

Exercise: A Treatment for Alzheimer's Disease?

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DISTINCTION

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ABSTRACT

Alzheimer's disease is a severe and brain degenerative disease. It is a form of dementia which, over time, leads to memory loss. Currently, there is no cure for Alzheimer's but there are treatments for it. However, in this paper, I will be looking at what type of exercise is suited for people with Alzheimer's as a treatment to slow down memory loss or increase cognition and another possible future treatment to reduce these symptoms of Alzheimer's.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia among older people, the main symptom of which is memory loss, ranging from forgetting names to places. It is not necessarily a genetically inherited disease (1% to 5% of cases found to be genetically inherited). AD leads to nerve cell death and tissue loss throughout the brain.

The effect of AD can be seen in Figure 1. The normal, healthy brain (Figure 1a) is larger in size compared to the brain of someone who has AD (Figure 1b). The greatest differences in size can be seen in the cerebral cortex and hippocampus, where there has been a lot of degeneration. These two areas in the brain are important to memory and learning, which decline significantly if you have AD.

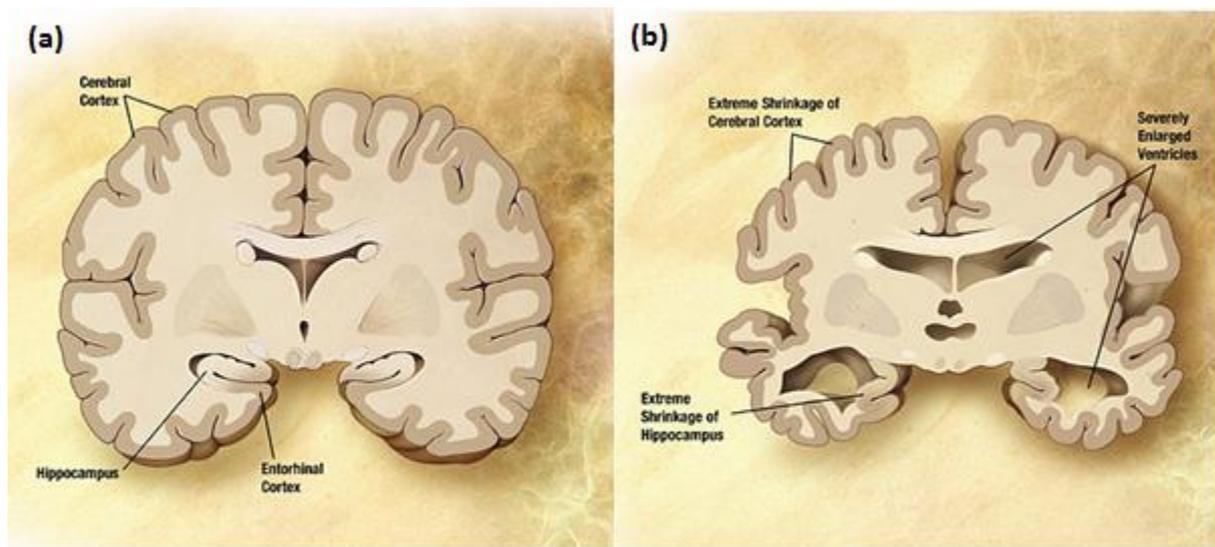


Figure 1

The death of nerve cells (neurons) is caused by two abnormal proteins in the brain which accumulate together in clumps, called 'plaques' (Schindowski et al 2007). These interfere with the connection between the nerve cells found all over the brain, of which there are more than 100 billion. The loss of neurons greatly affects the functions of the cerebral cortex and hippocampus including forming and storing memories, learning, movement and cognition. AD mainly interferes with the communication of neurotransmitters and the way electrical signals travel in the neurons.

Nerve cells communicate with each other by sending a chemical signal, called a neurotransmitter, across the synapse (the gap between two neurons, which can be

seen in the squared section of Figure 2a) when the electrical signal reaches the terminal of a nerve cell's axon. This neurotransmitter (represented by the red particles in Figure 2b) diffuses across the synapse towards the receptor end of a number of dendrites of the next neuron and the chemical signal is transduced back into an electrical signal, which continues moving along the nerve cell if sufficiently stimulated (their effect is cumulative). This can be seen in Figure 2b.

