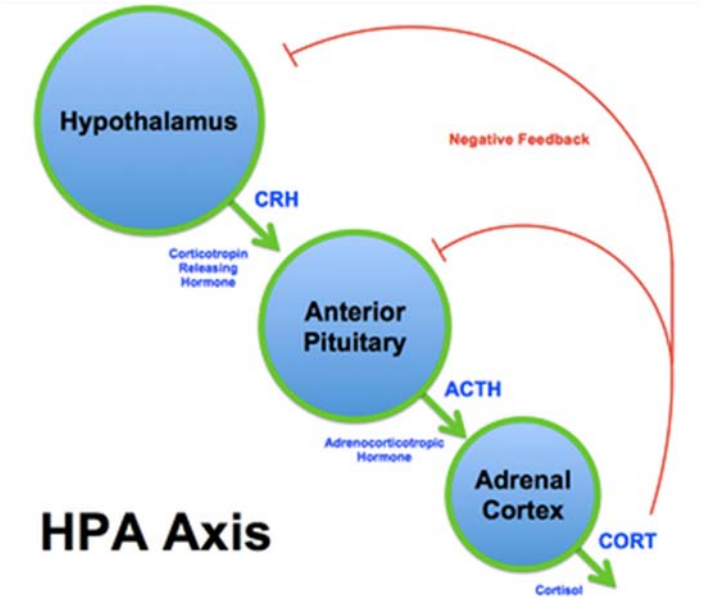
The possible links between neurogenesis, stress and depression

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

The hypothalamic-pituitary-adrenal axis is part of the neuroendocrine system and has been shown to be a critical regulator of the stress response. It can be considered to be the command centre and communication feedback system that senses stressors. There is a complex interaction between structures that release hormones culminating in the release of glucocorticoids- cortisol in humans. There is a negative feedback loop which prevents the system becoming overactive. The response is terminated through the same circuit that activated it.



Under normal physiological conditions the hypothalamic-pituitary-adrenal axis maintains low levels of cortisol. When there is exposure to chronic stress the negative feedback loop is impaired leading to hyperactivity of the HPA axis and high levels of cortisol. Chronic stress is harmful. Some individuals are more susceptible to the effects of stress than others- however it is unclear why this is so (Anacker *et al.* 2012, Ebner *et al.* 2017). Levone (Levone *et al.* 2015) states that resilience is "the ability to cope with environmental challenges ensuring survival". Resilient individuals do not develop stress related illnesses. Southwick (Southwick *et al.* 2005) states that it may be possible to enhance stress resilience using drugs that stabilise the hypothalamic-pituitary-adrenal axis.

Some depressed patients show a hyperactivity of the hypothalamic-pituitary-adrenal axis resulting in an increase in cortisol (Pierscionek *et al.* 2014). Patients whose HPA axis remains abnormal after treatment for depression, are more likely to relapse than those patients whose HPA axis returns to normal (Thomson *et al.* 2008).

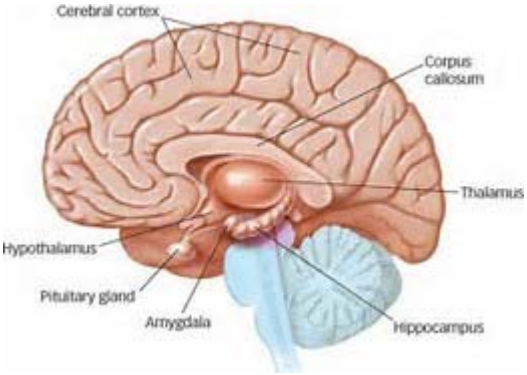
Adult Hippocampal Neurogenesis (AHN)

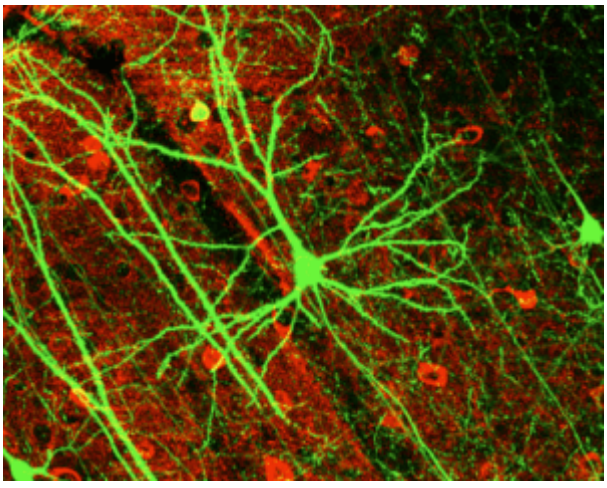
A neuron is an electrically excitable cell that receives, processes and transmits information through electrical and chemical signals. Neurons make our brains work. Neurogenesis refers to the growth and development of neurons. In most of the brain, no new neurons are added. However, the development of new neurons continues during adulthood in two regions of the brain. Adult

