for a number of years that the brain and the body where two entirely separate and different things. Descartes was the first to propose this functional difference between the two, he believed that the two needed separate things and thus two different branches of medicine appeared: general medicine for the body and psychiatry for the mind. This theory was widely accepted for a number of years, however, recently opinions have begun to change and scientists have begun to challenge the long standing theory of the mind-body divide. The formal discovery of the placebo effect, as so dramatically demonstrated by Klopfer in his article in the Journal of Progressive Techniques (1957) [1], (wherein a cancer patient went into remission when taking a drug which he believed would cure him (despite it only being saline solution), then became ill again having read an article stating that the drug did not work, and back into remission having been given a ‘double-strength’ version and finally died having read another article on its ineffectiveness), established that the mind can have a dramatic effect on the body, but it has only been comparatively recently that scientists have begun to consider the effects that the body can have on the mind. One of the avenues of research which is currently promising is the effects of exercise on the brain.

Regular physical exercise has long been known for containing many benefits to humans both physically and mentally. New research has shown regular exercise also improves the capacity to learn and to retain memory more efficiently both in the long term and short term memories. Investigations have also shown that physical exercise improves people who have mental diseases such as depression, conditions. Thus it is clear the effects of exercise must have biological significance to the brain as that is the section of the human body which causes these effects.

Exercise increases the release of certain neurotransmitters; these are naturally occurring chemicals in the brain, which are involved in the communication between nerve cells - called neurons. These neurons communicate by the balance of calcium and potassium being accepted or deported. The types of neurotransmitter produced by exercise are called monoamines and they are specifically serotonin, dopamine and norepinephrine. There are other types of neurotransmitters that are produced during exercise but these are the only ones studied to a greater extent because of the known benefits from them. The new neurons created are placed in the hippocampus; this is the sector of the brain which controls the learning and memory in the brain- although the reasons why this happens are still being investigated. [20]

One theory is at a cellular level the stress, though mild, generated while exercising stimulates additional calcium uptake. This extra calcium switches on more transcription factors in already existing hippocampus neurons. The transcription factors also start the
expression of the BDNF (Brain Derived Neurotrophic Factor) gene, which creates BDNF proteins. These proteins act to promote neurogenesis - the process that makes new neurons. The creation of new neurons is seen as a protective response to the increased levels. BDNF protects existing neurons as well as creating more by promoting synaptic plasticity – this increases the efficiency of signal transmission between different neurons and is generally considered the source of learning and memory. The effects of BDNF are reparative, and thus could help to maintain long term performance, which is good for humans because human brain tissue starts to degenerate at around the age of 30 years and the increased BDNF in people is known to reduce the problems with depression.

Another factor to consider is endorphins – endorphins are released by the pituitary gland when the body is responding to stress. Endorphins work by binding to the receptors in neurons and blocking the releases of neurotransmitters and hence blocking the transmission of pain impulses to the brain, this is shown in diagram 1 on the left. Exercise tends to release endorphins after 30 minutes from the start of the exercise. These endorphins tend to reduce the discomfort in exercise and the subsequent feeling of displeasure; although the extra endorphins aren't long lasting so regular exercise is needed if one requires longer lasting heightened endorphin levels.

Studies have shown any amount of exercise or regulatory has a measurable effect on neurotransmitters. Even short term exercise showed some improved cognition and for people who do exercises regularly showed reductions in brain and mental diseases, such as depression, probably because of the increased levels of neurotransmitters. An example would be long distance running creating increases levels of serotonin and norepinephrine, which is commonly associated with happiness and increased energy levels. Another study showed dopamine levels in the brain were increased during prolonged and lengthy exercise but soon returned to their normal levels again afterwards.

Investigations on exercise and age have shown that exercise benefits the brain for any person no matter what the age. However, the health benefits of exercise are strongest and longest lasting if humans develop the habit of exercising early on in life, especially at the ages around 8 and 9 (before puberty). Both anaerobic exercises and aerobic exercises also result in improvements for people with depression probably due to the extra neurotransmitters, endorphins and social benefits. Generally the more intense the exercises the higher the proportion of neurons are created and these intensive exercises are more
likely to be anaerobic exercises, such as sprinting when running, although, as mentioned in a previous paragraph, the extra endorphins are only made after 30 minutes from the start of the exercise, so perhaps to gain endorphins, known to reduce depression, more aerobic exercise such as going for a long distance run would be recommended. For this reason the general advice is to do a variety of different exercises in order to gain a wider range of positive effects.

The fact that there is quantifiable evidence that exercise improves the health of the brain and mental conditions like depression could mean that exercise is used as treatment method alongside the use of anti-depressants to treat people who have depression or bipolar disorder. Exercise could also be recommended to those who are genetically at a high risk of developing Alzheimer’s disease and Parkinson’s, to slow the onset of these age-related illnesses. These two concepts, and the potential future developments in their treatment, will be discussed below.

