Brain Matters

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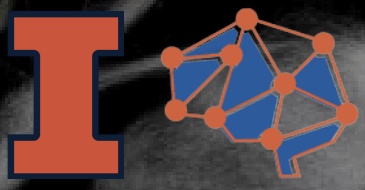

VOLUME VII

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Astrocytes and Their Role in Psychiatric Disorders

Pravika Srivastava

Abstract

Astrocytes are the most abundant glial cells in the central nervous system. They are recognized as active participants in neurodevelopment, neurotransmission and synaptic plasticity. Astrocytes are increasingly associated with the modulation of neuronal circuits and regulation of neurotransmitter balance. The dysregulation of these functions may contribute to the progression of psychiatric illnesses. The understanding of astrocytes and their relation to psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder is constantly evolving. Targeting astrocytes in the development of therapeutic interventions for psychiatric disorders is an emerging avenue of exploration. This paper discusses the exact function of astrocytes, their part in synaptic plasticity and how they play a crucial role in the development and presence of psychiatric illnesses, specifically schizophrenia and mood disorders.

What Are Astrocytes?

One of the most integral components of one's central nervous system are astrocytes. In the past, astrocytes were thought to act only as supporting cells for neurons; however, modern research suggests that they may play additional, multifaceted roles crucial to the proper functioning of the nervous system. Structurally, astrocytes possess numerous fine processes extending from their cell bodies, which form intricate networks that wrap around neurons and their synapses. It is oftentimes said that astrocytes are in "close structural association with synapses" (Notter, 2021). This feature in astrocytes greatly helps in regulating synaptic transmission. Functionally, they contribute to the maintenance of neuronal health and homeostasis by regulating nutrient and ion levels, as well as participating in the formation and maintenance of the blood-brain barrier.

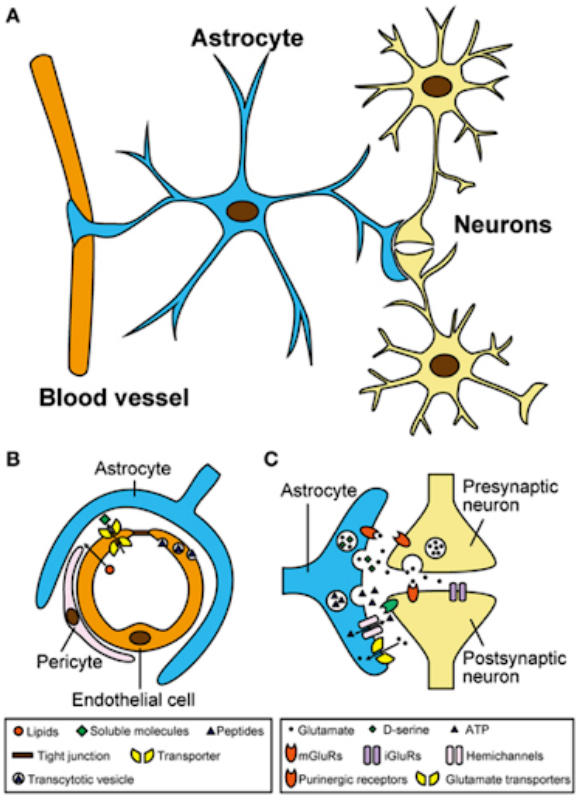

Figure 1. Visualization of Astrocyte Structure and Some of its Roles (Research Gate, 2016)