Hippocampal Neurogenesis (AHN) occurs in the subgranular zone of the dentate gyrus which is part of the hippocampus of the brain.

Hippocampal volume

Post mortem studies in humans have shown that the hippocampal volume is often reduced in depression. Impaired neurogenesis results in neuronal loss. Stockmeier (Stockmeier *et al.* 2004) suggests that reduced hippocampal volume in depressed patients is due to an increase in cell packing density.





The green structures are neurons

As many as 700 new neurons are added to the human hippocampus every day (Spalding *et al.* 2013). Alongside neurogenesis there is a substantial death of cells, resulting in the population of neurons remaining almost static. The slow rate of neurogenesis and the small number of new-born neurons (as many of these cells die after birth), raises a question whether such few neurons may at all be of relevance to the function of the human brain (Anacker 2014). Adult Hippocampal Neurogenesis has been implicated in the behavioural neurobiology of stress related disorders, especially anxiety and depression. The

causal relationship between AHN and the development of anxiety and depression remains controversial.

The loss of new neurons may alter the vulnerability to the effects of factors involved in the aetiology of depression. These neurons are involved in a vulnerability/resistance to depression rather than triggering a depressive episode, so new neurons may help to buffer the brain against stress (Snyder *et al.* 2011, Anacker *et al.* 2012). An impaired adult hippocampal neurogenesis confers vulnerability to depression (Bambico *et al.* 2013). It can be hypothesised that a robust AHN confers some resilience to depression.

Stress

Stress exerts a potent effect on neurogenesis (Gould *et al.* 1998). Stress increases cortisol blood levels. Unpredictable, non-controllable stress increases cortisol levels and reduces neurogenesis. Predictable controllable stress also increases glucocorticoids but increases neurogenesis. Cortisol has differential effects depending on which environmental stimulus precipitates its release. In some situations cortisol promotes neurogenesis, whilst in others it can reduce neurogenesis.

Chronic stress can cause a dysfunction of the hypothalamic-pituitary-adrenal axis feedback regulation. An increase in cortisol:

- Inhibits cell proliferation
- Reduces cell survival
- Reduces differentiation of new cells

Regulation of neurogenesis (Duman *et al.* 2001)

Down regulation of neurogenesis is caused by:

- Glucocorticoids- seen in stress and depression(Gould 1998)
- Inflammation
- Ageing

Upregulation of neurogenesis is seen in the presence of:

- Oestrogen
- Chronic antidepressant treatment
- Learning

- Environmental Enrichment
- Physical exercise
- Electroconvulsive therapy (ECT)

Depression

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and sense of well- being. Acute neurochemical changes can precipitate a depressive episode. Slower structural changes allow the depression to persist and increase the vulnerability to subsequent episodes.

Most studies to investigate the role of neurogenesis in stress and depression have been done using animal models. For ethical reasons it is not possible to design studies using human subjects. Ablation of adult hippocampal neurogenesis in rodents may be sufficient to potentiate depression and anxiety behaviours following a stressor (Thomson *et al.* 2008, Miller *et al.* 2015). Contradictory studies suggest this is not the case (Sahay *et al.* 2007, Levone *et al.* 2015) - reducing neurogenesis using x rays or cytotoxic drugs, does not induce depressive like behaviours per se(Santarelli *et al.* 2003, Bessa *et al.* 2009, David *et al.* 2009). The loss of new neurons may alter the vulnerability to the effects of factors involved in the aetiology of depression (Tanti *et al.* 2013). These neurons are involved in the vulnerability/resilience to depression rather than actually triggering a depressive response.

Santarelli (Santarelli *et al.* 2003) used a rodent model of depression where the depressive behavioural features were relieved using an antidepressant. AHN was then inhibited using localised x-ray irradiation. It was demonstrated that the antidepressant no longer worked- suggesting that particular antidepressant required a neurogenic dependent mechanism. Some antidepressants may have both neurogenesis-dependent and *in*dependent effects on mood and behaviour (David *et al.* 2009).