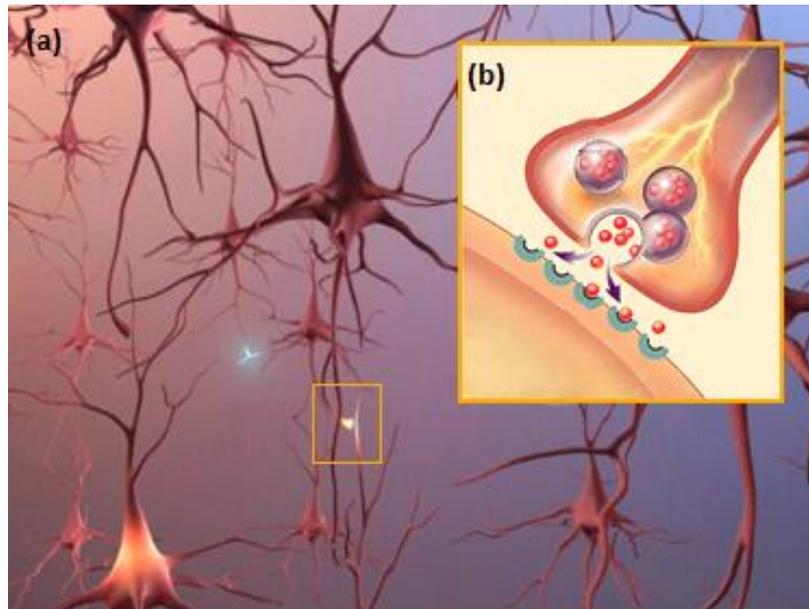


Figure 2

There are two main types of neurotransmitters released by the electrical signals in neurons: GABA (Gamma-Aminobutyric Acid) and Glutamate. These are used in 80% of the neurons in our brain. GABA and glutamate's role can be portrayed as traffic lights. GABA acts as the red light: it is inhibitory and stops action potentials (the event where an electrical signal is sent down the axon) and Glutamate is the green light, it is excitatory and starts and maintains action potentials. Like traffic lights, these two neurotransmitters work together antagonistically, controlling the brain's overall level of excitation and many other processes. Furthermore, the more often a signal passes between neurons, the more effective the neurotransmitter is. This also means that the more receptor sites in the dendrites, the stronger the connection between the two neurons and the more effective they will work. Receptors and neuron formation is brought about by brain-derived neurotrophic factor, BDNF (Tyler et al 2002).

BDNF is a protein found in the brain, specifically the hippocampus and cortex, which is known to facilitate memory formation and synaptic plasticity (the neurotransmitters' effective movement across the synapse) (Hellweg & Jocker-Scherubl 1994; Tyler et al 2002). Despite this, BDNF can be found in motor neurons, the central nervous system and the retina as well. When BDNF is secreted, it can stimulate the growth of new receptors and neurons in the brain. It

has been shown that a lack of BDNF plays a part in the development of AD as decreased levels of BDNF are detected in the brains of those who have the condition (Connor et al., 1997). Connor shows that BDNF is an important growth factor, especially when it comes to neurons, with AD preventing neurotransmitters from working efficiently and effectively, causing nerve cells to die.

In order to reduce the symptoms of AD, more BDNF needs to be secreted to stimulate neurogenesis (new neural connections). The more growth, the more neural connections between neurons (via neurotransmitters) and the more effectively the neurotransmitters will work because of the stronger connectivity.

A way that BDNF production can be increased is by doing exercise (Cotman & Berchtold 2002). Several studies have been conducted which show that exercise can promote BDNF production and also preserve cognitive function in the elderly (Kramer et al, 1997). Some animal studies (specifically on rats) have shown that voluntary exercise over several days increased levels of BDNF in the hippocampus which remains present even after a couple of weeks following exercise. Several studies (Cotman et al, 1996; 1998) showed exercised rats had higher levels of BDNF in their hippocampi and that there was also a positive correlation between the amount of exercise and BDNF levels.

