The Bidirectional Relationship Between Neurogenesis and Depression

Nadia Matveeva

Department of English, University of Washington

English 299A: Intermediate Interdisciplinary Writing - Natural Sciences

Prof. Christina Ma

November 21, 2022

Abstract

The intersection between neurogenesis and depression have recently become a popular topic in the neuroscience community. Current research suggests that there is a bi-directional relationship between the two. Depression is proven to decrease the volume of the hippocampus, and research suggests that this is because of slowed neurogenesis. During depression, gene expression that regulates neurogenesis is disrupted as the brain activates an inflammatory-immune response. Furthermore, studies suggest that decreased neurogenesis can cause depression, and investigations into antidepressants have found that they often upregulate neurogenesis or downregulate the immune response in the brain. The fields of neuroscience and psychology have focused on these two relationships. It is so far unknown which side of the relationship is more dominant, but current research is valuable to designing further treatment for depression.

The Bidirectional Relationship Between Neurogenesis and Depression

Neurogenesis and depression work together in a cyclic pathway. Neurogenesis is the process of proliferating, maturing, and integrating new neural cells in the brain. It occurs in and around the hippocampus, so this area is an important focal point for research on the topic (Flores et al., 2022). As stress hormones flood into the hippocampus, an immune response is mounted, depressive symptoms increase, and the effects compound on each other to exacerbate depressive symptoms (Beurel et al., 2022; Ruiz et al., 2016; Tang et al., 2016). Here I will describe the two sides of this relationship and other research that has further broadened knowledge of this topic. Examining comorbidities and observing how commercial antidepressants act on the brain has been incredibly important for designing new treatment plans for depression, and findings originating from research on depression often circle back to neurogenesis. In sum, the relationship between depression and neurogenesis is intricate. The brain is still yet to be fully understood, so research on neurological conditions often carries contradictions, and there is a high turnover rate. The potential within neuroscience to help people with depression is immense, and we are just beginning to understand when and how neurogenesis plays a role.

The Hippocampus

The hippocampus is a small area of the brain buried deep in the temporal lobe that is responsible for encoding spatio-temporal memories and managing stress. For instance, a mouse may employ its hippocampus to navigate a maze, or may parse through time to recall where a researcher buried a cube of cheese (Knierim, 2015). Memories are further categorized into semantic or episodic. Semantic memories are facts (“I like cheese”), while episodic memories narrate our day-to-day lives (“They buried the cheese in the corner 5 minutes ago”). During memory tasks, the hippocampus communicates with other parts of the brain: the few of interest

to this paper are the hypothalamic-pituitary-adrenal axis, responsible for regulating stress, and the subgranular zone of the dentate gyrus, where most neural cell proliferation occurs. The hypothalamic-pituitary-adrenal axis (HPA axis) is especially significant in studies on depression (Planchez et al., 2020), as it modulates hormones called glucocorticoids (GCs) (Planchez et al., 2020; Ruiz et al., 2018). GCs activate during depressive episodes, and the HPA axis attempts to regulate GCs so that we can make a proper response to the stressor. The hippocampus allows us to organize our memories, and thereby our world, by both location and time.

Depression

8% of the U.S. population suffers from Major Depressive Disorder (Beurel et al., 2020). Some key symptoms of depression include anhedonia, depressed mood, and suicidal ideation. Despite this disorder being one of the top 10 causes of suicide in the U.S., only 28%-50% of patients recover from depression (Jin et al., 2016). Depression is multifaceted and hard to treat, often comborid and exacerbating conditions such as cancer, diabetes, and renal diseases (Beurel et al., 2020). This paper is chiefly motivated by the neurogenesis-depression hypothesis, but the depression-inflammation schema is also important for understanding brain activity during depressive episodes. Researchers have found that the brain combats depression similarly to an immune response: it directs resources toward immune cells and inflammation rather than homeostasis activities (Ruiz et al., 2016). Homeostasis covers basic activities that humans need to survive like waste management and temperature control, but for this paper's purposes, homeostasis is equivalent to cell cycle regulation. Both hypotheses appear to overlap; regardless of whether the brain is inflamed due to immune response or stress, neurogenesis will decrease and depression will increase. This can happen alongside autoimmune diseases, which implicates

the aggravating of other diseases as mentioned in Beurel et al. (2020). As a result, depression research is necessary to improve the quality of life for all populations.

