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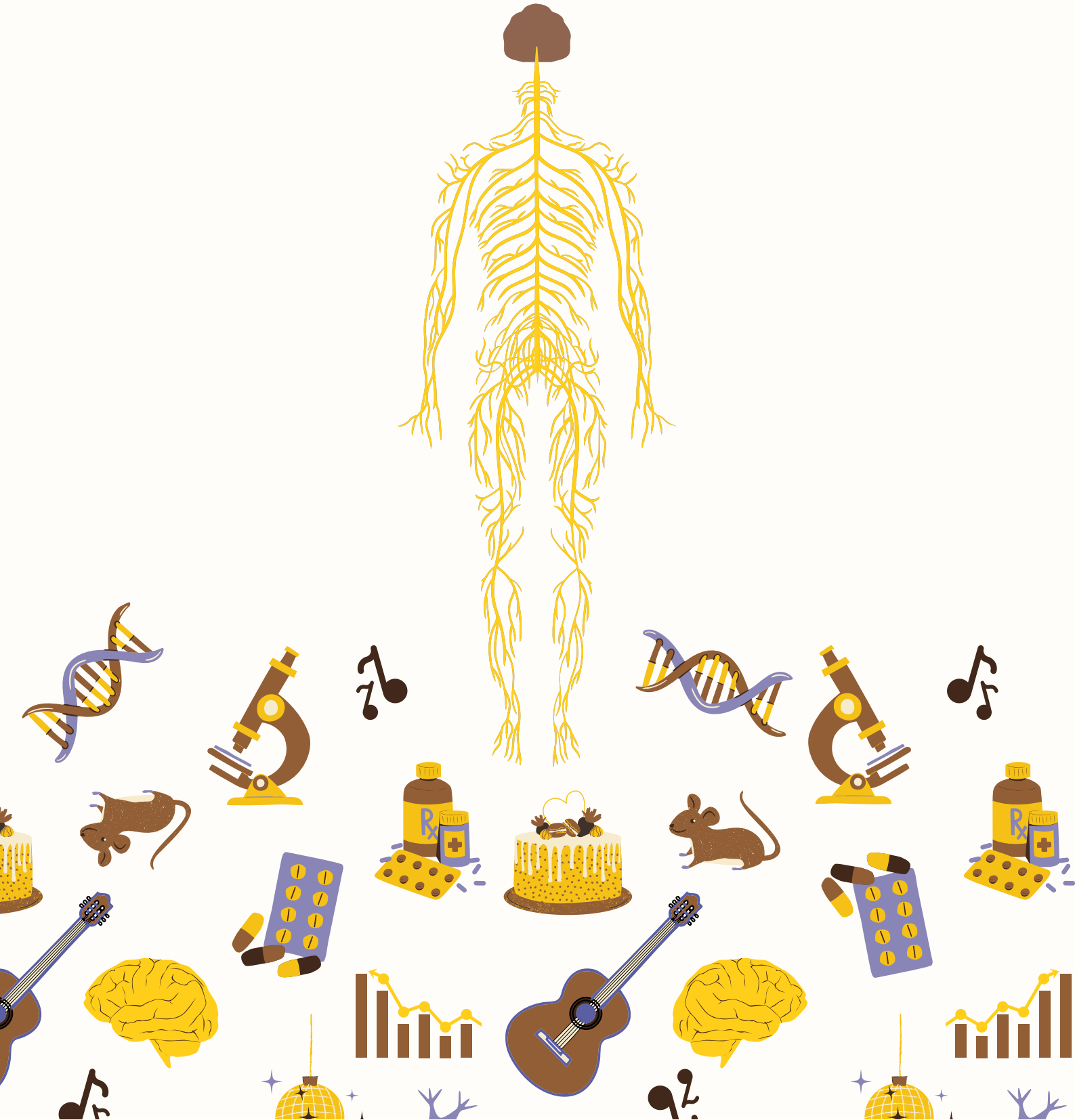
# NEUROSOC

## MAGAZINE



**Welcome to the third issue of the UCL Neuroscience Magazine! Our final issue of the year! It has been a delight to see the magazine grow this year. Many more people have taken part and this helps our magazine be a truly collaborative, inclusive, and diverse piece of work.**

Last issue I talked about the importance of making science accessible. With the growth of the magazine, I have thought that alongside science being accessible, it must also be inclusive. In a lecture I attended this year, a Professor discussed a clinical trial he had been part of which examined the effect of inositol in reducing the risk of neural tube defects in pregnant women that had previously suffered miscarriages as a result of neural tube defects. The trial was designed to randomise the pregnant women to receive inositol and folate, or a placebo and folate. There is strong evidence for folic acid promoting the healthy development of the neural tube; reducing the risk of defects. Many of the patients in this trial did not want to be randomised. They did not want to take inositol because they did not know what the effects would be. The team of all male researchers could not understand why this was – why would these women not want to try a new, potentially life-saving treatment? To me, it was obvious. Those women had gone through the trauma of miscarriages and did not want to take anything unknown in case it caused them to experience the same trauma again. When the male researchers finally consulted the women, that was the exact answer they were given. This taught me one very important lesson – when designing medical research, one must consult the stakeholders of that research. A substantial proportion of studies are predominately conducted by and enrol white men. It is unfair to apply the outcome of such research to the general population. If the findings of clinical trials are to be applied to a broad demographic, then the experimental design must include and consult an equally diverse demographic.

Of course, much fantastic and exciting research is being done in the field of neuroscience, and we also celebrate that. There are many discoveries being made all of the time, and I hope that the Neuroscience Magazine can be a gateway for people to learn something, or be introduced to a new subfield. After all, the aim of this work is to educate and engage. Ideally the Neuroscience Magazine serves as a steppingstone to people finding out more about the research being done in the beautifully interdisciplinary world of neuroscience.

Again, I would like to thank everyone who has contributed any amount of their time to this magazine. It would not have been possible without the combined work of everyone involved. This is the last issue of the magazine I will be apart of, and it has been a pleasure to be part of this fun and educational project since its inception nearly two years ago.

Thank you.

**Alice Wright**
*Chief Editor*
*UCL Neuroscience Society*

# Contents

**Written by Yuhan Bai** **Edited by Laura Rizzo**

# Blindness and the Brain

**Before you start reading this article, I would like you to do a quick visual experiment with me: pay attention to your peripheral visual field – your visual field that extends beyond the centre of your gaze – but fix your gaze at the centre of the screen. This will involve turning your head away. Can you still see the words of this article? Can you still read and understand them?**

This experiment introduces the concept of central and peripheral vision. If neurotypical, you will be able to see that there are words in your peripheral visual field, but you may not be able to read or understand them. In contrast to the words in our central visual field, words in the peripheral visual field are subject to the crowding effect whereby they overlap each other. This can make the words difficult to comprehend. The crowding effect in peripheral vision is particularly noticeable in text-based reading, but it can also manifest in anything involving visual perception. Fortunately, most of us are blessed with a healthy brain can overcome this effect – all we have to do is to change our gaze fixation, and shift our central vision to wherever we want the fine details. However, when the brain is no longer healthy, everything it perceives can look like information in a peripheral visual field – overlapping and impossible to comprehend. In this article, I would like to introduce to you a rare neurodegenerative condition: posterior cortical atrophy (PCA).

The pathological underpinning of PCA has been found to be related to Alzheimer's disease. Although it has been recognised that Alzheimer's disease typically leads to temporal lobe atrophy and memory impairments, increasing evidence suggests that Alzheimer's symptomology actually presents on a spectrum. This means that Alzheimer's disease can lead to initial decay starting from other cortical areas, such as the occipital and parietal lobes – shrinkage in these regions may lead to visual perception difficulties. Patients with PCA usually go to their GP and present with problems in reading or driving. Often they get referred to opticians, rather than neurologists, and go through optical tests just to find out that their symptoms are unexplainable; essentially there are no issues at the level of the eye (e.g., retina, optic nerve etc.). Patients will still experience visual perception difficulties, and they might even be thought to be 'mad'. This can lead to considerable amounts of mental distress and confusion. Sadly, most often patients are unable to get an informative diagnosis until they experience moderate to severe cognitive impairments, meaning that the degeneration is already widespread and profound.

To our relief, PCA has been getting increasing recognition this decade. Due to the awareness that patients with PCA experience brain blindness (e.g., visual crowding), neuropsychologists have made some attempts to design aids to help. For example, reading aids can increase the space between letters and help patients with text-based learning - increasing spaces between letters can reduce the effect of visual crowding.