An article in the New York Times (April 2012) describes a 2007 study where mice had 'readily wired many new neurons into the neural network' in response to exercise. These new neurons fired when the mice ran and performed cognitive skills due to BDNF production, showing that exercise helps stimulates neurogenesis. A similar study (Marais et al, 2009) backs up these claims looking at chronically stressed rats. However their study also showed a reduced depressive-like behaviour. Studies such as these have evidently shown that exercise can stimulate BDNF production.

Most of the studies which demonstrate that exercise increases BDNF levels have not been on humans. But there have been a few studies to confirm that exercise increases cognitive function such as Bernward's (2007), showing that intense physical exercise (of two sprints of three minutes at increasing speed) increases BDNF levels and improves learning.

This research shows that exercise can increase BDNF production, stimulating neurogenesis (Gómez-Pinilla et al 2002), which in turn promotes the number of neurons in the cerebral cortex and the hippocampus. If AD sufferers exercise, this should mean that their cognitive function and memory improves and does not get worse.

DISCUSSION

AD is a severe, degenerative brain disease mostly affecting the elderly (75% of US AD sufferers above the age 75). With our aging population, AD currently affects 35.6 million people but will increase to 115 million by 2050. A reasonable treatment could be advised but it must be one that improves the quality of life of sufferer. Some treatments could have ethical implications or are not appropriate for the elderly.

Exercise has shown to increase BDNF levels (Gómez-Pinilla et al, 2002; Tang et al 2007)) and to improve memory (Cotman et al 2007). Perhaps this may be a possible treatment to maintain cognitive function and memory, but also stimulate neurogenesis. There are many different exercise regimes advertised today in the media, ranging from endurance training to walking. High impact and endurance training have shown to improve learning by increasing BDNF levels (Seifert et al 2010; Winter et al 2007) but exercise such as this is not suitable for those with AD because the majority of people are over the age of 60. As stated, treatments should improve both the person's quality of life as well as their health.

Walking may not seem like exercise, as we all do it daily, but it can benefit cognitive function. A daily twenty minute walk is sufficient with 150 minutes of moderate-intensity exercise being advised for adults (2008 US Physical Activity Guidelines). However, people with AD may not be physically fit enough to complete 150 minutes and so three walks of ten minutes per week is deemed enough for the elderly. In addition, walking does not require huge effort and is enjoyable as well, especially outside. Exercise does not necessarily mean hours at the gym; it should not be exhausting in order to be effective for the brain; that is for those who want to get fitter and not necessarily maintain their cognitive function.

Most of the rodent studies do not use walking as the 'exercise' but running on a wheel. Work by Erickson et al (2010), does use walking, where 65 year olds walked for 10 minutes per week, which increased in 5 minutes increments until they were walking for 40 minutes per week by week seven. They carried on having 40 minute walks from then on. Their study showed that walking led to an increase in the volume of the hippocampus (results shown in Figure 3 below), increased BDNF in the bloodstream (Graphs C and D, left and right hippocampi respectively) and an improvement in memory performance (Graphs E and F, left and right hippocampi respectively).

