EXERCISE: DEPRESSION AND NEUROGENESIS

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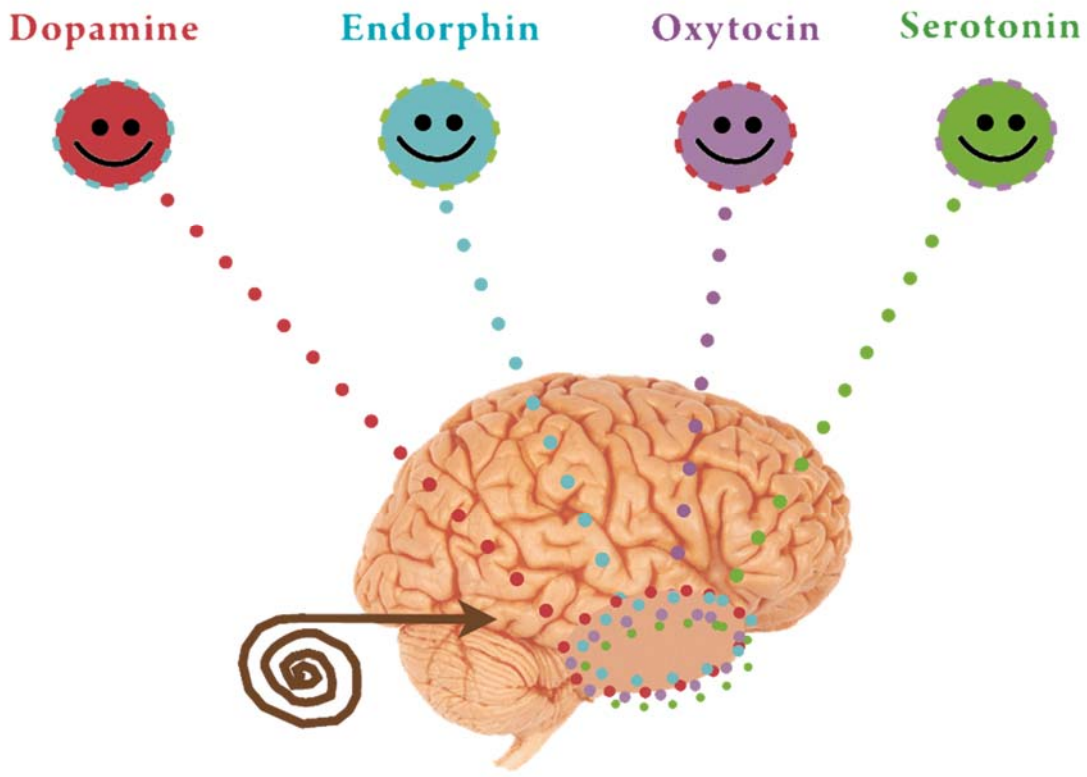
The effects of exercise are multiple and varied and include the ability to alleviate depressive symptoms and to enhance the production of new neurons (neurogenesis). It is possible that the beneficial effects of exercise act directly on the molecular machinery of the brain itself (Cotman *et al.* 2002). The type, intensity and duration of exercise must be considered - as has the animal species, strain and age.

MECHANISMS OF ACTION

The ENDORPHIN hypothesis- shows endogenous opiates such as beta endorphins are released following exercise and this results in an improvement of mood. (Steinberg *et al.* 1985) (Persson *et al.* 2003, Persson *et al.* 2003).

The MONOAMINE hypothesis – shows exercise increases dopamine, serotonin and noradrenaline. These monoamines are typically reduced in depression. Exercise increases tryptophan which increases the synthesis of serotonin.



PSYCHOLOGICAL hypothesis- exercise can distract from depressing thoughts, can increase self- esteem, can provide a sense of achievement and improve social interaction.

THERMOGENIC hypothesis-exercise can increase core temperature and as a result increase the temperature to specific brain areas which can lead to relaxed feelings.