The Role of Astrocytes in Neurotransmission and Synaptic Plasticity

Neurotransmission and synaptic plasticity are critical functions of astrocytes that are necessary for the nervous system's essential processes and function. By actively contributing to the control of neurotransmitter levels in the synaptic cleft (the narrow space between two neurons in which chemicals are exchanged), astrocytes have a significant impact on neurotransmission. The process by which neurotransmitters—chemical messengers in the brain—are reabsorbed into presynaptic neurons following their release into the synaptic cleft is known as neurotransmitter reuptake. Ensuring appropriate neurotransmitter levels and controlling neuronal transmission depend on this mechanism. Neurotransmitters like gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter, and glutamate (the most abundant neurotransmitter in the body), a major excitatory neurotransmitter, are taken up by astrocytes after their release into the postsynaptic cell. Astrocytes assist in stopping the signaling between neurons by removing these neurotransmitters from the synaptic cleft, avoiding overstimulation and preserving the equilibrium of neuronal activity. In addition to neurotransmission, they also play a crucial role in synaptic plasticity. They release signaling molecules, such as gliotransmitters, which can modulate the strength of synaptic connections. Synaptic connection is what controls the consistency of transmissions between two specific cells. The significance of these connections between two neurons can be influenced by various factors such as the frequency of activation, the relevance of information and neurotransmitter type, just to name a few. Moreover, astrocytes control a process known as synaptic pruning, which strengthens and improves significant synaptic connections while removing less significant ones. (NIMH. 2023, March). Astrocytes influence long-term potentiation (LTP) and long-term depression (LTD), two forms of synaptic plasticity associated with learning and memory. LTP is the process by which synaptic connections strengthen and LTD involves weakening them. Glutamate, ATP and cytokines are all compounds that astrocytes regulate in the process of plasticity (Ota, Y., Zanetti, A. T., & Hallock, R. M. 2013).

These factors modulate LTP and LTD, influencing the persistence and strength of synaptic changes associated with memory formation.

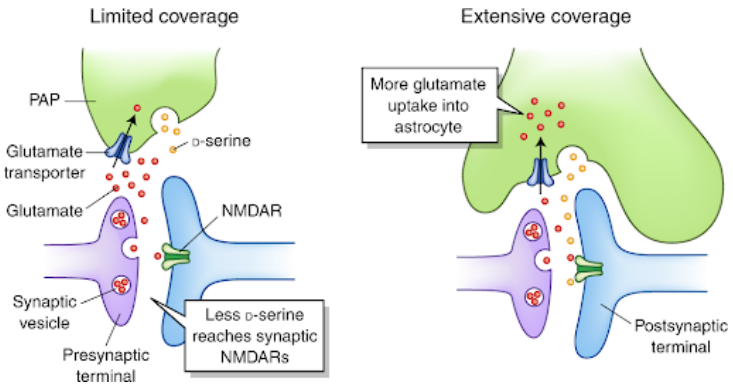

Figure 2. Diagram of Plasticity of Structural Interactions, Synaptic Elements and Astrocytes (Santello et al., 2019).

Psychiatric Disorders and Their Prevalence

Psychiatric disorders, also referred to as mental health disorders, are a broad category of problems that impact a person's thoughts, feelings, actions, and general state of health. These complicated illnesses are frequently caused by a mixture of biological, psychological, environmental, and hereditary variables. They impact a wide range of individuals and, as shown in a study from The World Health Organization in 2019, approximately 1 in 8 people suffered from some variation of mental illness. Additionally, these numbers drastically increased after the COVID-19 pandemic (World Health Organization, 2022). There are a broad range of categories for psychiatric disorders such as, depressive, anxiety, bipolar, neurodevelopmental, etc. are a few amongst the many different types of illnesses. The prevalence of psychiatric disorders varies upon many different factors such as which disorder it is, geographic location as well as cultural factors. Mental illness encompasses many different conditions ranging from mild to moderate to severe. There are two distinct categories when it comes to mental illnesses: Any Mental Illness (AMI) and Serious Mental Illness (SMI). AMI includes all recognized mental illnesses. SMI is a smaller and more severe subgroup of AMI. (National Institute of Mental Health, 2023).

Schizophrenia & Mood Disorders

Schizophrenia is a serious and chronic mental disorder that greatly impacts a person's thinking, emotions and behavior. Symptoms of schizophrenia can be characterized as either positive and negative. Positive symptoms involve things that are physically/outwardly visible and add factors into one's behavior, whereas negative symptoms are much more subtle, difficult to observe and tend to subtract a factor from one's behavior. (National Library of Medicine, 2019). Mood disorders are another type of psychiatric illness. They significantly impact one's mood regulation and can impact their daily tasks and overall mental well being. Some common mood disorders include major depressive disorder and bipolar disorder. They also impact one's emotions and behavior through a series of hallucinations, disorganized thinking, etc. However, mood disorders emphasize a persistent feeling of sadness and can eventually lead to a lack of interest in everyday activities that an individual once enjoyed (National Library of Medicine, 2019).

How Do Astrocytes Relate to these Disorders?