Neurogenesis

Neurogenesis is the proliferating, maturing, and integrating of new cells into the brain. Research has found that this occurs in the olfactory bulb and hippocampus (Knierim, 2015). Due to these findings, researchers hypothesize that neural proliferation may be related to creating new sense memories and processing stress (Fang et al., 2018). Neurogenesis is also associated with depression; studies have repeatedly found that the hippocampus shrinks in volume in patients with depression (Chen et al., 2019; Fan et al., 2022; Planchez et al., 2020). Many different components regulate cell growth, including gene expression, and depression interferes with these systems. Human research on neurogenesis is complex and underdeveloped, but mouse models and computational analysis have allowed us to examine the links between depression and neurogenesis.

Pathways Between Neurogenesis and Depression

Neurogenesis and depression are intrinsically linked. So far, it is unclear which component of this relationship is dominant, but the link between the two is evident. The risk for depression is thus multifaceted, causing symptoms to compound because of its relationship to neurogenesis.

Depression Leads to a Decrease in Neurogenesis

When depressed, neurogenesis events decrease in frequency. Inducing depression in rat models and subsequently tracking brain volume is one way to observe neurogenesis. Ruiz et al. (2018) found that after experiencing early life stress through maternal separation, rats exhibited depressive behaviors, which led to a decrease in neural tissue development. The cohort

experienced increased immobility and latency to move in the forced swimming test, a reliable way to identify depression in rats. Furthermore, the cell volume in the dorsal hippocampus decreased, which is preliminary evidence for a decrease in neurogenesis. Stressed mice also experienced an increase in activity in the hypothalamic-pituitary-adrenal axis (HPA), which is regulated by the hippocampus. The HPA-hippocampus interaction serves to mediate the impacts of stressors (Planchez et al., 2020). Glucocorticoids (GCs) are activated when stress occurs, which are controlled by the HPA axis. GCs are stress hormones that motivate our "fight or flight" response (Beurel et al., 2020), and they cause a reallocation of resources away from neurogenesis as the brain tries to cope with a stressful situation (Planchez et al., 2020). An elevation of basal GC levels can increase the risk for depression and anxiety, making the survival of newborn neurons less likely (Ruiz et al., 2016). Hence, we can observe that stress and depression cause hormone fluctuations, which affect the proliferation of new cells.

Furthermore, the hippocampus plays a role in forming and storing episodic memories and proliferating new cells, so exploration of the depressed phenotype and its effect on memory can also help us predict neurogenic function. Fang et al. (2018) predict major depressive disorder (MDD) “has a retrograde effect on episodic memory”, indicating that MDD damages the hippocampus to the extent that old episodic memories become harder to access. Memories stored within the depressive state are impaired, as are earlier memories before the onset of depression. Impaired retrieval may correlate with hippocampal damage or loss of function. People with MDD have also been found to focus more on semantic memory rather than episodic. Fang et al. (2018) hypothesize that this is not simply because retrieving episodic memories is emotionally painful but also that depression causes a deficit in episodic memory. Neurons proliferate chiefly in a region of the hippocampus referred to as the subgranular zone (Ruiz et al., 2018), and Fang

et al. (2018) suggests that the excitable state of the new neurons is important for pattern separation, a function that allows your hippocampus to form episodic memories. Thus, studies on memory further evidence the relationship between neurogenesis and depression.

Research also suggests that new neurons may attenuate stress (Schoenfeld et al., 2017); the same excitability that may help us store memories could potentially be important for regulating stress. Cells become active when they experience an electrochemical gradient, which is the passage of charged molecules across their membrane. This causes a charge to occur inside the cell, which can create energy for division and other cell activity. New neurons have lower membrane resistance, allowing molecules to pass through more often, and thus can experience electrochemical gradients at greater rates. This creates excitability, which can prime synapse connections between neurons, thus helping in creating memories (Planchez et al., 2020) and staving off stress and depression. Thus, a decrease in neurogenesis due to depression would impair the stress response and decrease likelihood of remission. The depression-inflammation hypothesis further supports this claim. If depression acts like an immune response (Beurel et al., 2020), then the excitability of brain structures due to neurogenesis could mean faster healing of that area. Neurogenesis is instrumental for creating new, excitable neurons that help us cope with routine stress.