Patients with PCA also often struggle with tasks that involve visual search. So, some environmental adaptations have been developed to aid everyday activities for patients who struggle to find the objects they want or need. For example, in one patient's house, a cabinet was made more distinguishable (e.g., using different colour contrast to imply different object placements such as an area painted blue for putting keys) to help the patient to find objects.

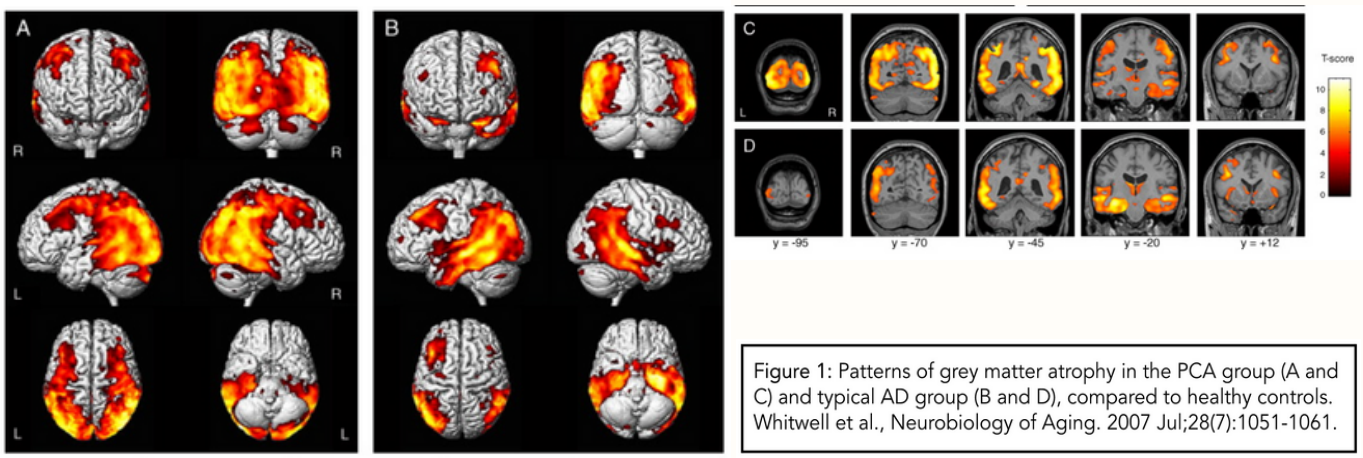



Figure 1: Patterns of grey matter atrophy in the PCA group (A and C) and typical AD group (B and D), compared to healthy controls. Whitwell et al., Neurobiology of Aging. 2007 Jul;28(7):1051-1061.

Meanwhile, endeavours in understanding the condition never stop. Although it has been recognised that patients with PCA experience problems predominantly in visual perception, their profound difficulties in action suggest that the story might not be this simple. Patients with PCA often struggle in reaching for objects, walking and sitting themselves down on chairs, and those are what most dramatically impair day to day functioning. Vision does play a crucial role in these tasks – a vision deficit will indeed contribute to movement problems – but smooth movements are achieved by successful multi-sensory perceptual integration. We don't know whether other perceptual domains are impaired in PCA because there have simply been little investigations into this. A couple of years ago, some researchers were examining verticality perception in PCA and discovered something unexpected. In one experiment, patients experience bias in perceiving vertical lines - when observing a vertical object they perceive it to be tilted at a different angle. This is an expected result as patients with PCA have deficits in visual perception. Surprisingly, when the patients closed their eyes and used their hands to grip a rod and align it vertically, the same bias persisted. This suggests that not just vision is impaired, but other perceptual domains may also be affected by PCA. Two possible explanations were proposed: patients with PCA might also have proprioception impairment – they are not able to receive reliable sensory signals from their own arms; or patients with PCA have a distorted mental concept of verticality. Future endeavours should attempt to investigate these two possible explanations. Additionally, tools that remind patients of orientational concepts should be developed to help with everyday activities.

**Sadly, there is currently no cure for PCA. With the increasingly rapid developments in Alzheimer's disease research, it is possible that ways to prevent or delay abnormal neurodegeneration could be identified. In the meantime, better diagnostic procedures must be implicated, and understanding the different variants of Alzheimer's disease can benefit the development of tools to support patients and their caregivers in coping with the condition.**


# Fos in spatial maps

**The hippocampus is most noted for its role in spatial mapping and contextual memory. Spatial maps - internal maps of one's environment - are generated by place cells. Contextual memory is managed by engrams (physical imprints of cognitive learning), which are often characterised by ensembles of Fos expressing cells. Not much is known about how engrams are formed, and how, if in fact at all, cells expressing the transcription factor Fos are involved in the formation of spatial maps. In their recent study, Noah Pettit and his colleagues from Harvard shone some light on this problem.**

**Written by** Mikolaj Sobieralski
**Illustrated by** Suruthi Esaichelvan
**Edited by** Laura Rizzo

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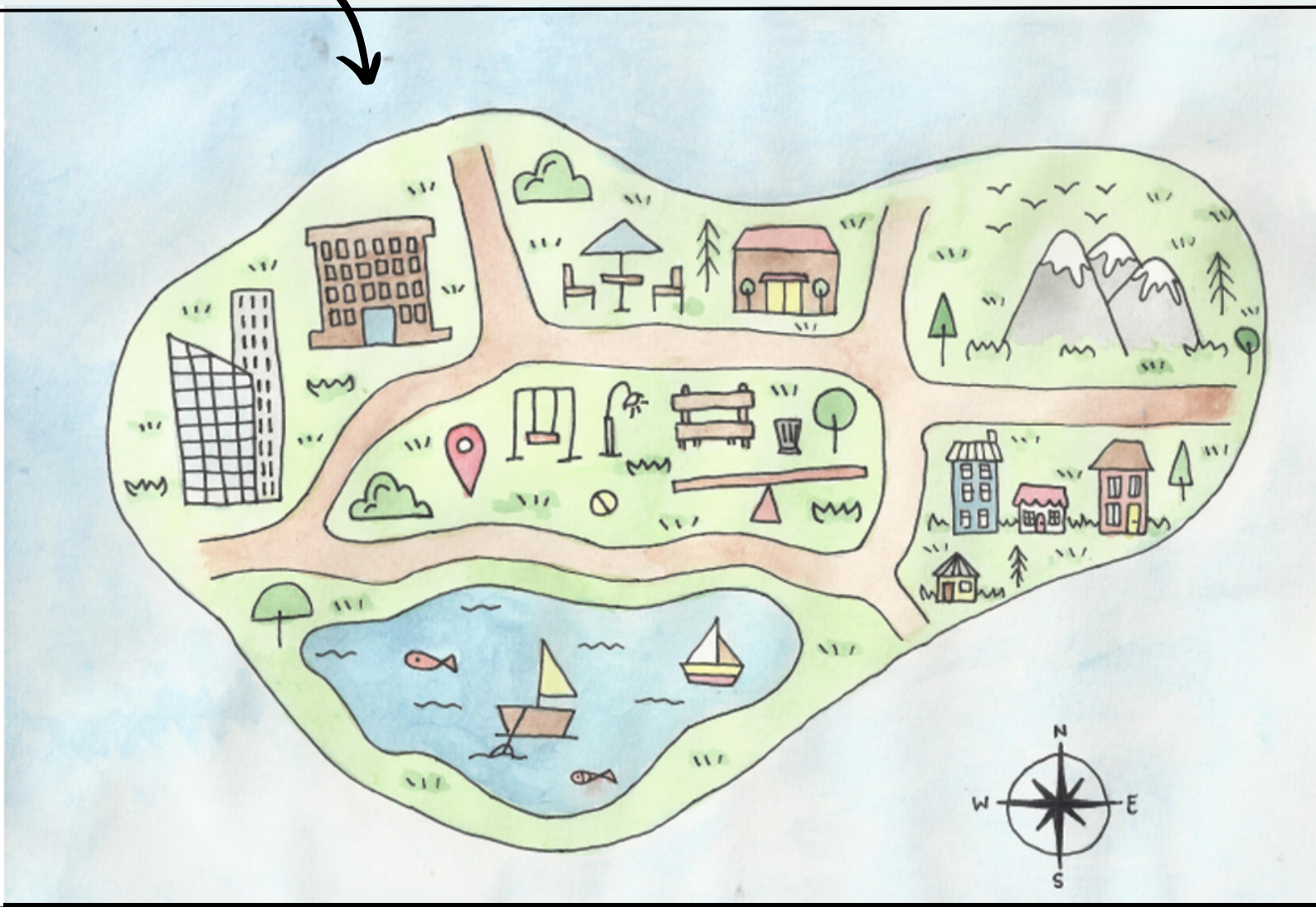
The team of researchers studied the activity of neurons in the CA1 region of the hippocampus in mice. The animals were placed on an air-cushioned ball in front of a big VR screen. Their movements on the ball represented their movement on the screen. Their task was to run along a virtual straight corridor until they reached the reward zone, where, once they licked, they would get a reward. For the first few runs, the mice licked almost uniformly along the corridor, searching for the treat, but after a while they got a hang of it and were much more accurate with which part of the corridor they licked. Throughout this, the researchers studied the formation of spatial maps of the corridor, and the behaviour of Fos-expressing cells.