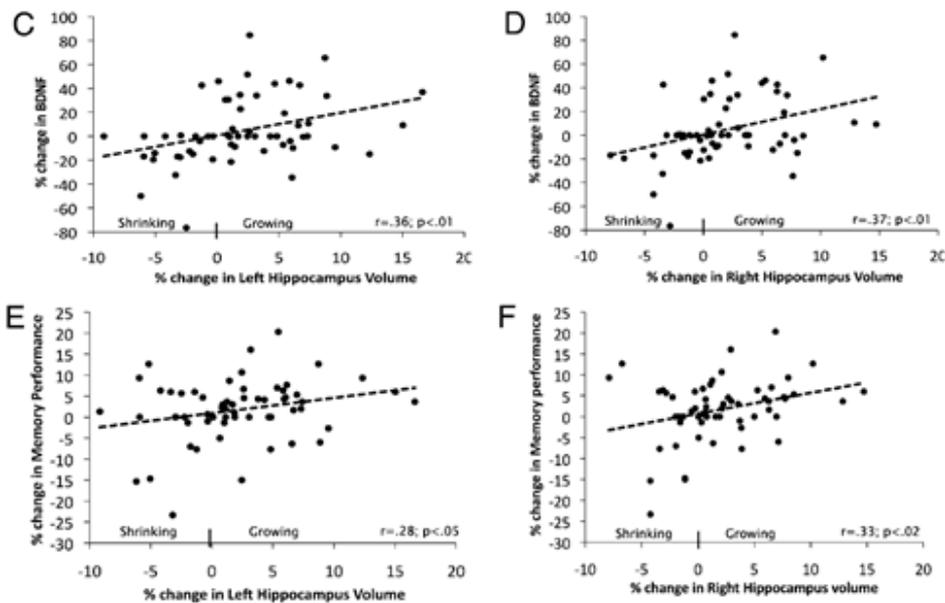


Figure 3

This bodes well for AD sufferers because walking for 10 minutes per week as their exercise is reasonable and achievable. However, by week seven of this regime, it might be advised to complete four 10 minute walks per week instead of doing the full 40 minute walk in one session. Of course, people with AD should not be restricted to walking just 10 minutes per week if they are capable of walking for longer, but Erickson et al, (2010) show that a 10 minute walk can increase both BDNF levels and memory performance. Walking has more pros than cons: it first of all maintains and improves a person's health, increases BDNF levels leading to better cognitive function, and it is an opportunity which allows the elderly to spend time outside. Another advantage is that exercise creates a beneficial effect towards those with depression. Zheng et al (2006) demonstrates this with rats, but it is likely that exercise will also have a positive effect on humans too, because rats produced higher levels of BDNF after exercise and the study concludes that the change in behaviour might be related to the BDNF levels in the hippocampus.

A problem with this might be that there are not enough carers to support those with AD to go for a walk and make a long term commitment to it. Most elderly with AD live in care homes where there are carers who take care of them all day, every day. If the carer does have the time, they are more likely to only be able to look after one person rather than more. This means that in a care home of 40 residents supporting those with dementia forms, such as AD, all of the carers would have to do at least 400 minutes of walking between them so that all the residents go on a walk. This will increase to 1600 minutes in total by week seven if they follow the exercise regime in Erickson's study. However, it is more likely that the carers would not have any spare time to go on a walk unless there is one carer per resident which is highly unlikely. Moreover, a recent article in The Telegraph explains that

the funding for face-to-face care will be cut, leading to fewer opportunities for residents in a home to go on walks, and less carers. The decrease in the number of carers will affect the residents of the care home because they rely on them and need support.

Furthermore, if the person with AD lives by themselves, ten minute walks may not be advised because they could get lost due to their memory loss. This is not the case for people who do not yet have a severe form of AD but the effect of memory loss may start acting on them and those who do have a mild form of dementia might get confused as to where they live rather than forgetting completely. Therefore people with AD should go on a walk with a relative or carer in order to be safe and to ensure that they return home safely. Walking is a possible treatment to reduce memory loss in anybody, because even those without AD suffer brain atrophy as they get older (Gow et al 2012).

Erickson shows that an increase of BDNF levels also improves memory. Since the BDNF produced from doing exercise has been shown to improve memory performance and increase hippocampus volume, perhaps BDNF levels can be increased in another way such as by taking BDNF supplements or drinks which have a high BDNF content. A reason why another alternative treatment should be suggested is because exercise may not be suitable for the elderly if the regime cannot be maintained over a long period of time or they are not fit or healthy enough to carry out the exercise. Therefore another way that the elderly could increase their BDNF levels is by ingesting supplements or drinks with a reasonable enough amount of BDNF in them in order to be beneficial and effective.

On the market today, there are 'protein shakes' which are drinks that contain a high quantity of protein such as whey protein in order to enhance muscle development and improve athletic performance. They are very popular among people trying to increase the amount of muscle in their body or to lose weight. According to *Consumer Reports*, annual sales of nutrition products in the USA are over \$2.7 billion. This figure shows that nutrition products such as 'protein shakes' are very popular and must be successful, otherwise why else would people buy such a product? Like protein shakes that increase muscle growth, maybe a drink containing a high enough quantity of BDNF can be produced and consumed. Creating a drink like this will be preferred more by the elderly with AD because the process of taking in the BDNF protein is more straightforward than having BDNF directly injected. Also, the person with AD might be able to make the drink themselves if their form of AD is still mild. Moreover, making a drink does not require a specialist, such as a nurse, compared with those required for an injection; a carer at a care home can prepare the drink easily.