Decreased Neurogenesis Leads to Depression

A decrease in neurogenesis is often followed by depression. Neurogenesis is most often modified by inducing neuroinflammation, a way to impair and destroy neurons using a toxin. Neuroinflammatory drugs are often used for this task, as depression is hypothesized to be a form of inflammation. The brain responds to neuroinflammation the same way it does in other parts of the body: by directing resources away from normal activity and toward repair (Beurel et al.,

2020). When Zhang et al. (2020) primed parts of the brain that maintain homeostasis with interferon-gamma, a neuroinflammatory agent, mice exhibited depressive behavior. This included hiding behavior, cognitive changes, immobility, and anhedonia. Mice also had decreased neuron density in the prefrontal cortex and hippocampus. Overall, neuroinflammation caused decreased neurogenesis, which primed depressive symptoms. Tang et al. (2016) used lipopolysaccharide infusions to inhibit neurogenesis and produced similar results. The authors also observed lowered cell proliferation and newborn cell survival and decreased sucrose preference similar to Zhang et al. (2020). They were also able to link depressive behavior and neurogenesis directly, and found that the "core and characteristic symptoms of depression" were correlated with decreased neurogenesis. Depressive symptoms also occur in an inflamed state (Tang et al., 2016). As the immune cells (cytokines) respond to neuroinflammation, the newborn neurons are unable to thrive, and depression symptoms become apparent. Furthermore, blocking neuroinflammatory pathways post-inflammation causes a notable decrease in depressive symptoms (Zhang et al., 2020). By inducing neuroinflammation, we can observe that decreased neurogenesis causes depression.

Gene Expression

Findings on structures that modulate gene expression have further compounded the results previously described. MicroRNAs downregulate gene expression by destroying proteins (products of gene expression) and transcription factors (signals to stop and start gene expression). When researchers modified the miR-17-92 cluster in mice, they observed altered adult neurogenesis, elevated anxiety, and depressive behaviors (Jin et al., 2016). This microRNA directly targets neurogenesis-related genes, maintaining proliferative neural progenitors. Specifically, it regulates the glucocorticoid pathways, as well as neural stem cells. When

downregulated, the glucocorticoid pathway becomes overactive and the stress response is heightened. This exacerbates depression. Related to signaling pathways between cells and neural development is another microRNA: miR-146a-5p (Fan et al., 2022). Its functionality supports the immune-inflammation depression hypothesis; it interacts with the STAT-TH17 pathway, a set of transcription factors that agitate an immune response. During an immune response, resources are drawn away from cell cycle regulation. Thus, when mice experienced unpredictable, chronic stress, these microRNAs increased immune response and downregulated neurogenesis, accelerating the depressive phenotype (Fan et al., 2022). A different transcription factor, unrelated to the aforementioned miRNAs, is PPARdelta. Its main functions pertain to lipid and glucose homeostasis, inflammation, proliferation, and cell differentiation (Chen et al., 2019). Chen et al. (2019) found that antidepressant effects are evident when PPARdelta is overexpressed, but when knocked out by immune response, researchers observed the depressive phenotype. Neurogenesis was also slowed. PPARdelta allows for phosphorylation in DNA to occur, and this signals cell regrowth to begin. Consequently, increasing its expression will increase neurogenesis, which decreases depressive symptoms. Stress, however, downregulates the expression of PPARdelta (Chen et al., 2019), thus leading to depression. As microRNAs interact with transcription factors, the immune response to depression is modulated, causing changes to neurogenesis.

Treatment

Current treatments for depression further support the link between neurogenesis and depression. Neuromodulation is used to combat depression, and it works through increasing neurogenesis. Observing changes in the brain post-antidepressant administration is one of the most effective ways to track the bidirectional relationship between neurogenesis and depression.