Exercise increases the blood flow to the brain which increases neuronal activity and enhances neurogenesis.

Exercise can be voluntary or forced. A running wheel is used to study voluntary exercise in rodents. A running wheel is a rewarding piece of running apparatus. Exercise reward is critical to stress resistance. As the rodent is free to exercise as and when it likes- there is no increase in the stress hormone corticosterone. The voluntary exercise can result in up to a 3 fold increase in neurogenesis (Olson *et al.* 2006). Forced exercise is studied using a treadmill. Researchers can control the speed, frequency, intensity, duration and timing of the exercise. The animal is forced to run even when not motivated to do so. The animal is gently prodded or experiences a small electric foot shock. This in itself produces mental and physical stress. There is an increase in corticosterone levels and a reduction in neurogenesis.

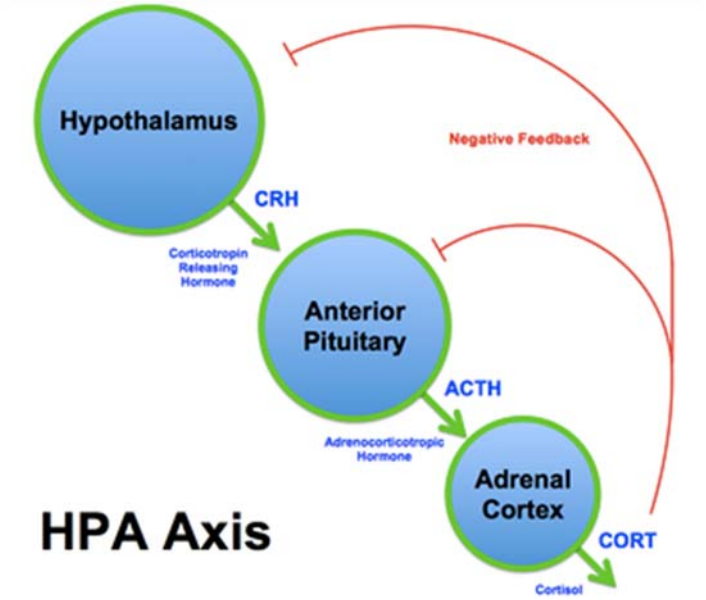
Forced exercise can be seen in military personnel, professional athletes and patients who have been prescribed an exercise program to follow. Dopamine is released and the exercise may result in stress resistance even if the exercise is forced.

Not all treadmill running evokes a stress response. Palmer(Palmer *et al.* 1999) showed that rats trained on a treadmill for 20 weeks, gradually increasing speed and duration minimised the stress evoking effects of running on a treadmill. There is an exercise induced increase in neurogenesis. Stress has a negative effect on neurogenesis (Snyder *et al.* 2009). Regular treadmill running results in the body adapting to the forced exercise and it provides a balance between the positive and negative effects of treadmill running. Regular runners show a biological adaptation. Irregular runners experienced more stress and didn't adapt as readily. Byrne (Byrne *et al.* 1993) showed that regular moderate physical exercise improves coping with stress. There is a reduction in corticosterone levels which counteract stress and improves neurogenesis.

A study by Leasure (Leasure *et al.* 2008) looked at forced vs voluntary exercise on rats over a period of 8 weeks. The distance covered by the 2 exercise groups were the same. As the experiment covered 8 weeks- adaptation occurred. After several weeks exercise no longer elevates corticosterone. Li (Li *et al.* 2013) showed that long term chronic treadmill running does not change basal levels of serum corticosterone. Leasure's study showed that the forced exercise produced more neurons than the voluntary exercise.

Regular exercise has positive benefits for psychological health (Duman *et al.* 2008) (Fuss *et al.* 2010). Herrara (Herrera *et al.* 2016) suggests both voluntary and forced running are rewarding when using a running wheel and a motorised running wheel respectively. Treadmill training differs in that an electric shock motivates the animal to run. This shock provides a difficult confound to overcome (Greenwood *et al.* 2013).