Some antidepressants can promote cell proliferation and generation of new neurons in the hippocampus. Malberg (Malberg *et al.* 2000) showed that chronic but not acute treatment with antidepressants increases neurogenesis. Antidepressants take several weeks to work- this is similar to the timeframe that it takes new born cells to become integrated functional neurons. Some

antidepressants do not stimulate neurogenesis suggesting that the reduction in adult hippocampal neurogenesis alone is unlikely to induce depression. Young adult-born neurons have been shown to inhibit the overall activity of the dentate gyrus of the hippocampus, by recruiting local interneurons and inhibiting the activity of the dense network of mature granule cells (Anacker *et al.* 2017).

There is now considered to be a "Neurogenic Theory of Depression". This theory offers new perspectives into the aetiology of anxiety and depression. The hypothesis that a reduction in adult hippocampal neurogenesis leads to depression is controversial (Petrik *et al.* 2012). Other conditions that increase AHN eg exercise, could also provide antidepressant effects. Neurogenesis may be particularly relevant for achieving sustained spontaneous remission from depressive symptoms (Anacker 2014).

New treatments

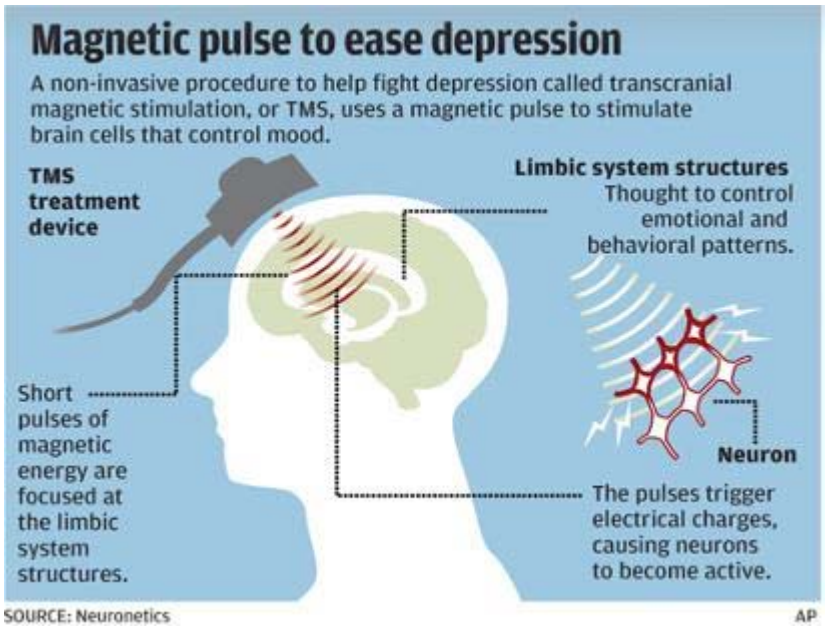
Drugs have been developed that target different stages of the HPA axis that culminates in the production of cortisol. Drugs that inhibit the synthesis of cortisol showed a resolution of depressive symptoms (Thomson *et al.* 2008). However these drugs are toxic, have a wide range of unpleasant side effects and are poorly tolerated. Drugs that block the glucocorticoid receptor have been developed, but again have a limited safety profile. Drugs that target the hormones Corticotropin Releasing Hormone and Adrenocorticotropic Hormone to block their production have been developed and these have been shown to prevent the reduction of neurogenesis in rodents. Their efficacy in humans has yet to be reported (Thomson *et al.* 2008).

Drugs that target the hypothalamic-pituitary-adrenal axis are an important part of future research to develop safe and effective treatments that overcome the negative effects of dysregulation of the HPA axis. Further trials to find drugs that target the HPA axis is exciting in improving the treatment of affective disorders.

Treatment Resistance

Current drug treatment fails in 20-30% of patients. These patients are termed "treatment resistant". They may however respond to electroconvulsive therapy (ECT). Electroconvulsive therapy (ECT) is a more potent stimulator of cell proliferation than antidepressant medication (Warner-Schmidt *et al.* 2006).