Neuromodulation can be either invasive or noninvasive. One prevalent noninvasive way to neuro-modulate is by prescribing antidepressants, specifically, selective serotonin reuptake inhibitors (SSRIs) (Flores et al. 2022). Antidepressants upregulate hippocampal cell proliferation, differentiation, and maturation which may lead to changes in the depressive phenotype (Flores et al., 2022).

Exercise and other enriching activities can also help combat stress levels and thus allow for greater hippocampal control and increased neurogenesis as glucocorticoid (GC) levels decrease (Planchez et al., 2020). Stress causes nerve atrophy through the excessive release of GCs, which act as a poison to brain structures in large amounts, impeding it from doing typical behaviors such as division. As such, decreasing GC release has a positive effect on neurogenesis. For example, in mouse models, physical activity and enrichment were shown to treat depression (Yuan et al., 2015). Exercise activates serotonin receptors, which regulate neurogenesis and GC pathways. This shows that exercise combats reduction of cell proliferation (Yuan et al., 2015). Furthermore, miRNAs modulate serotonin receptors (Jin et al., 2016), so depression treatment may also upregulate the transcription factors and miRNA genes necessary for maintaining neurogenic homeostasis. Other more invasive methods of neuromodulation include deep brain stimulation, transcranial magnetic stimulation, and electroconvulsive therapy (Flores et al., 2022; Planchez et al., 2020). Flores et al. found that stimulating circuitries with invasive methods has an effect on the proliferation and differentiation of neural cells. These treatments are observed to positively affect depressed patients, so it is safe to assume that neurogenesis and depression are correlated in treatment. Computational models further evidence this, as Fang et al. (2018) found that better pattern separation, typically attributed to the hippocampus, also leads to less severe depression. Pattern separation is how the hippocampus creates unique memories for similar

experiences (Knierim, 2015). Taken together, the bidirectional relationship between neurogenesis and depression, and therapies targeting the hippocampus seem to suggest that there is a relationship to neurogenesis.

There has also been some research done on the link between autoimmune drugs and treating depression. It is known that autoimmune diseases have "some of the highest rates of comorbid depression" (Beurel et al., 2020). Beurel et al. (2020) postulate that cytokine (immune cell) expression, namely Th17, is correlated with depression in autoimmune diseases. These cells are leaders of immune response and hyperactivity throughout the body, making it likely that they are responsible for immune system hyperactivity in the brain too. Mounting a constant immune response draws resources away from other homeostasis activities like cell division. Consequently, targeting immune pathways decreases the depressive phenotype. This harks back to the research of Zhang et al. (2020), as the neuroinflammatory agent they used, IFN-gamma, activates an immune response in the very same cytokines. Furthermore, Beurel et al. (2020) also found that anti-diabetic drugs downregulate the PPARdelta transcription factor explored by Chen et al. (2019), creating depressive symptoms. This again supports the hypothesis that there is a link between inflammation and depression. PPARdelta is hinted to regulate neurogenesis, so it is consistent that targeting PPARdelta decreases neurogenesis and thus leads to a susceptibility for depression. MiRNAs have been used for neurological treatment in the past, indicating that there is a potential for using transcription factors and miRNAs to treat depression too.

Conveniently, some antidepressants also work in anti-inflammatory pathways. Further, autoimmune drugs are found to decrease comorbid depression symptoms (Beurel et al., 2020), and even talk therapy can activate anti-inflammatory pathways. Taking into consideration what we know about neurogenesis and depression, and how neuroinflammation does correlate with

some cytokines, we know that all three factors are related. In the future, more work should be done on utilizing anti-inflammatory action to treatment for depressive persons.

Discussion

The research on depression and neurogenesis overlaps and interacts. As inflammation causes depression, neurogenesis declines and reciprocally affects depression. Areas like the hippocampus, dentate gyrus, and hypothalamic-pituitary gland are centers of activity for these various brain functions, and thus research on one often leads to findings on another.