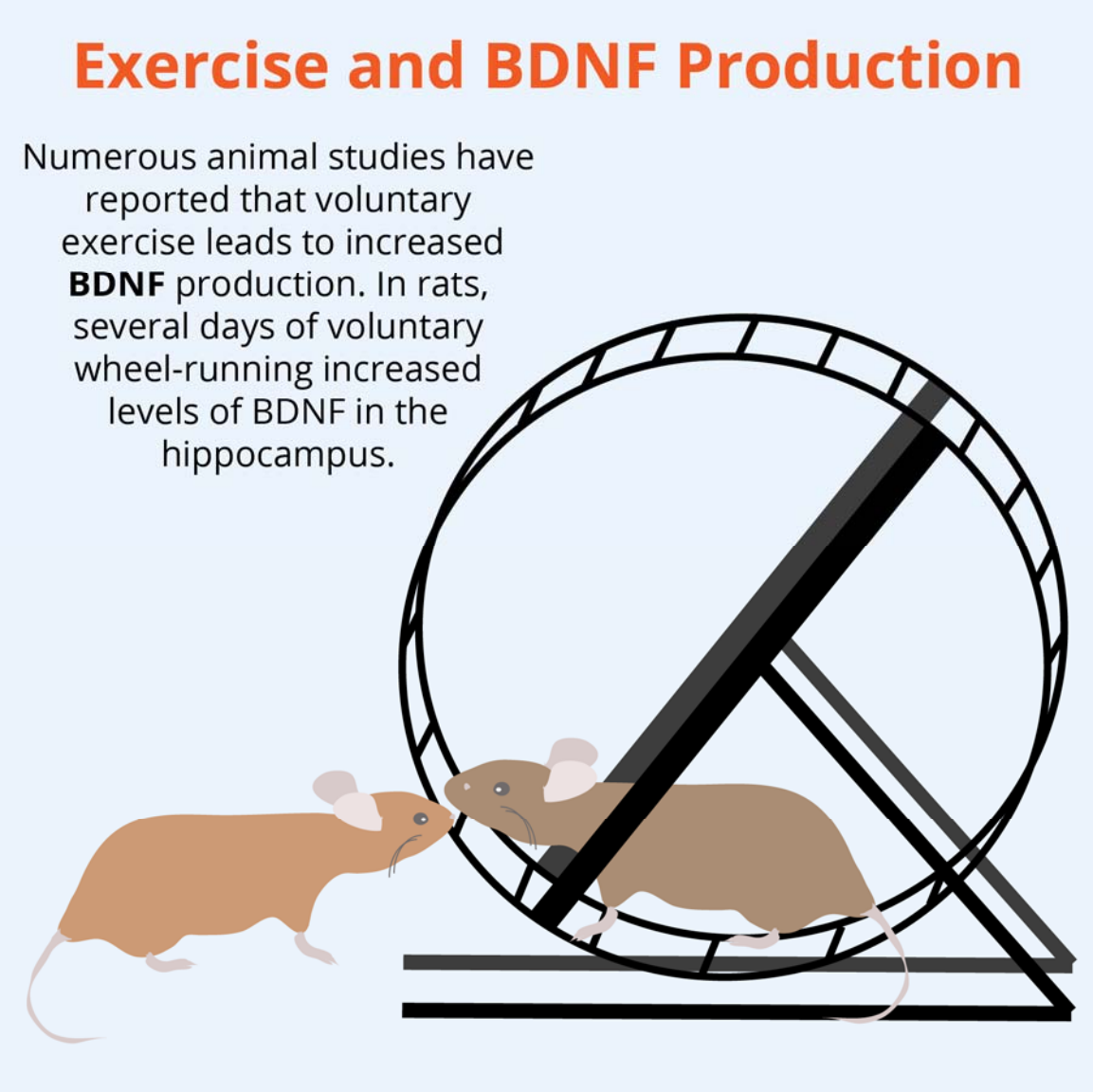
Exercise intensity can have an effect on whether it is considered to be stressful or not. Mild intensity exercise is stress free and there is an increase in neurogenesis. Intense exercise results in the release of corticosterone and there is no increase in neurogenesis (Olson *et al.* 2006).