DISCUSSION
Depression, defined as a more than one period of low mood, with a loss of pleasure in previously pleasurable activities, is a significant contributor to suicides (with up to 60% of suicides being committed by depressed people) and affects around 350 million people worldwide. It is hypothesised to be caused at least in part by low levels of endorphins [2], and current treatments for moderate and severe depression revolve around psychotherapy and the use of antidepressants. Antidepressants mostly (being a broad class of drug) work by increasing the levels of endorphins in the body, a case in point being serotonin-norepinephrine reuptake inhibitors, which work by reducing the reuptake of serotonin and norepinephrine by neurotransmitters, and hence increasing the amount of those endorphins present in the synaptic cleft, resulting in a better mood. However, antidepressants have a number of side effects due to their interference with neurotransmitter levels. Most antidepressants have the capacity to result in nervousness, headaches, anorexia, decreased sexual function and increased suicidal thoughts [3]. There is also the possibility of fatal drug interactions with comparatively common drugs, causing serotonin syndrome [4]. Finally, any moderately significant change in dosage dramatically increases the suicide rate, which means that dosage must be carefully planned and that, when a patient is coming off medication, they must be monitored to prevent suicide. Exercise, by contrast, does not have these side effects, which makes it potentially useful for treatment of depression.

The reason why exercise decreases depression, but lacks the risks of antidepressive drugs, is partly because it increases the production of serotonin without increasing its retention in the synaptic cleft, thus eliminating the risk of abnormal function. This is due to the BDNF-serotonin feedback loop. Serotonin production raises the rate of BDNF production, which in turn raises serotonin levels [5]. Low levels of BDNF have been associated with increased stress in mice during maze puzzles [6], and the ‘depression score’ (which takes into account various symptoms in depressed patients, higher is worse depression) of children with a mutation which reduces BDNF secretion (Val66Met) is higher than children without it, where abuse has been suffered; indicating a lack of serotonin [7]. This indicates that, since serotonin levels rise, up to a point, with BDNF levels, there is the possibility of creating new antidepressants which stimulate the production of BDNF, although great care would have to be taken not to over-stimulate production, as that has been shown to result in learning deficiencies in mice[8]. There is the capacity for genomic medicine to take a hand
here, since patients with mutations which reduce the production of either BDNF or serotonin, and hence those likely to be at risk of depression, may require higher doses to achieve the same effect. Gene-sequencing would identify these, which would drop the risk of suicides while under treatment significantly.

An identical effect, but reversed, can also be gained from exercise through the synthesis of serotonin following fatigue [9]. Tryptophan (serotonin precursor) levels and serotonin synthesis are associated with fatigue, yet lowering tryptophan levels during exercise has little or no effect on fatigue, (although it is a mild hypnotic of itself). Branched chain amino acid levels, which inhibit tryptophan transport into the brain, also decrease as fatigue increases. This, then is another element of the benefits of exercise in the treatment of depression- directly increased serotonin levels. Serotonin itself cannot cross the blood-brain barrier, but tryptophan can, and is absorbed through the digestive tract, which leads to it being prescribed for people who are unresponsive to conventional antidepressives. However, with higher dosages (although not unduly high- tryptophan consumption to excess may lead to eosinophilia-myalgia syndrome, which is potentially caused by an inability to degrade histamine, leading to high histamine levels, which can prove fatal [10]), combined, perhaps, with BDNF- producing supplements, it should be possible to treat at least moderate depression solely with side-effect-less drugs.

Exercise can also be very beneficial for a number of neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease.

Alzheimer’s is a progressive neurological disease which leads to the loss of neurons in the brain, this leads to decreased intellectual ability mostly in the areas of memory and reasoning. This loss of intellectual ability is mostly down to the plaques and tangles which the diseases causes to develop in the brain. These plaques lead to the death of brain cells and thus the impairment of the memory and reasoning. [11,12] Figure 2 on the right shows a comparison between a healthy brain and a brain affected with Alzheimer’s. As you can see, the brain with Alzheimer’s has shrunk in size in comparison with the healthy brain and also contains a number of plaques and neurofibrillary tangles. The brain shrinks due to the death of nerves and tissue within the brain; the areas which shrink the most include the cortex and the hippocampus. The cortex is responsible for thinking, planning and remembering while the hippocampus is involved with the creation of new memories. The shrinkage of these areas thus causes the intellectual decline within memory and reasoning experienced by most sufferers of the disease. [14]

It is believed that Alzheimer’s currently affects around 417,000 people in the UK and
currently there is no cure for the disease, nor do scientists know exactly what causes it. Because of this, treatments are simply used to slow the progress of the disease and try and relieve some of the symptoms associated with it.