There are many different facets to this research. This paper first demonstrated that hippocampal volume decreases in depression (Chen et al., 2019; Fan et al., 2022; Planchez et al., 2020). Later research determined that there are links between inducing or inhibiting neurogenesis and depression within the hippocampus (Planchez et al., 2020; Ruiz et al., 2016, Zhang et al., 2020). By looking at gene expression, we can further elucidate how cell communication may be involved in neurogenesis. MiRNAs and transcription factors determine how and where cells are made, so they are relevant in understanding depression. When certain miRNAs are antagonized, neurogenesis can decrease or increase, which demonstrates that depression may also impact the expression of immune responses. Mir-146-5p takes care of inflammation, while miR-17-2 regulates glucocorticoid levels - both factors that exacerbate depression (Fan et al., 2022; Jin et al., 2016). Finally, observing the effects of medications shows us how recovery impacts neurogenesis. For example, it has been found that some autoimmune medications can have a positive effect on depression, supporting the neuroinflammatory depression hypothesis (Beurel et al., 2020).

However, research on depression still has notable limitations. Most research is done on male mice and rats, overwhelmingly so. Researchers must stop excluding female subjects from

research, as this population is disproportionately affected by depression (Jin et al., 2016). Looking for sex differences causes researchers to find sex differences because of confirmation bias, something that exacerbates ill-treatment of women in medical situations. Women are diagnosed less, and experience more adverse experiences with treatment simply because they are excluded (Fader et al., (ed), 1999). Making efforts to work with women rather than around them could make medical situations and research more approachable for women. Furthermore, treatment studies need to be revisited. Some studies on medication lacked support or were outdated and uninformed of the new findings on neurogenesis. Autoimmune medication should be explored further, as the connection between autoimmune disorders and depression indicates that treatments could overlap. Finally, steps towards human studies need to be made, especially with studies that control for neurotypicality and neurodivergence. Human studies of this nature are sensitive, so computational modeling may be a better option, but regardless, more demographics need to be explored. As with the case of women, researchers shy away from including neurodivergent populations because they are pathologized. Researchers are beginning to advocate for viewing disability as a product of our societies limitations; though neurodivergent people may have impairments in their mind or biology, it is only seen as a problem because society imposes restrictions upon them (Dwyer, 2022). Shifting toward a social model of disability would make it easier to work with and understand. More needs to be done to include these demographics in depression research, as continuing to ignore them is injustice and discrimination toward a large portion of our population.

Conclusion

Depression and neurogenesis are intrinsically linked; depression causes decreased neurogenesis, and neurogenesis can reduce depression. Researchers have observed this through

many different methods and have found that stress and depression impact the brain in ways that cause lowered neurogenesis. As glucocorticoids are activated, the HPA axis deregulates, and neurogenesis lessens, shortly followed by depression (Beurel et al., 2020). Antidepressants and anti-inflammatory medication bring these systems back under control and aid in remission. However, recovery is still uncommon, only observed in 28-50% of patients. More research needs to be done on the cyclic pathways of neurogenesis and depression to improve the quality of life of our most vulnerable populations.

Works Cited

Beurel, E., Toups, M., & Nemeroff, C. B. (2020). The bidirectional relationship of depression and inflammation: Double trouble. *Neuron*, *107*(2), 234–256. https://doi.org/10.1016/j.neuron.2020.06.002

Chen, F., Yu, X., Meng, G., Mei, Z., Du, Y., Sun, H., Reed, M. N., Kong, L., Suppiramaniam, V., Hong, H., & Tang, S. (2019). Hippocampal genetic knockdown of pparδ causes depression-like behaviors and neurogenesis suppression. *International Journal of Neuropsychopharmacology*, *22*(6), 372–382. https://doi.org/10.1093/ijnp/pyz008

Dwyer, P. (2022). The neurodiversity approach(es): What are they and what do they mean for researchers? Human Development, 66(2), 73–92. https://doi.org/10.1159/000523723

Faden, R., Federman, D., Mastroianni., AC. (Eds.). (1999). *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies (Vol #2).* National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK236583/

Fan, C., Li, Y., Lan, T., Wang, W., Long, Y., & Yu, S. Y. (2022). Microglia secrete mir-146a-5p-containing exosomes to regulate neurogenesis in depression. *Molecular Therapy*, *30*(3), 1300–1314. https://doi.org/10.1016/j.ymthe.2021.11.006

Fang, J., Demic, S., & Cheng, S. (2018). The reduction of adult neurogenesis in depression impairs the retrieval of new as well as remote episodic memory. *PLOS ONE*, *13*(6). https://doi.org/10.1371/journal.pone.0198406