The HPA axis is part of the neuroendocrine system and has been shown to be a critical regulator of the stress response. Some depressed patients have a hyperactivity of the HPA axis. Exercise attenuates the HPA axis response to stress. Exercise trained individuals show a hyposensitive HPA axis response and

a reduction in depression by regulating the HPA axis response to stress (Brosse *et al.* 2002).

Brain Derived Neurotrophic Factor (BDNF) is a growth factor released during exercise.



Forced and voluntary exercise differ in their effect on BDNF levels. BDNF supports the survival and differentiation of neurons, enhancing neurogenesis.

BDNF can be directly injected into the hippocampus to enhance cell proliferation and neurogenesis (Olson *et al.* 2006). BDNF signalling plays a role in regulating neurogenesis (Lee *et al.* 2002). A direct infusion of BDNF leads to recovery from depressive symptoms (Eldomiaty *et al.* 2017). BDNF expression could be a target for antidepressant therapy (Russo-Neustadt *et al.* 2001). Combining pharmacology with exercise appears to be more effective as a

clinical treatment for depression than either intervention alone (Russo-Neustadt *et al.* 2001).

Exercise can be used to treat depression. Guidelines for moderate depression is structured supervised exercise three times a week for 45-60 mins for a period of 10-14 weeks. Marlatt (Marlatt *et al.* 2012) suggests that the neurogenic response to exercise is stronger than antidepressant medication alone. Callaghan (Callaghan *et al.* 2011) states that preferred exercise rather than prescribed intensity exercise improves psychological outcome in depressed patients. Preferred intensity introduced the exercise gently and incrementally. The participants had control over the level of exercise they could handle and this appeared to increase their enjoyment of exercise. It has been suggested the national guidelines for recommended exercise frequency and intensity are perhaps over ambitious for depressed individuals who often lack the motivation to exercise.

Antidepressant drugs effectively treat depression in the majority of patients, however up to 50% do not achieve full remission and there is a risk of residual symptoms, relapse and recurrence (Blake 2012). There is a time lag for the onset of therapeutic drug effects and adverse side effects are often reported. Adherence is often poor and patients prematurely discontinue antidepressant treatment. The effect of exercise is rapid and it can help to improve residual depression symptoms and prevent relapse.

The benefits of exercise are long lasting. Di Lorenzo (DiLorenzo *et al.* 1999) showed that exercise improved depression for up to 12 months after follow-

up. Blumenthal (Blumenthal *et al.* 1999) showed that patients receiving exercise treatment to manage depression showed higher remission rates than controls. The frequency of the exercise is important. High frequency had lower depression scores than low frequency. Exercise and depression relationship is dose dependent. Exercise has shown to be as effective as cognitive behavioural therapy (Greist *et al.* 1979, Lawlor *et al.* 2001).

Treatment resistant patients who were prescribed antidepressants and exercise showed a 21% response rate and 26% remission (Mura *et al.* 2014). This result was better than been treated by antidepressants alone. Combining exercise and medication resulted in a rapid increase in BDNF levels, whereas the increase with antidepressant treatment alone is not as rapid.

To Summarise:

- Most types of exercise enhance neurogenesis and cell proliferation
- Moderate intensity exercise that is of preferred rather than prescribed intensity is beneficial to treat depression
- Intense exercise is stressful and increases the stress hormone corticosterone with no resultant increase in neurogenesis
- Forced exercise induces a stress response which may override the positive influences of physical activity on neurogenesis
- Regular low/moderate intensity forced exercise results in a biological adaptation which minimises the exercise induced stress response.

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