Another more recently developed treatment for resistant depression is Transcranial Magnetic Stimulation (TCMS). TCMS has an antidepressant effect in humans reversing the effects stress has on the hypothalamic-pituitary-adrenal axis. TCMS may or may not enhance adult hippocampal neurogenesis. The literature is contradictory. Some studies state it does not stimulate cell proliferation (Henn *et al.* 2004, Malberg 2004). Vaidya (Vaidya *et al.* 2007) states TCMS does not appear to enhance adult hippocampal neurogenesis. Ueyama (Ueyama *et al.* 2011) suggests that AHN may be required for the antidepressant effect of TCMS. Ultimately the mechanisms underlying TCMS are currently unknown as the literature is contradictory. If AHN is not involved- this questions the fact that neurogenic changes are necessary for the mood elevating effects of antidepressant treatment



Summary

- The hypothalamic-pituitary-adrenal (HPA) axis is a critical regulator of the stress response. There is a negative feedback loop which prevents the system becoming overactive.
- Chronic stress impairs the negative feedback loop leading to elevated levels of cortisol. Chronic stress is harmful. Some individuals are more

susceptible to the effects of stress than others. Resilient individuals do not develop stress related illnesses.

- Some depressed patients show a hyperactivity of the HPA axis resulting in increases in cortisol. Patients whose HPA axis remains abnormal after treatment for depression, are more likely to relapse than those patients whose HPA axis returns to normal.
- Hippocampal volume is often reduced in depression. This may be due to an increase in cell packing density.
- Adult Hippocampal Neurogenesis (AHN) is the continual generation of new brain cells in a particular brain area. Alongside neurogenesis there is a substantial loss of cells, resulting in the population of neurons remaining almost static.
- AHN has been implicated in anxiety and depression. The causal relationship between AHN and the development of anxiety and depression remains controversial.
- The loss of new neurons may alter the vulnerability to the effects of factors involved in the aetiology of depression. These neurons are involved in a vulnerability/resilience to depression rather than triggering a depressive episode, so new neurons may help to buffer the brain against stress.
- Antidepressants take several weeks to work. This is similar to the time frame it takes new born cells to become integrated functional neurons.
- Antidepressants that target the HPA axis are an important part of future research.
- Antidepressants may have neurogenesis dependent and independent effects on mood and behaviour. Some antidepressants promote neurogenesis whilst others do not. This suggests that AHN alone is unlikely to induce depression.
- Electroconvulsive therapy is a more potent stimulator of cell proliferation than antidepressant medication.
- Transcranial magnetic stimulation may or may not enhance AHN. The literature is contradictory.

The above information has summarised the attempts in the literature to link adult hippocampal neurogenesis to anxiety, stress and depression. The literature is contradictory in places. The search for novel drug treatments is an

exciting field in psychopharmacology. As treatment resistance is a well -known phenomena- the possibility of new drugs and other non- pharmacological treatments that perhaps enhance neurogenesis, is an exciting opportunity for scientists and clinicians to increase the range of treatment options available to manage psychiatric disorders.

REFERENCES

Anacker, C. (2014). "Adult hippocampal neurogenesis in depression: behavioral implications and regulation by the stress system." Curr Top Behav Neurosci **18**: 25-43.

Anacker, C. and R. Hen (2017). "Adult hippocampal neurogenesis and cognitive flexibility - linking memory and mood." Nat Rev Neurosci **18**(6): 335-346.

Anacker, C. and C. M. Pariante (2012). "Can adult neurogenesis buffer stress responses and depressive behaviour?" Mol Psychiatry **17**(1): 9-10.

Bambico, F. R. and C. Belzung (2013). "Novel insights into depression and antidepressants: a synergy between synaptogenesis and neurogenesis?" Curr Top Behav Neurosci **15**: 243-291.

Bessa, J. M., D. Ferreira, I. Melo, F. Marques, J. J. Cerqueira, J. A. Palha, O. F. Almeida and N. Sousa (2009). "The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling." Mol Psychiatry **14**(8): 764-773, 739.

David, D. J., B. A. Samuels, Q. Rainer, J. W. Wang, D. Marsteller, I. Mendez, M. Drew, D. A. Craig, B. P. Guiard, J. P. Guilloux, R. P. Artymyshyn, A. M. Gardier, C. Gerald, I. A. Antonijevic, E. D. Leonardo and R. Hen (2009). "Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression." Neuron **62**(4): 479-493.