One treatment which is currently being explored for Alzheimer’s is physical exercise. Physical exercise for those with Alzheimer’s can be very beneficial. Not only does the exercise improve the general health of the patient, reduce the risk of stroke and help reduce the risk of osteoporosis it can also help improve memory and slow down the loss of intellectual ability. Although scientists currently are not entirely sure why exercise has such an impact on memory in patients with Alzheimer’s there are some theories as to why it does. One theory currently being explored started with a study conducted recently at the University of Nottingham. This study, conducted on mice, found that a stress hormone, corticotrophin-releasing factor known as CRF, is released during exercise. They found that when put under stress the CRF increased the signs of nerve cell communication in the mice’s brains which suggests that the stress hormone could be responsible for protecting the brain from the damage associated with Alzheimer’s. [15] This therefore is one theory as to why exercise helps slow down the effects of Alzheimer’s. One other theory would be that exercise causes BDNF to be released into the blood stream. This hormone is responsible for the manufacture of new neurons and so an increase in concentration of the hormone in the blood stream would lead to a larger number of neurons being created. This therefore would help to slow down the damage caused by Alzheimer’s as the new neurones replace the ones which have died due to plaques or tangles.[16,17] One study conducted at the University of California on a range of animals backs this theory up. The study titled ‘Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer’s disease’ found that “In each case, when compared with control groups not treated with BDNF, the treated animals demonstrated significant improvement in the performance of a variety of learning and memory tests. Notably, the brains of the treated animals also exhibited restored BDNF gene expression, enhanced cell size, improved cell signalling, and activation of function in neurons that would otherwise have degenerated, compared to untreated animals.” This study shows the effects which BDNF can have on the brain and its function and suggests another reason as to why exercise has such a positive effect on the brains of those suffering from Alzheimer’s.

Whatever the reason for the improvement found in patients with Alzheimer’s who are treated with exercise one thing is certain; exercise is proving to be a beneficial treatment for slowing down the progression of the disease.
CONCLUSION
To conclude, exercise massively affects how the brain develops at a cellular level and the consequent implications, such as mental diseases like Alzheimer’s disease and depression. Exercise can be beneficial for people with Alzheimer’s disease because, under mild stress caused by exercise, the brain activates more CRF which in turn increases the communication within nerve cells. These communications can allow people to delay the progress of Alzheimer’s and thus it is concluded the stress hormone is at least partly responsible for protecting the brain.

However there is no universally agreed theory as to why exercise is so good for Alzheimer’s patients. Another theory is that the BDNF hormone creates new neurons that can replace the ones destroyed by the plaques and tangles in the brain improving learning and memory, a major problem with people who has Alzheimer’s disease. It is probably a combination of these two factors that makes exercise extremely beneficial for people with neurological diseases as well as the social benefits that exercise, such as increasing communication between people in a team environment, can bring.

As well as improving neurological conditions exercise can also improve the lives of people with depression. As exercise can work in a similar manner to antidepressants by increasing the percentage of endorphins in the brain and also increase the levels of BDNF in the brain like anti-depressants. However, exercise doesn’t result in as many side effects as antidepressants, such as nervousness, headaches, anorexia, decreased sexual function and increased suicidal thoughts. Thus exercise could be an alternative option to anti-depressants for people suffering with mild depression or it could be used alongside anti-depressants to increase the effectiveness of the treatment. Especially because regular exercise has many beneficial side effects, such as reduces obesity, reduced chance of heart disease and diabetes which the person wouldn’t receive by only relying on the use anti-depressants. In other words the use of exercise for treating patients with neurological diseases and depression would also improve the patients overall health and well-being, which is why it is now recommended to participate in 30 minutes of exercise 5 times a week.

Finally, after our research we have come to the conclusion that as well as exercise a BDNF supplement could be introduced to help treat depression and help slow down the onset and progress of Alzheimer’s. This supplement would be similar to any other vitamin supplement and would contain the hormone BDNF; it would be infused with the patient’s brain. We hypothesize that, should this be produced, it would be a great addition to the range of treatments available for these conditions. Once an optimal dose of the hormone is found this supplement could be used to regulate BDNF levels in patients and help with the symptoms of Alzheimer’s. In order for this to be successful research would need to be conducted to find the optimum dose, as studies have suggested that too large amounts of the hormone could actually have a negative impact on the person’s mood [19]. Once this is found however we hypothesize that it would be a suitable alternative to exercise should an Alzheimer’s patient be unable to participate in physical exercise as it would give the same hormone boost as the exercise itself does, thus simulating the hormone rise.
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