In order to measure the changes in Fos expression during the task, the researchers used genetically modified mice, which expressed a green fluorescent protein (GFP) that was managed by a Fos promoter. This meant that Fos expression was coupled with cell fluorescence. To measure Fos expression, the team measured the cell fluorescence before and after the task. They identified the cells that expressed the most Fos (Fos-high) and those that expressed the least (Fos-low), and compared them. But they didn't stop there. They also studied another group of mice that were not conditioned to receive a reward at the end of the corridor - they simply explored it - to see if there were any differences in stimulus preference between Fos-high and Fos-low cells.

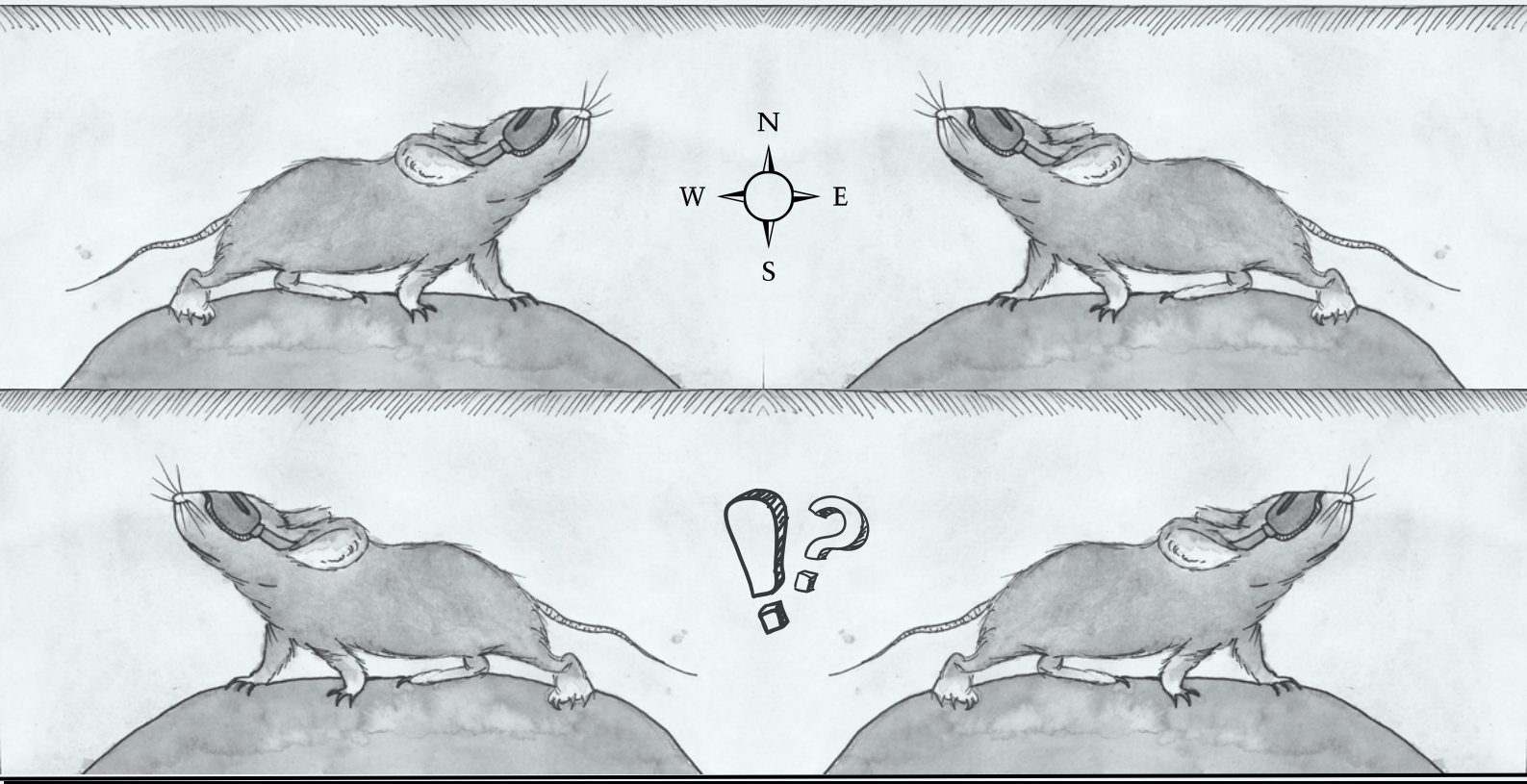
**They also observed yet another group of mice in which they deactivated the Fos gene (Fos-KO), to see how the spatial map of the environment would change.**



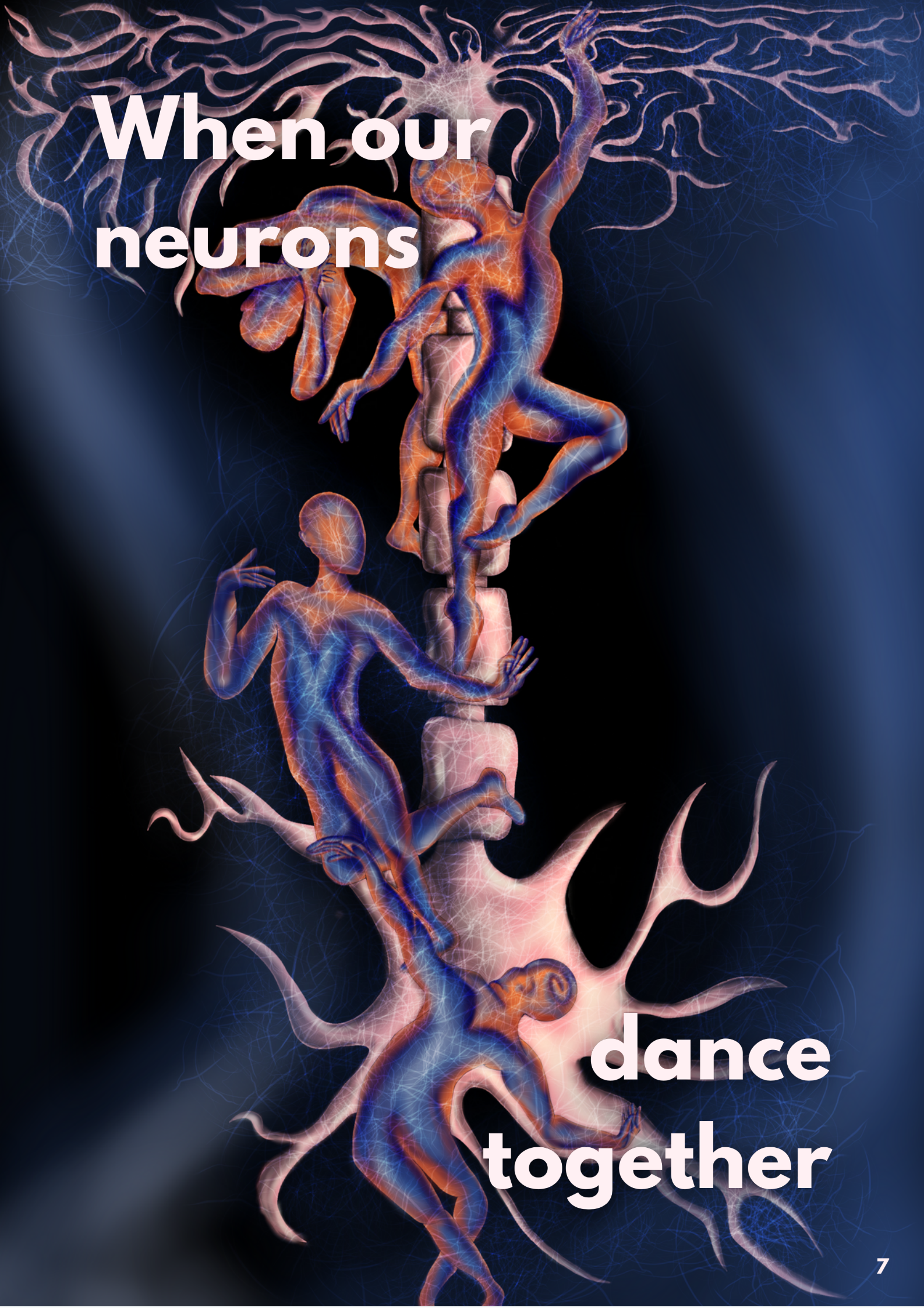

**One of the main findings of this study was that Fos-high cells had higher place field prevalence, and their place fields were more reliable across trials than Fos-low cells.**