Protein shakes normally come in powder form and then liquids such as water or milk and other vitamin supplements are used to create the protein drink. There are already products containing BDNF which can be bought, but it is only for research and laboratory use at the moment and not available commercially. Perhaps making

BDNF in a suitable form for consumption could be developed for future use and treatment for people with AD.

Since a BDNF drink is yet to be made and is not currently available to buy as a consumer product, a way in which BDNF levels can be increased without doing regular walks or exercise is by consuming foods which contain a suitable amount of BDNF. An article in the *Nutra Ingredients-USA* explains how a nutraceuticals company in Illinois conducted a pilot study to see what affect whole coffee fruit concentrate (Neurofactor™) has on humans. After the pilot study, the Illinois-based company discovered that following consumption of Neurofactor™, BDNF levels increased by an average of 140% compared to a baseline reading (before Neurofactor™ or any other product was consumed). This result can be seen in the figure below, with Neurofactor™ which contains whole coffee fruit concentrate being shown as the most effective source of BDNF. Neurofactor™ has been compared with other products such as using a placebo, green coffee bean extract and several more products (as shown by Figure 4). The outcome of this study is impressive and shows that food that we could consume can increase BDNF levels and then improve memory and reduce the effects of memory loss by increasing hippocampus volume. The study is awaiting publication and as during the study only ten people participated, the nutraceutical company is looking to conduct a larger study to confirm the validity of their results.

Although the study mentioned above is not reliable because it has not been published yet, another study has been conducted and published, demonstrating that a certain coffee fruit extract increases BDNF levels by about 140% as well.

Modulatory Effect on Plasma Levels of BDNF

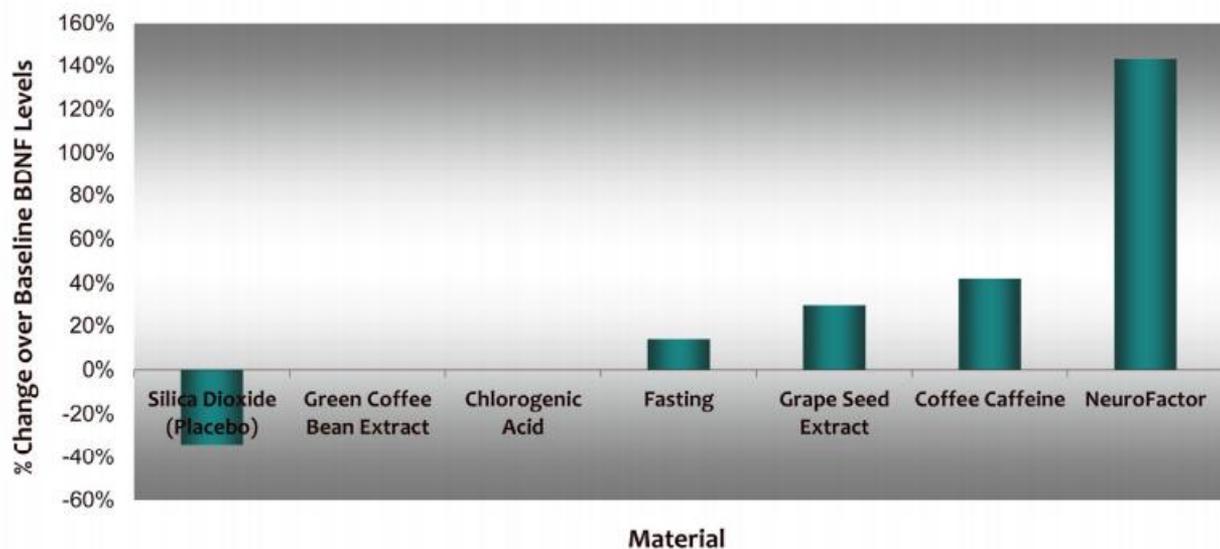


Figure 4

The work conducted by Reyes-Izquierdo et al (2013) demonstrates that Whole Coffee Fruit Concentrate Powder (WCFC) increased BDNF levels by 143% after