Flores, A. D., Yu, W. S., Fung, M.-L., & Lim, L. W. (2022). Neuromodulation and hippocampal neurogenesis in depression: A scoping review. Brain Research Bulletin, 188, 92–107. https://doi.org/10.1016/j.brainresbull.2022.07.009

Kim, I. B., & Park, S.-C. (2021). The entorhinal cortex and adult neurogenesis in major depression. *International Journal of Molecular Sciences*, *22*(21), 11725. https://doi.org/10.3390/ijms222111725

Jin, J., Kim, S.-N., Liu, X., Zhang, H., Zhang, C., Seo, J.-S., Kim, Y., & Sun, T. (2016). MIR-17-92 cluster regulates adult hippocampal neurogenesis, anxiety, and depression. *Cell Reports*, *16*(6), 1653–1663. https://doi.org/10.1016/j.celrep.2016.06.101

Harris, E. P., McGovern, A. J., Melo, T. G., Barron, A., Nolan, Y. M., & O'Leary, O. F. (2022). Juvenile stress exerts sex-independent effects on anxiety, antidepressant-like behaviours and dopaminergic innervation of the prelimbic cortex in adulthood and does not alter hippocampal neurogenesis. *Behavioural Brain Research*, *421*, 113725. https://doi.org/10.1016/j.bbr.2021.113725

Knierim, J. J. (2015). The hippocampus. *Current Biology*, *25*(23). https://doi.org/10.1016/j.cub.2015.10.049

Larivee, R., Johnson, N., Freedgood, N. R., Cameron, H. A., & Schoenfeld, T. J. (2022). Inhibition of hippocampal neurogenesis starting in adolescence increases anxio depressive behaviors amid stress. *Frontiers in Behavioral Neuroscience*, *16*. https://doi.org/10.3389/fnbeh.2022.940125

Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., & Cui, R. (2017). The role of neural plasticity in depression: From hippocampus to prefrontal cortex. *Neural Plasticity*, *2017*, 1–11. https://doi.org/10.1155/2017/6871089

Planchez, B., Surget, A., & Belzung, C. (2020). Adult hippocampal neurogenesis and antidepressants effects. *Current Opinion in Pharmacology*, *50*, 88–95. https://doi.org/10.1016/j.coph.2019.11.009

Ruiz, R., Roque, A., Pineda, E., Licona-Limón, P., José Valdéz-Alarcón, J., & Lajud, N. (2018). Early life stress accelerates age-induced effects on neurogenesis, depression, and metabolic risk. *Psychoneuroendocrinology*, *96*, 203–211. https://doi.org/10.1016/j.psyneuen.2018.07.012

Tang, M.-ming, Lin, W.-juan, Pan, Y.-qin, Guan, X.-ting, & Li, Y.-cong. (2016). Hippocampal neurogenesis dysfunction linked to depressive-like behaviors in a neuroinflammation induced model of depression. *Physiology & Behavior*, *161*, 166–173. https://doi.org/10.1016/j.physbeh.2016.04.034

Schoenfeld, T. J., McCausland, H. C., Morris, H. D., Padmanaban, V., & Cameron, H. A. (2017). Stress and loss of adult neurogenesis differentially reduce hippocampal volume. *Biological Psychiatry*, *82*(12), 914–923. https://doi.org/10.1016/j.biopsych.2017.05.013

Yuan, T.-F., Paes, F., Arias-Carrión, O., Ferreira Rocha, N., de Sá Filho, A., & Machado, S. (2015). Neural mechanisms of exercise: Anti-depression, neurogenesis, and serotonin signaling. *CNS & Neurological Disorders - Drug Targets*, *14*(10), 1307–1311. https://doi.org/10.2174/1871527315666151111124402

Zhang, J., He, H., Qiao, Y., Zhou, T., He, H., Yi, S., Zhang, L., Mo, L., Li, Y., Jiang, W., & You, Z. (2020). Priming of microglia with ifn‐γ impairs adult hippocampal neurogenesis and leads to depression‐like behaviors and cognitive defects. *Glia*, *68*(12), 2674–2692. https://doi.org/10.1002/glia.23878