This means that Fos-high cells showed more predictable activity in similar parts of the virtual corridor, which allowed the researchers to decode the mouse's position more accurately than from Fos-low cells. A second outcome of the experiment was that the place fields of Fos-high cells were uniformly distributed along the whole environment, whereas Fos-low cells showed a less even distribution and a bias towards the reward zone. What is more interesting is that in the cohort with no reward, Fos-high cells still showed reliable and highly prevalent place fields. This indicates that they have a stronger link to place code than Fos-low cells, and so primarily encode position rather than reward or valence. The researchers were also able to establish a causal relationship between Fos and hippocampal function during spatial navigation. Although Fos is not required for place field formation, as many Fos-KO cells still had place fields, it did appear essential in regulating the activity of the CA1 neurons, and in the creation of highly accurate and reliable spatial maps.

**In conclusion, this study demonstrates the significance of Fos as not only a marker of neural activity, but also an important factor in hippocampal function. There are many questions yet unanswered, but this might be a step towards uncovering the true mechanisms of contextual memory and cognitive maps, which not only broadens our knowledge but could help treat memory disorders.**




*For more information, view the original study:*
*Pettit, N.L., Yap, EL., Greenberg, M.E. et al. Fos ensembles encode and shape stable spatial maps in the hippocampus. Nature 609, 327–334 (2022). https://doi.org/10.1038/s41586-022-05113-1*


When our
neurons
dance
together

Written by Eleanor Swanson
Artwork by Nara Ito
Edited by Levana Tse

**On weekends, London bars and clubs come alive with the thumping rhythm of bodies moving in synchrony on the dance floor. During the week, dance studios in the city are filled with aspiring young artists and amateurs that want to learn and have fun. Throughout the pandemic, Tiktok dances connected people across the globe. Dancing, however, is not a trend. It has been a part of human life for thousands of years. Even before written language existed, dance was performed in cultural rituals, to tell stories, express emotions, celebrate, and as a means of social interaction. Neuroscience research is currently expanding our knowledge of why we dance and how the practice can be beneficial to not just our bodies, but also our minds. Currently, dance and movement therapy is used in the management of multiple nervous system-related conditions. One of these conditions is autism - a neurodiversity likely linked to disrupted oscillatory neuronal firing in the brain. This article will explore how understanding dance on a neural level might facilitate a new therapy for people on the spectrum.**

Autism is defined as a neurodevelopmental condition of unknown cause, and it impacts individuals to varying degrees. On a behavioural level, people with autism might have difficulty with certain social and speech skills, repetitive actions, and non-verbal communication. People with autism may also find unfamiliar situations distressing, and can find certain stimuli overwhelming - e.g., bright lights or loud noises. Therapies for autism range, just like the severity of the condition. Each person must be supported in an individualised manner to best cater to their needs. Behavioural, communication, educational, and family therapies are often used. Additionally, people often take medications to treat or manage co-morbidities - several surveys have reported that depression is more prevalent in people with autism than in the general population. But what if we could help alleviate dysfunctional struggles in autism by targeting neurons non-invasively?

The landmark review paper "Dance on the brain", published in 2021, poses a new idea for how to view dance: the synchronicity hypothesis. This theorises that our neurons begin to fire in synchrony during dance. This creates an oscillatory rhythm that syncs up neuronal firing between multiple individuals. So, when we dance together, our neurons fire together. Dance is thought to engage several different brain regions including social, emotional, rhythmic, and creative domains. This likely increases functional connectivity between those brain regions, which contributes to a more integrated feeling between body and brain. Dance also trains memory, praxis, social cohesion, non-verbal expression of emotion, and many other vital neural functions. Importantly, the neural synchrony created during dance likely elicits a pleasurable feeling within us, a potential reason for why humans dance so much.

Due to its profound effects on our mind-body connection and neural synchronicity, dance might be able to improve brain function in people with changes in their oscillatory rhythms, such as people with autism. A new form of electroencephalogram (EEG) that can be used while the subject is moving allows researchers to measure neural activity during dance, and how brain waves are altered when people mirror each other's movements. Julia Basso at the Embodied Brain Lab at Virginia Tech is conducting a study to measure the effects of dance on brain activity in people with autism so that they can uncover more about the synchronicity hypothesis. Since people with autism tend to have disordered brain wave signals, mirroring someone else during dance might "re-awaken" the dormant mirroring neurons and re-establish neural rhythms and interconnectivity between brain regions. Hopefully, in the future, our increased understanding of the brain during dance might enable non-invasive, non-pharmacological support for the 700,000 children and adults with autism in the UK.

# Everything you need to know about

# Serotonin Toxicity

**Written by Beyza Çetin** **Artwork by Nara Ito** **Edited by Levana Tse**

**Purposeful consumption of antidepressants is common in adolescents, to try to manage a range of mental illnesses. However, this may cause serotonin toxidrome (ST), which can be expressed as both a toxicity and a syndrome - a toxicity is a spectrum. Since antidepressants have been the fastest expanding category of human drug exposures in all age categories over the last decade, ST has become an increasingly prevalent and major clinical problem. Besides the huge growth in antidepressant usage, the consumption of caffeine and herbal products such as Hypericum perforatum (St. John's wort), along with other medications that patients use regularly may cause serotonergic effects and thus, may lead to ST. ST can affect everyone, old and young. Surprisingly, since antidepressants can cross the human placenta and fetal blood-brain barrier, it has even been observed in an unborn baby! Several examples of infant toxicity from SSRIs, including citalopram and escitalopram, have been described. This demonstrates that ST has the potential to be a major problem.**

Firstly, the neurotransmitter serotonin is generated in neurons by the hydroxylation and decarboxylation of L-tryptophan - a dietary amino acid. Tryptophan is obtained through food such as meats, dairy, fruits, and nuts. The gastrointestinal epithelium produces approximately 90% of all serotonin, and is a key component of the gut-brain axis. As serotonin cannot penetrate the blood-brain barrier, a serotonin-containing drug to treat serontonergic conditions is futile. Blood levels of serotonin are therefore also poor indicators of the well-being of the serotonergic system in the brain.

A drug is serotonergic if it exerts its effects through interacting with the serotonergic system, such as via enhancing or inhibiting neurotransmission. Any molecule that modifies the impact of serotonin in the body is referred to as a serotonergic substance. Monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and serotonin releasers (SRs) are the only medicines that have been consistently shown to cause ST. Other medications have been reported as a risk for ST in small cases, but have not been fully investigated.

ST arises as a result of increased serotonin synthesis or release, impaired metabolism, inhibition of serotonin reuptake, and/or direct agonism of serotonin receptors. This can result in a variety of potentially fatal symptoms. Approximately 7300 cases of ST are reported each year and approximately 100 of these patients pass away. ST is predominantly defined by the behavioural characteristics of autonomic hyperactivity, hemodynamic alterations, tremors, and consciousness disturbances. Mental health characteristics of ST include agitation, anxiety, confusion, restlessness, and excitement.