consuming a 100mg dose of this powder. The results obtained from the study indicate that WCFC could be used to 'modulate BDNF-dependent health conditions'. AD is not necessarily BDNF-dependent because there is an array of symptoms, with memory loss as the severe symptom, but BDNF is important for people with AD because it is a neurotrophic growth factor which induces neurogenesis. This study is promising and shows that WCFC increases BDNF levels by a significant amount and could increase memory performance and improve cognition, but the pilot study conducted by the nutraceuticals company in Illinois have demonstrated that green coffee bean extract does not increase BDNF. Further studies definitely need to be conducted in order to verify that their product, Neurofactor™ is as effective as it seems. Nevertheless, WCFC can be bought now in the form of capsules from websites such as Amazon or directly from the website of the company that produced and carried out the pilot study: Futureceuticals and their website: www.coffeeberry.org/ . Furthermore in the study by Reyes-Izquierdo et al (2013), they have shown that other coffee extract powders such as 'Green Coffee Caffeine Powder,' and 'Grape Seed Extract,' have increased BDNF levels as well, but these results need to be supported by other clinical studies in order to be certain that this is the case.

But for now, people with AD could ingest green coffee extract or grape seed extract capsules as they can be bought online or purchased in a shop (for example Holland & Barrett). Both green coffee and grape seed extract have been shown to increase BDNF levels by 31% in the work produced by Reyes-Izquierdo and her team which can stimulate neurogenesis and increase both hippocampal volume and memory performance, both important for people with AD. It is important because there is significant shrinkage of the hippocampal volume and a reduction in the number of neurons in the brain. Ingesting green coffee or grape seed extract should, in theory, increase BDNF levels and improve memory and cognition in those with AD. Although there have only been a couple of studies conducted, the idea of using green coffee extract, WCFC or grape seed extract as a way to treat memory loss in people with AD sounds promising and could possibly be introduced as a treatment in the future. As many people with AD are older than 65, they can avoid exercising which could be exhausting and may not be of significant benefit for them. Thus, drinking green coffee bean extract could be a potential treatment, and hopefully further research on this will take place and could provide more evidence that green coffee bean extract could reduce memory loss and other symptoms associated with AD (including increasing cognition).

CONCLUSION

Tough exercise regimes or the completion of low level exercises such as walking, have already been recommended to people with AD (Petersen, Mayo Clinic). In terms of the BDNF drink and ingesting green coffee or grape seed extract supplements, further research and clinical trials do need to be conducted in order to verify that BDNF can be obtained in this way to stimulate neurogenesis and help stave off AD, and maybe other forms of dementia where memory loss and cognition declines as the disease progresses. However these theories, which I have discussed, all have the potential to become future treatments of AD in order to reduce memory loss and increase cognition.

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http://www.alz.org/braintour/3_main_parts.asp

BDNF boosting coffee fruit concentrate could have applications in sports recovery as well as cognitive health:

<http://www.nutrainredients-usa.com/Industry/BDNF-boosting-coffee-fruit-concentrate-could-have-applications-in-sports-recovery-as-well-as-cognitive-health>

Beyond the Reward Pathway (GABA and Glutamate):

<http://learn.genetics.utah.edu/content/addiction/reward/pathways.html>

Brain-derived Neurotrophic Factor:

<https://www.stanford.edu/group/hopes/cgi-bin/wordpress/2010/06/brain-derived-neurotrophic-factor-bdnf/>

Brain-derived Neurotrophic Factor:

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Coffeeberry

<http://www.coffeeberry.org/>

Can exercise prevent memory loss?

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Elderly warned of growing isolation as face-to-face care cut:

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Exercise Guidelines for Children, Adults, and Older Adults:

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Futureceuticals: Coffee-Fruit

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How exercise can jog the memory:

<http://well.blogs.nytimes.com/2012/05/30/how-exercise-can-jog-the-memory/>

How exercise could lead to a better brain:

http://www.nytimes.com/2012/04/22/magazine/how-exercise-could-lead-to-a-better-brain.html?_r=3&pagewanted=all&

Neurofactor Increases Plasma Levels of BDNF in Humans

<http://coffeefruits.com/wp-content/uploads/NeuroFactor-BDNF-Clinical-Study-Results-Overview-FutureCeuticals-Inc.-1.pdf>

Preventing Alzheimer's: Exercise still best bet:

<http://www.mayoclinic.com/health/alzheimers/MY00002>