Dysfunctional synaptic pruning has been observed in schizophrenia (Sekar et al., 2016), which can lead to inflammation in the brain, disruption of balance of neural circuits as well as irregular brain connectivity (Birnbaum & Weinberger, 2017). These genetic variations in affecting astrocyte function can cause individuals to be more susceptible to this disorder. Moreover, astrocytes play a critical role in neuroplasticity, which is commonly known as the brain's ability to adapt and reorganize. Neuroplasticity is oftentimes impaired in such psychiatric conditions (Santello, M., 2019). In mood disorders, dysfunctional astrocytes can influence weak synaptic connectivity and prevent regulation in reuptake and release of neurotransmitters, leading to such disorders. In addition to this, it has been noted that astrocytes also help in regulating neurotransmitter levels which are typically dysregulated in the disordered brain. They play an intricate role in maintaining the balance of these neurotransmitters and dysfunction of this role may contribute to symptoms of such disorders (NIMH, 2023). Dopamine imbalance is highly common in schizophrenia (Correll, C. 2020). If astrocytes are unable to undergo the process of neurotransmitter uptake and regulate their levels, it may lead to something similar to dopamine imbalance which eventually contributes to the symptoms of schizophrenia.

Conclusion

The evolving understanding of astrocytes and their roles in the central nervous system emphasizes their importance to psychiatric disorders. Through their regulation of neurotransmitter balance, synaptic transmission, and plasticity, they have exerted great influence over the neuronal circuits necessary for mood regulation. By investigating the complex relationship between astrocytes and psychiatric disorders, further research may lead to new approaches for managing complex conditions and improving treatment for individuals that suffer from such illnesses. Thus, continued research and studies on astrocytes holds immense potential to advance and better our understanding and treatment of psychiatric disorders.

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Déjà Vu: What Happens in the Brain

Ananya Sampathkumar

Abstract

Déjà vu is a common phenomenon that most healthy people experience. Despite its commonness, it is difficult to stimulate in a lab situation, making information on this experience scarce. In order to combat this, researchers have come up with multiple theories on where déjà vu takes place, what occurs, and why it actually happens. Researchers have also begun to study mental disorders that involve déjà vu in order to possibly learn more about the elusive experience. Understanding déjà vu is crucial to gaining a fuller understanding of memory, and how the brain reacts when memories are altered or off kilter; as further technology is developed, scientists will be able to test out all theories surrounding déjà vu and narrow down the true cause.

Introduction

Despite the common manifestation of déjà vu in mental illness, 97% of healthy individuals experience it (Khomutov et al., 2023). Déjà vu is the French word for “seen before” and refers to when an individual feels they are feeling an experience identical to that they have lived before (Texas A&M, 2016).

Oftentimes, this feeling can be described as unnerving, leading some researchers to incorporate déjà vu with what is known as the “dreamy state.” The dreamy state is a term that refers to the many symptoms (which can often be difficult to distinguish between) that lead to the conscious being distorted (Gillinder et al., 2022). Despite the commonality of these emotions, there is very little known about déjà vu and the other processes in the “dreamy state.” The main reason for this is simple: these internal processes are very difficult to study. According to Dr. Michelle Hook of Texas A&M, there is “no clear, identifiable stimulus that elicits a déjà vu experience (it is a retrospective report from an individual); moreover, it is very difficult to study déjà vu in a laboratory” (Texas A&M, 2016). As a result, there is very little that we know about déjà vu as a phenomenon; however, there are many different theories being explored surrounding the feeling.

Where Déjà Vu Takes Place

When it comes to discussions of where déjà vu takes place, a common theory is the optical system. For many, déjà vu is triggered by seeing a specific object, place, person in their visual system. From there, it is thought that these signals were compared to current memories, thus causing déjà vu. However, researchers have found proof of otherwise. In their 2006 study, Researchers Akira O'Connor and Chris Moulin at University of Leeds studied a blind participant who claimed to experience déjà vu. Being blind, the participant’s déjà vu was caused by familiar sounds and smells that brought up memories and part experiences such as a particular piece of music playing as he unzipped a jacket (University of Leeds, 2006). This was the first time this particular situation was reported, opening much discussion on the possible location of déjà vu in the brain.