Serotonin (5-hydroxytryptamine, 5-HT) excess causes overstimulation of postsynaptic receptors in the CNS, primarily of the 5-HT1A type. This is linked with hyperactivity, hyperreflexia, and anxiety; whereas the 5-HT2A type is correlated with hyperthermia, incoordination, and neuromuscular excitation. 5-hydroxytryptophan (5-HTP) dietary supplements can help increase serotonin levels in the brain. However, people who are currently taking antidepressants really should not take 5-HTP without consulting their physician or prescribing pharmacist. Antidepressants may interact with 5-HTP to trigger ST.

There are two different criteria to detect ST, named Sternbach and Hunter. Once examined by a clinical toxicologist, the Hunter criteria proves to be not only more specific (97% vs 96%) but also more sensitive (84% vs 75%) than the Sternbach criteria and thus more preferable.

**ST is potentially under-diagnosed in the UK. Some symptoms of ST overlap with those of other psychiatric conditions, and may therefore be misdiagnosed. This is called 'diagnostic overshadowing'. Furthermore, individuals on combinations of medication, or those taking medicines with previously unknown serotonergic characteristics, may face diagnostic quandaries. ST is usually associated with cobminations of serotonergic drugs, though some case reports have documented ST in cases of SSRI monotherapy - though that is extremely unusual. ST is difficult to detect since the symptoms are vague and can have mimickers. To make matters worse, more than 85% of clinicians are unfamiliar with ST as a clinical diagnosis. If diganostic procedures are improved, then better treatment can be given sooner.**

# Why Have Scientists Called on a Need to ‘Redefine Anhedonia?’

**Written by Yammi Yip** **Edited by Laura Rizzo**

**Anhedonia is a psychiatric symptom characterised by loss of interest or pleasure in what used to spark such feelings. It presents as a key feature of many psychiatric conditions, particularly in major depressive disorders. Intriguingly, anhedonia is also a predictor for poor treatment response in depression, and of relapse in addiction. Therefore, we have yet to reach a full understanding of the underlying neurobiology of anhedonia. The traditional definition of anhedonia, the inability to experience pleasure, as described by Théodule-Armand Ribot in 1896, has remained largely unchanged over the past century. But recently scientists have called on a need to redefine anhedonia. Why should it be redefined and how might that aid the future research and treatment of anhedonia in psychiatric conditions?**

To understand anhedonia, we could turn to the research on reward processing and hedonia (ancient Greek for pleasure). Scientists have discovered that reward processing in the brain can be divided into three stages of the pleasure cycle: wanting, liking, and learning (Figure 1). A study that used the Monetary Incentive Delay task, where participants are presented with visual stimuli that represent varying amounts of monetary outcomes, revealed that each stage is regulated by distinct brain networks.

The ventral striatum and anterior insula showed increased activity in anticipation of the reward (wanting), whereas the orbitofrontal cortex, ventromedial prefrontal cortex and posterior cingulate cortex were activated in the receipt of the reward (liking). This highlights the alternate brain networks for the liking and wanting components of pleasure and reward.

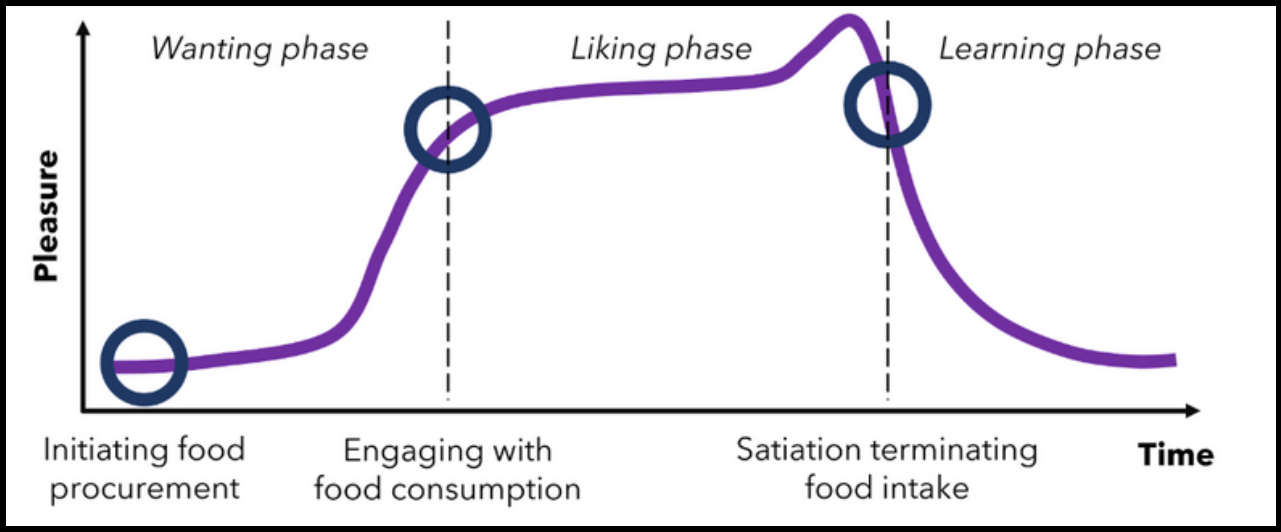



Figure 1: The pleasure cycle. Adapted from Thomsen, Whybrow, and Kringelbach, 2015.

These new insights into reward processing suggest that anhedonia may not simply be the inability to experience pleasure. It could be a result of specific deficits within the pleasure cycle. Indeed, reduced levels of dopaminergic transporters and homovanillic acid (the primary metabolite of dopamine) have been found in the brains of individuals with major depressive disorders, pointing towards a deficit in the dopaminergic network underlying motivation.

Further evidence, such as PET scans, have shown markedly reduced dopaminergic transporter binding in individuals with anhedonia and depression. Behavioural studies have also demonstrated that individuals with major depressive disorders are less willing to work for higher rewards, and less sensitive to reward magnitude during decision making. This indicates a deficit in reward learning: the last stage of the pleasure cycle. These findings emphasise the need to broaden the definition of anhedonia beyond just a lack of pleasure and include the motivational aspect of anhedonia.

Anhedonia is also presented heterogeneously across psychiatric conditions - appearing as a long-lasting trait in schizophrenia, but a transient symptom in mild depression. Anhedonia is also evident in drug addiction. People physically or psychologically dependent on substances (alcohol or other drugs) can experience excessive desire for a substance, often without the expected feeling of pleasure, especially in later stages of drug addiction. This variation in the expression of anhedonia across conditions indicates that it may manifest from deficits in distinctive parts of the brain's pleasure system. Again, this calls for a need to move away from the unidimensional definition of anhedonia.

Why is it important to reconceptualise anhedonia? Traditionally, it has been measured with self-report questionnaires like the Snaith-Hamilton Pleasure Scale, where participants agree or disagree with statements of hedonic response in pleasurable scenarios. However, these self-report measures have little consideration of the wanting and learning components of reward. This limitation is demonstrated in studies where individuals with depression and schizophrenia have seemingly intact feelings of pleasure from self-report assessments, despite experiencing anhedonia. This highlights the need to recognise that anhedonia could stem from deficits in some or all dissociable components of wanting, liking and learning. Reconceptualising anhedonia would aid researchers and clinicians in adopting a more comprehensive understanding of it.