Duman, R. S., J. Malberg and S. Nakagawa (2001). "Regulation of adult neurogenesis by psychotropic drugs and stress." J Pharmacol Exp Ther **299**(2): 401-407.

Ebner, K. and S. Singewald (2017). "Individual differences in stress susceptibility and stress inhibitory mechanisms." Current Opinion in Behavioral Sciences **14**: 54-64.

Gould, E., P. Tanapat, B. S. McEwen, G. Flugge and E. Fuchs (1998). "Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress." Proc Natl Acad Sci U S A **95**(6): 3168-3171.

Henn, F. A. and B. Vollmayr (2004). "Neurogenesis and depression: etiology or epiphenomenon?" Biol Psychiatry **56**(3): 146-150.

Levone, B. R., J. F. Cryan and O. F. O'Leary (2015). "Role of adult hippocampal neurogenesis in stress resilience." Neurobiol Stress **1**: 147-155.

Malberg, J. E. (2004). "Implications of adult hippocampal neurogenesis in antidepressant action." J Psychiatry Neurosci **29**(3): 196-205.

Malberg, J. E., A. J. Eisch, E. J. Nestler and R. S. Duman (2000). "Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus." J Neurosci **20**(24): 9104-9110.

Miller, B. R. and R. Hen (2015). "The current state of the neurogenic theory of depression and anxiety." Curr Opin Neurobiol **30**: 51-58.

Petrik, D., D. C. Lagace and A. J. Eisch (2012). "The neurogenesis hypothesis of affective and anxiety disorders: are we mistaking the scaffolding for the building?" Neuropharmacology **62**(1): 21-34.

Pierscionek, T., O. Adekunte, S. Watson, I. N. Ferrier and A. Alabi (2014). "Role of corticosteroids in the antidepressant response." ChronoPhysiology and Therapy **4**: 87-98.

Sahay, A. and R. Hen (2007). "Adult hippocampal neurogenesis in depression." Nat Neurosci **10**(9): 1110-1115.

Santarelli, L., M. Saxe, C. Gross, A. Surget, F. Battaglia, S. Dulawa, N. Weisstaub, J. Lee, R. Duman, O. Arancio, C. Belzung and R. Hen (2003). "Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants." Science **301**(5634): 805-809.
Snyder, J. S., A. Soumier, M. Brewer, J. Pickel and H. A. Cameron (2011). "Adult hippocampal neurogenesis buffers stress responses and depressive behaviour." Nature **476**(7361): 458-461.
Southwick, S. M., M. Vythilingam and D. S. Charney (2005). "The psychobiology of depression and resilience to stress: implications for prevention and treatment." Annu Rev Clin Psychol **1**: 255-291.
Spalding, K. L., O. Bergmann, K. Alkass, S. Bernard, M. Salehpour, H. B. Huttner, E. Bostrom, I. Westerlund, C. Vial, B. A. Buchholz, G. Possnert, D. C. Mash, H. Druid and J. Frisen (2013). "Dynamics of hippocampal neurogenesis in adult humans." Cell **153**(6): 1219-1227.
Stockmeier, C. A., G. J. Mahajan, L. C. Konick, J. C. Overholser, G. J. Jurjus, H. Y. Meltzer, H. B. Uylings, L. Friedman and G. Rajkowska (2004). "Cellular changes in the postmortem hippocampus in major depression." Biol Psychiatry **56**(9): 640-650.
Tanti, A. and C. Belzung (2013). "Hippocampal neurogenesis: a biomarker for depression or antidepressant effects? Methodological considerations and perspectives for future research." Cell Tissue Res **354**(1): 203-219.
Thomson, F. and M. Craighead (2008). "Innovative approaches for the treatment of depression: targeting the HPA axis." Neurochem Res **33**(4): 691-707.
Ueyama, E., S. Ukai, A. Ogawa, M. Yamamoto, S. Kawaguchi, R. Ishii and K. Shinosaki (2011). "Chronic repetitive transcranial magnetic stimulation increases hippocampal neurogenesis in rats." Psychiatry Clin Neurosci **65**(1): 77-81.
Vaidya, V. A., K. Fernandes and S. Jha (2007). "Regulation of adult hippocampal neurogenesis: relevance to depression." Expert Rev Neurother **7**(7): 853-864.
Warner-Schmidt, J. L. and R. S. Duman (2006). "Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment." Hippocampus **16**(3): 239-249.