While the hypothalamus was not thought to directly play a role in déjà vu, research has found that a stimulated hypothalamus can also lead to the feeling of déjà vu. Andres Lozano, Professor of Neurosurgery and Canada Research Chair in Neuroscience, led the effort to experimentally treat a man with morbid obesity through a DBS surgery. DBS stands for deep brain stimulation, and this surgery often is used on patients with movement disorders such as Parkinson’s disease. Lozano and his team were attempting to identify possible appetite suppressants in the patient’s hypothalamus, and found that activating the electrodes caused the patient to experience déjà vu. The patient reported a memory of being with his friends in a park when he was 20, and as the strength of the stimulation was increased, the description of the memory got more detailed. This experiment was repeated again in a double-blind situation, and the results also stated that the participants experienced déjà vu. Researchers said that the feeling of déjà vu increased as the part of the hypothalamus closest to the fornix was stimulated. The fornix is a group of fibers that carry signals within the limbic system that is located close to the hypothalamus in the brain. Despite this seeming to point to the fornix and hypothalamus’s participation in the process of déjà vu, there is little research surrounding their involvement in the processes behind other “dreamy state” emotions (Wiley-Blackwell, 2008).

Additionally, there are several theories surrounding which parts of the brain react to déjà vu stimuli. The main theory is that it takes place in the corticolimbic network. The corticolimbic network’s main functions are motor programming and control, decision making, mnemonic function and emotional regulation. The main parts of the brain assumed to participate in the emotion of déjà vu are hippocampus, rhinal cortices, parahippocampal gyri, and the amygdala. The hippocampus is a part of the limbic system that deals with episodic memory and spatial reasoning and the rhinal cortices also generally work with memory and object recognition. Specifically with déjà vu, the feeling that you have experienced something before, the hippocampus and rhinal cortices seem to be crucial. Furthermore, the amygdala works with emotions and aggression and the parahippocampal gyri works with memory retrieval and encoding (Gillinder et al., 2022).

Even though it is difficult to place the exact places déjà vu takes place in the brain, these parts of the brain are associated with the “dreamy state” and déjà vu as a result.

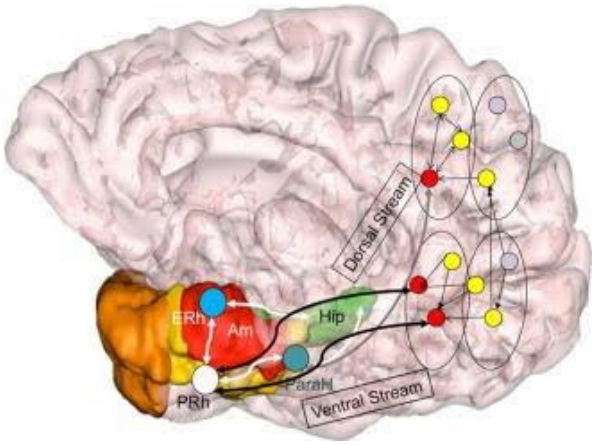

Figure 1. Brain visualization of several different systems in the brain. Dorsal stream connects the parietal areas with parahippocampal cortex. The rhinal cortices attaches to anterior hippocampus, and the parahippocampal cortex attaches to posterior hippocampus. Coloured dots represent neuronal activity areas in the occipital and parieto-occipital cortex (Gillinder et al., 2022).

Possible Reasons for Déjà Vu

When it comes to déjà vu, scientists have a multitude of theories as to why déjà vu occurs in the brain. One of these theories is the electrical malfunction theory. This theory proposes that déjà vu is a result of mismatched synaptic transmissions. Seizures are often caused by many abnormal electrical signals that interrupt the regular transmission of typical electrical signals. However, any differences in connections between nerve cells can cause a seizure in the brain (John Hopkins, 2019). Patients with epileptic seizures have said that they often experience déjà vu before a seizure; seizures are often caused by dysfunctional neuron activity in the brain. As a result, scientists theorize that déjà vu could be caused by lesser malfunctions in neuronal activity (Texas A&M, 2016).