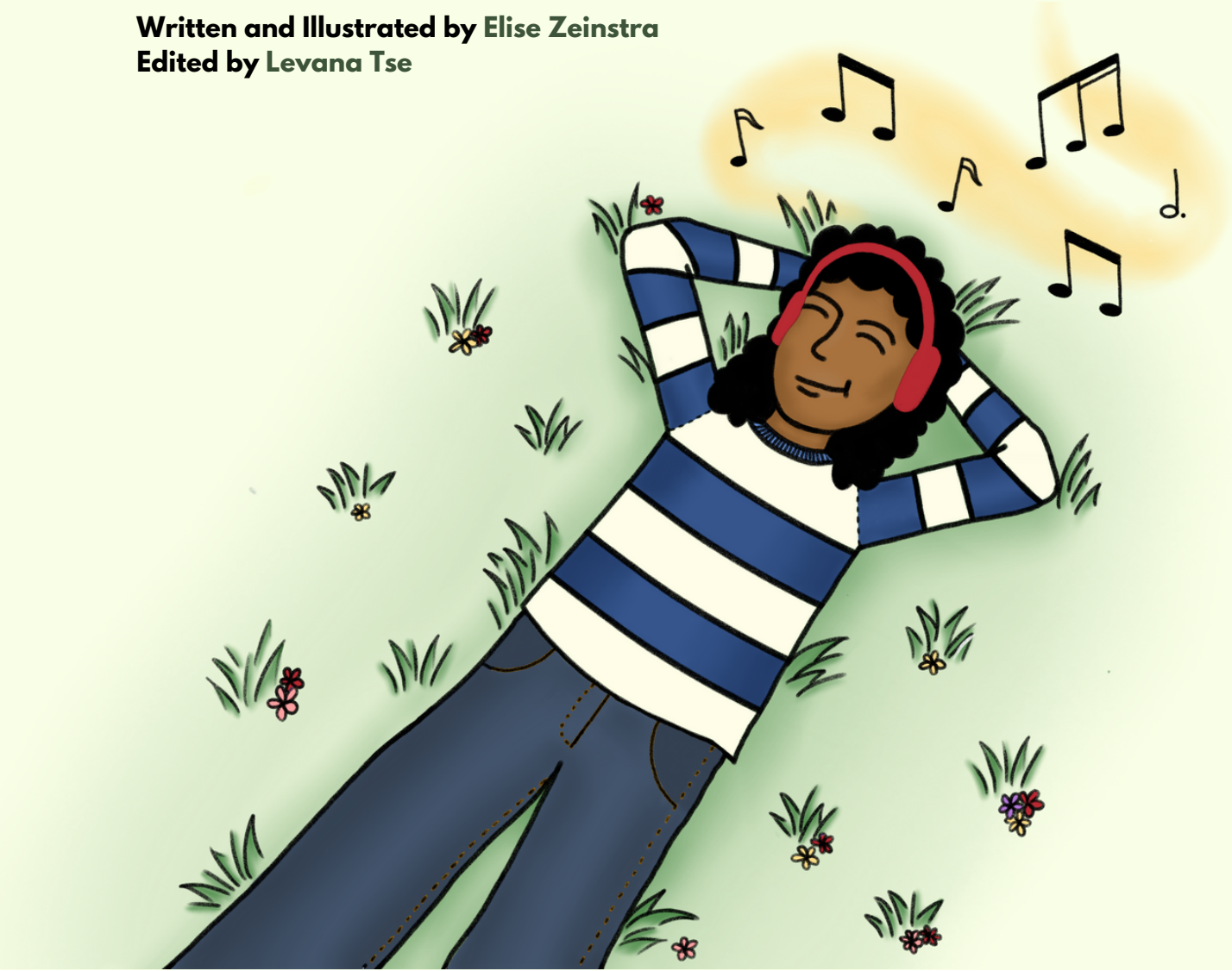
**Incorporating our insights from affective neurosciences, we could redefine anhedonia as "the lack of ability to experience, pursue, and/or learn about pleasure". By recognising the multifaceted nature of anhedonia, we can better elucidate the specific brain mechanisms underlying it, thereby working towards more precise diagnoses and treatments of anhedonia.**

*For more information, please refer to the following source that inspired this article:*
*Rømer Thomsen, K., Whybrow, P. C., & Kringelbach, M. L. (2015). Reconceptualizing anhedonia: novel perspectives on balancing the pleasure networks in the human brain. Frontiers in behavioral neuroscience, 9, 49. https://doi.org/10.3389/fnbeh.2015.00049*

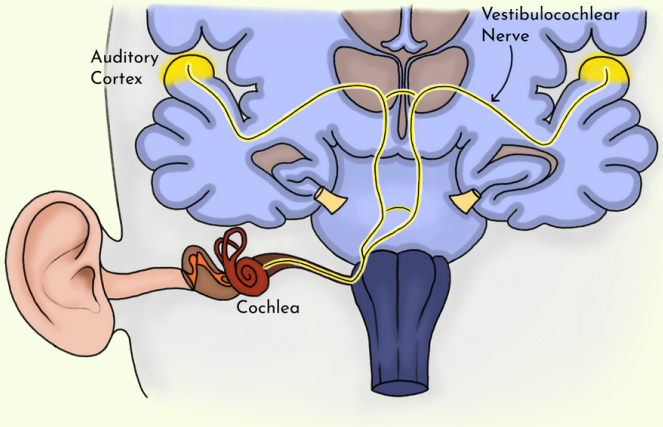
# Melody & the Mind

**Music has such an enormous range - from heavy metal to Afrobeats, to EDM, to folk. It seems for every life event or experience there is a fitting piece of music to accompany it. Music is undeniably closely intertwined with human life, but why does music have such an effect on our emotions? What does music actually do to our brain?**

**Written and Illustrated by Elise Zeinstra**
**Edited by Levana Tse**



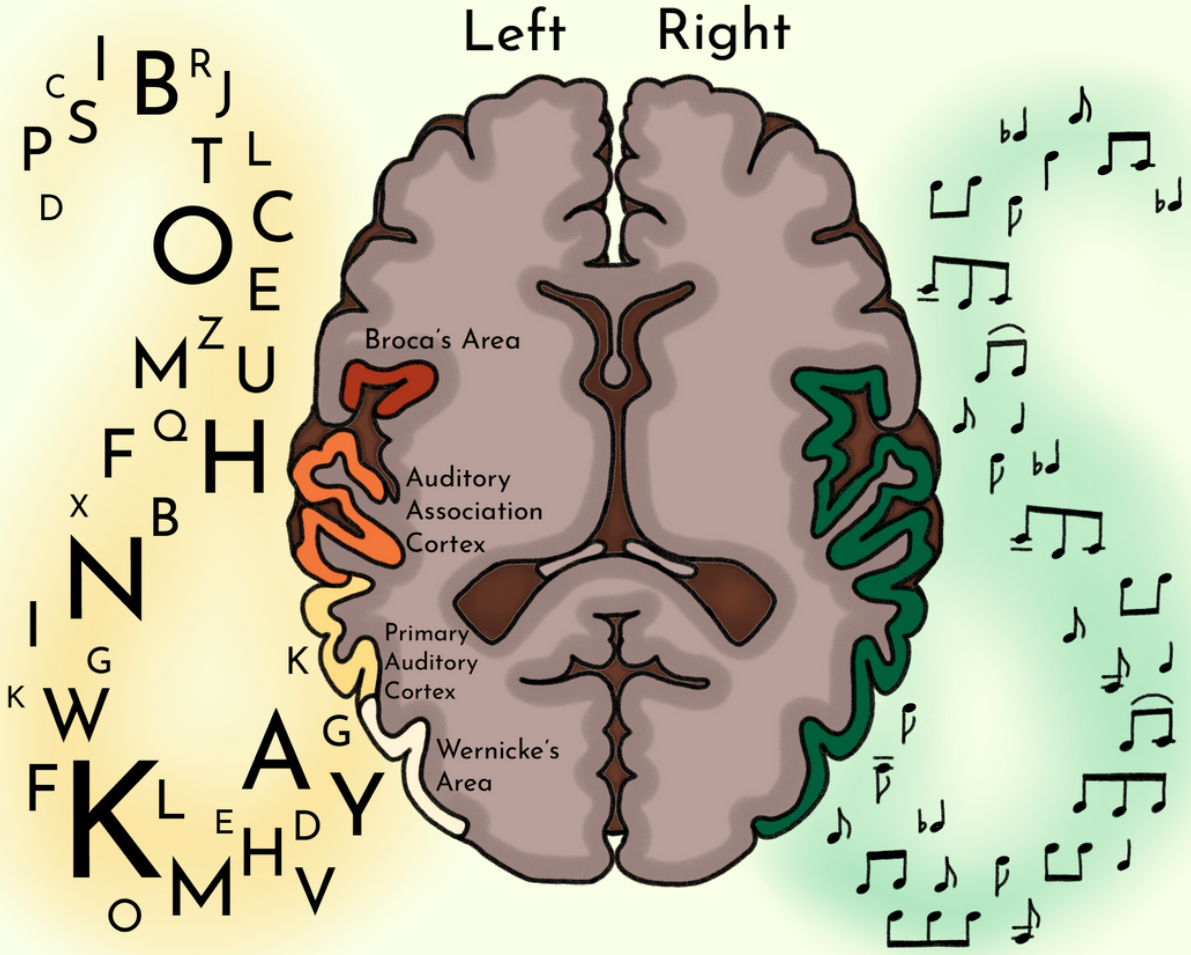
To start at the beginning, any sound in our environment first needs to reach the ear. The sound waves travel through the structures of the ear and end up in the cochlea, where they cause vibrations in the cochlear fluid. These vibrations are picked up by the neurons of the spiral ganglion. This ganglion is connected to other parts of the cochlea and the vestibulocochlear nerve. The vestibulocochlear nerve fires signals through the medulla, pons, and midbrain before finally reaching the auditory cortex in the temporal lobe.




Irrespective of the type of music people prefer - which is largely dependent on cultural and temporal factors - many people experience deeply personal and introspective thoughts and emotions when listening to their favourite music. While much remains unknown about the neural mechanisms behind music appreciation, there are some theories on how music can evoke certain thoughts and emotions.

Firstly, one of the suspected mechanisms behind music-evoked emotional experiences relies on the connectivity of the auditory cortices with other brain regions. A study by Wilkins et al. from 2014 showed that the default mode network, an area important for the generation of internally focused thoughts, is most connected when subjects were listening to their favourite music. Music-evoked alterations in the connectivity of default mode network structures (including the anterior medial prefrontal cortex, posterior cingulate cortex, and angular gyrus) to the auditory cortices might explain the introspective mind-wandering experiences many of us have when listening to music we like. This study also showed that brain connectivity between auditory areas and the hippocampus was altered in subjects listening to their favourite song. Surprisingly, these changes in the functional connectivity only depended on whether subjects liked or disliked the music. The changes were not affected by the type of music, nor the presence or absence of lyrics. As the hippocampus is vital for memory and emotion, this might be another reason why the music we love can evoke so many feelings.

Another way music 'speaks' to us may be explained through parallels found between the processing of language and music in the brain. A book by Jourdain from 1998 discusses the possible connections between areas in the right cerebral hemisphere involved in emotion and music, and areas in the left hemisphere involved in language and rhythm. Language tends to be focused on communicating with others, thus being externally focused, whilst listening to music sparks more internal thoughts and feelings. However, when subjects listen to music, they show increased activity in the nucleus accumbens, amygdala, and cerebellum. This suggests an overlap in the pathways involved in processing of music and language. Although instrumental melodies do not include spoken word, this underlines the power of music to bring across a message that can be interpreted by the brain similarly to spoken language. This is colloquially referred to as the "feel" of music.




Furthermore, in a conference paper from 2018, Wang and Agius discussed a possible function of mirror neurons in music-evoked emotional experiences. Mirror neurons are neurons that fire when someone else performs actions or expresses emotions, as if that person was experiencing them firsthand. This empathic mirror neuron system may play a role in the ability of music to influence our emotional states: sad music makes us feel sad and happy music makes us feel happy.

**In conclusion, there is still a degree of mystery as to how our favourite tunes can make us feel so many things. In reality, it is probably a complex combination of network connectivity, and the interaction of several different brain regions and types of neurons that lead to these effects on our thoughts and emotions. A lot of the mechanisms involved in these brain-stimulating musical concerts are likely yet to be discovered. So whether it is Eminem, Vivaldi or Taylor Swift you prefer, they will probably alter your brain in ways we don't know about yet. And this doesn't even touch on the neural mechanisms underlying how we choose our favourite music, and how taste changes over time.**

# Depression & Synaptic plasticity

**Over the years, the prevalence of depression has been rising due to a range of complex, interacting factors - arguably predominantly socioeconomic. Because of this, the development of antidepressants has become a major pharmaceutical research focus. In many cases, the efficacy of some antidepressants in some patients - such as serotonin-reuptake inhibitors (SSRI) - has driven hypotheses of the pathophysiology underlying depression. However, there is an inconsistency in the success of antidepressant medications, and lots of apparently conflicting results from research. Recently researchers have postulated that the potential connection between synaptic plasticity and depression may provide a new insight for the development of antidepressants.**

**Written and illustrated by Wendy Wu**
**Edited by Laura Rizzo**

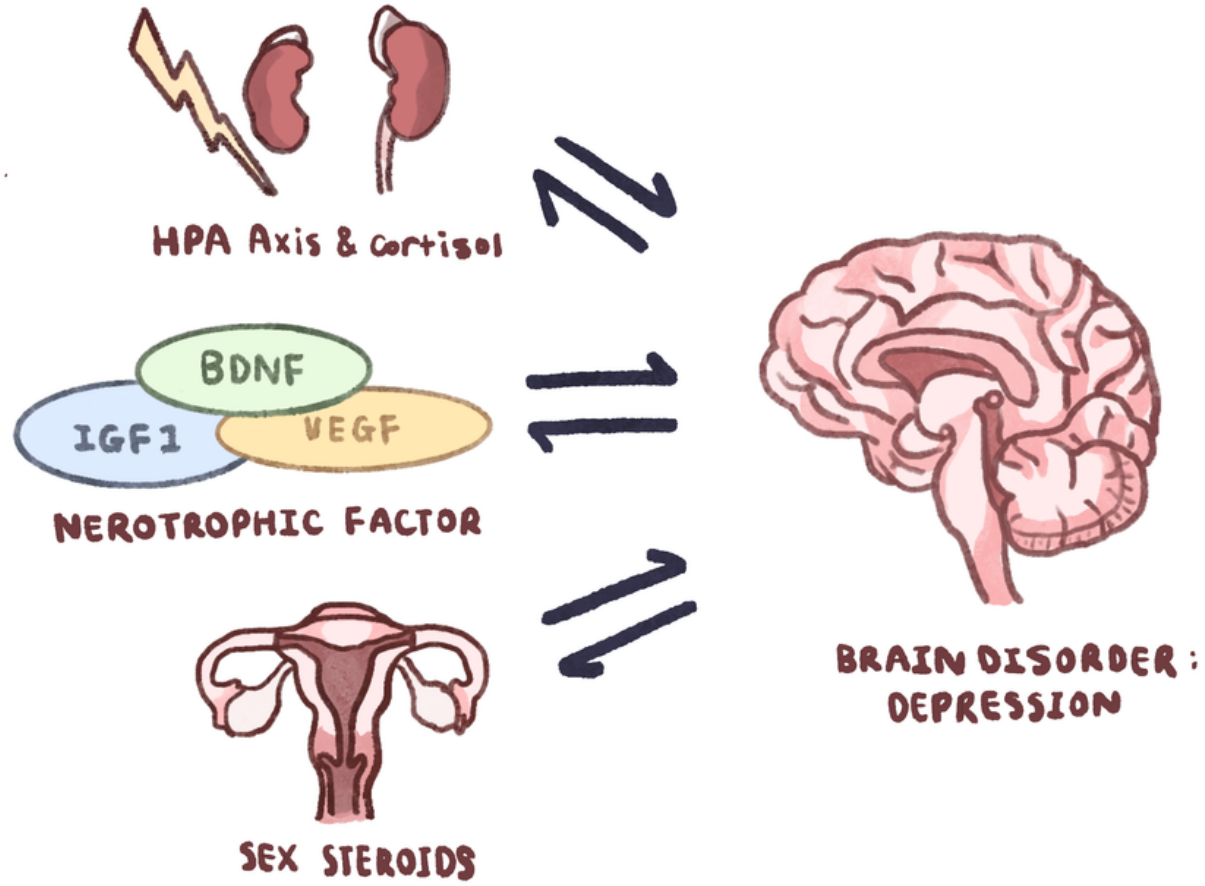
## What is depression?

Depression is a major contributor to the global burden of mental illness. It is estimated that approximately 4% of the global population is currently experiencing depression. Depression is characterised by psychological, somatic, and behavioural features that can lead to a diagnosis. The psychological features are perhaps the most well-known: feeling hopeless or guilty, having low self-esteem, and experiencing anhedonia (the reduced ability to experience pleasure). In extreme cases patients may have thoughts of, or act on suicidal ideations.

There are several identified biological risk factors for depression. They include the abnormal overactivation of the hypothalamic-pituitary-adrenal (HPA) axis, decreased neurotrophic factor expression, and fluctuating levels of sex hormones. These can lead to the disruption of synaptic function and the loss of neurons - mainly in the prefrontal cortex (PFC) and hippocampus.

## What is synaptic plasticity?

Synaptic plasticity is the ability of the brain to rewire its structure by generating new connections between neurons. Synaptogenesis is the process by which new connections, or synapses, are formed. This alters neural circuits to adapt to various experiences. Synaptic plasticity is activity dependent - it is commonly referred to as Hebbian plasticity, which states that "cells that fire together, wire together". It is clear though that this brain function is critical in forming short-term and long-term memories. Dysfunction in synaptic plasticity is strongly correlated with the pathophysiology of many neurological conditions, including depression.




## The HPA axis and Glucocorticoids

One of the chronic symptoms of depression is an amplified stress response. That enhances activation of the HPA axis and increases the levels of circulating glucocorticoids. Long-term exposure to stress can have deleterious effects on the brain and other organs.

The biological mechanism underlying how stress may disrupt synaptic plasticity is not clear. However, a hypothesis proposed by Popoli and his colleagues suggests that chronic stress can disrupt the function of extra-synaptic NMDA receptors. NMDA receptors are sensors for oxidative stress, and can trigger the loss of dendritic spines and branches. As a result, the connections between neurons deteriorate. It was also suggested that over-exposure to long-term stress influences the expression of neurotrophic factors, which will now be discussed.

## Neurotrophic Factor Expression

The neurotrophic factors, including brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2) and insulin-like growth factor 1 (IGF1), have been shown to affect depression. A significant decrease in BDNF expression is often associated with depression. Additionally, various intracellular signalling pathways that connect neurotrophic factor expression and synaptic plasticity have been found. These signalling pathways include protein kinase B, and the mitogen-activated protein (MAP) kinases Raf, MEK and ERK. The kinases are involved in tyrosine kinase receptor activation, which in turn activates phosphatidylinositide 3-kinase (PI3K). In the mouse hippocampus - an important site for learning and memory - PI3Ks are phosphorylated by calcium/calmodulin-dependent protein kinase II (CaMKII). CaMKII is activated by NMDA receptors, and is a key enzyme in synaptic plasticity. It recruits AMPA receptors to the postsynaptic membrane, which promotes long-term potentiation (LTP). LTP is a form of synaptic plasticity whereby synapses are strengthened due to recent activity patterns. Therefore, reduced neurotrophic factor expression in depression can correlate with a reduction in the PI3K-LTP pathway.

Rapamycin complex 1 (mTORC1) is a protein complex required for synaptogenesis. It is also regulated by neurotrophic factor signalling. Research led by Feyissa and Jernigan found a decreased expression of mTORC1 signalling in the PFC of patients with depression. This suggests that in patients with depression there may be impaired expression or function of neurotrophic factors, which downregulates synaptic plasticity in the brain. Though how this pathology links with the presentation of symptoms of depression is unclear.

## Sex Hormones

Depression is reportedly more common in women than in men. It is possible this is partly affected by societal pressures on men to refrain from expressing emotions deemed as "weaknesses". It is also likely partly due to differing hormonal cycles.

The fluctuating levels of gonadal steroids in the female reproductive life cycle are possibly a substantial contributor to the increased reported prevalence of depression in women. A depressed mood has been correlated with a decrease in oestradiol levels - a steroid hormone mainly secreted by the ovaries. Reduced oestradiol levels affect neurotransmitter activity, neurogenesis and neurotrophic factor expression. For example, recent research has shown that serotonin levels in the brain positively correlate with oestradiol levels. Low levels in both are often associated with depressive symptoms, and could explain why the risk of depression increases during menopause.

Oestrogen is likely also implicated in depression. It acts on many signalling pathways involved in the modulation of synaptic plasticity: MARK-EPK, PI3K-Akt, and mTORC1 signalling. These pathways are also associated with the oestrogen-induced improvement of memory in both rodent models and human studies - mediated by enhanced synaptic plasticity.

**In conclusion, over-activation of the HPA axis, reduced levels of neurotrophic factor expression, and the fluctuation of ovarian hormones all play an important role in affecting synapse number and function. It is often observed that these factors reduce synaptic plasticity in cases of depression. Is it possible that by targeting these signalling pathways, new antidepressants can be developed.**

*This article is based on the scientific review published by Duman et al. on 03 March 2016 in Nature Medicine.*

Written by Ilina Moitra Edited by Alice Wright

# The birth of bioinformatics

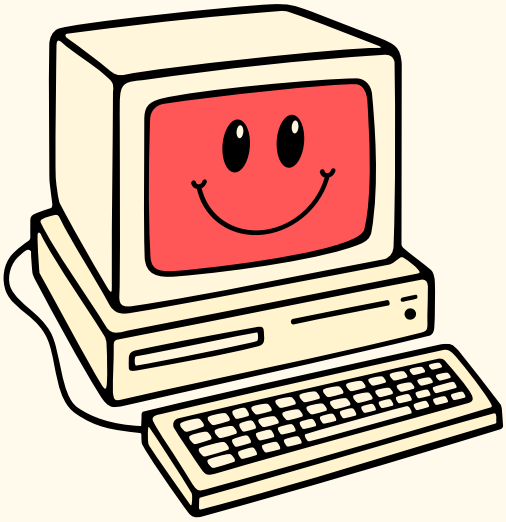
**70 years ago, Rosalind Franklin's work utilising X-ray crystallography paved the way for the discovery of the "molecule of life" - deoxyribonucleic acid or DNA. In 1961, Marshall Nirenberg was able to demonstrate how DNA is translated to amino acids, following which different teams around the world raced to decipher the genetic code - a hugely fruitful endeavour. In 1977, Frederick Sanger (one of the only two-time recipients of the Nobel Prize in Chemistry) developed a method for sequencing our DNA, a technique still used today and the very basis of current genetics-based life science research. Since the discovery of the structure of DNA in 1953, and the consequent birth of modern molecular biology, we have rapidly unlocked key elements in the mysteries of how our genes work.**

Bioinformatics has revolutionised our ability to understand the same molecule and the information it holds in novel and dynamically evolving ways. Professor Margaret Oakley Dayhoff is commonly considered the pioneer of the field of bioinformatics. In 1961, she began developing a tool towards investigating amino acid sequences, and started creating a comprehensive database of protein sequences and structures that eventually led to the assembly of the then largest nucleic acid sequence database in 1980. Based on this early foundational work, as of 2003 the human genome was successfully sequenced and shortly after, gene editing techniques such as CRISPR/Cas9 were developed. Thus evolved the field of bioinformatics, which widely refers to the use of informatics or data-analysis based approaches to biology (particularly with reference to DNA and amino acids), allowing for expansion in the usable information we can obtain from biological findings.

Bioinformatics-based approaches often require an interdisciplinary approach and involve broader fields of study such as mathematics, computer science, statistics, biology, chemistry, and physics, and often require a collaborative venture involving experts in several fields. Currently, there are several open-access packages and web-based resources that support bioinformatics research available. One of the more common uses of such softwares and open-source data is to identify novel candidate genes for diseases, identify single nucleotide polymorphisms (SNPs) and other forms of mutation, study biological pathways affected by SNPs, and simulate theoretical protein structure and function in the event of a mutation. There is great effort being made to catalogue information obtained through such in silico studies and ensure that this is available globally to clinicians and researchers.

Understanding how genetic information is stored, passed on, and altered allows us to better understand their contribution to health and disease (aiding prevention and correction) and promotes better understanding of our individual biological circumstances. We now rely heavily on "omics", which includes branches such as genomics (gene-focused), transcriptomics (mRNA-based), and proteomics (protein-centric) to identify, diagnose, profile, and treat several biological conditions. Neurological disorders such as ageing-related disorders (including dementias), multifactorial genetic disorders, and currently understudied rare disorders have especially benefited from the advent of bioinformatics-based studies. Finding suspected risk genes and elucidating the biological process they may be involved in, for example, can allow targeted studies and consequent therapies, furthering translational medicine at an accelerated pace. Bioinformatics studies also rightfully challenge the notion of the once established genotype-phenotype correlation, which was at one point believed to be a direct, strong, and unalterable and also have illustrated the potential for misdiagnosis based purely on phenotypic studies.

**Bioinformatics-based techniques allow us to perform better, targeted, and less wasteful science. The same previously carefully curated databases from elegant, well-designed experiments now have the capacity to provide information they previously did not.**
**Preliminary bioinformatics studies can also help inform experimental design and expedite the timeline of studies, allowing for more efficient experimentation. Additionally, machine learning allows for the automation of data analysis using artificial intelligence and holds further promise in the amount of data we can examine and re-examine and do so with increased accuracy and efficiency.**



**Bioinformatics has been at the core of unlocking our understanding of our DNA and what it holds for our future, both as individuals and collectively. An aggressively and constantly evolving field, it holds the key to the future of translational medical research and healthcare, and challenges the biological "fate" that DNA was once thought to dictate.**

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