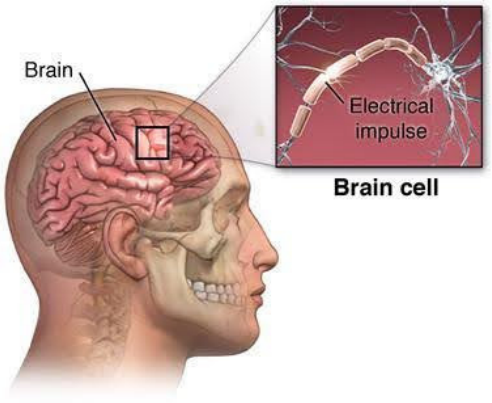

Figure 2. The neuron sets off an electrical impulse in order to communicate with one another. Seizures are caused by abnormal electrical activity (John Hopkins, 2019).

A second theory surrounding the occurrence of déjà vu is the neural pathway mismatch. Brains are equipped to process a certain amount of sensory information, but there is a lot of information in the world. Due to sensory information being classified as short term memory, scientists believe that long term memory is engaged instead, causing the brain to pull information from past memories and experiences (Texas A&M, 2016). In the visual cortex, several pieces of information travel through the neuronal pathways, with all of them reaching the destination at the same time. Due to the visual cortex processing the current information while the sensory cortex processes past information, there is a “mismatch” in the information between the two cortices, causing the brain to believe that this situation is familiar despite it being new.

The third theory is called the “glitch” theory. Scientists believe that déjà vu could be caused by the neurons in the brain mistakenly recognizing a stimulus and firing. This causes the brain to confuse the past and present, and for the body to feel déjà vu. This “glitch” is often compared to a hypnagogic jerk (Texas A&M, 2016). Hypnagogic jerks happen when someone is sleeping and their body involuntary jerks. These two processes are similar in the way that the body is experiencing one thing and the neurons fire for something else (either a different experience or for wakefulness.)

The fourth theory is known as the split perception theory. The idea is that the person perceives the same stimulus twice, but in different states of true perception. The first stimulus is perceived when distracted, quickly or in a period of delusion of some sort, and as a result, the input is weaker than most regular stimuli. This stimulus is then perceived again; this time, the stimulus is grasped fully. This second viewing of the stimulus causes our minds to believe that this stimulus is strangely familiar in some way, but not being able to place why as a result of the unregistered original stimulus. This theory helps to explain why our brains would be unable to place why we feel this moment has occurred before (Brown & Marsh, 2010).

However, when it comes to theories of déjà vu, it is incredibly difficult to study and prove any of these methods with our current technology due to the inability to replicate such emotions in a clinical setting. As a result, scientists have turned to other methods in order to gather information on the elusive experience.

Mental Disorders Related to Déjà Vu

Since déjà vu is challenging to replicate, scientists have turned to other subjects to learn more about the phenomena such as mental disorders. One mental disorder that has been linked to déjà vu is anxiety. In a case study from 2014, a man diagnosed with anxiety and depersonalization who experiences extreme déjà vu was compared. In comparison to other patients who experience déjà vu such as dementia patients, this man was completely aware of his déjà vu happening.

He claims he was constantly living in a loop due to his extreme déjà vu, and lived in constant anxiety. While this case study does draw a possible link between déjà vu and anxiety, the only evidence scientists currently have is regarding the location of the neural signals. Both anxiety and déjà vu take place in the hippocampal formation, which could show a possible connection via location of signals (Wells et al., 2014). However, there has not been enough research for this possible connection to be confirmed.

On the other hand, scientists have conducted a test on patients with temporal lobe epilepsy and déjà vu. Scientists tested 16 patients with temporal lobe epilepsy and tried to evoke the "dreamy state" by stimulating the hippocampus and amygdala. They did this in different ways: six patients had a collective nine dreamy states as a result of seizures, 14 patients had a collective 43 dreamy states due to electrical stimulation, and three patients had a collective five dreamy states as a result of chemical stimulation. Furthermore, the study shows that the amygdala was involved in 73% of stimulation cases, the anterior hippocampus in 83% and the temporal neocortex in 88% (Bancaud, Brunet-Bourgin, Chauvel & Halgreen, 1994). Mental disorders that involve déjà vu as a symptom are incredibly helpful in the study of déjà vu due to the difficulty of stimulating déjà vu, and will continue to aid in the research on déjà vu.

Summary

While déjà vu is generally just described as a feeling of having experienced something before, it is far more than an emotion. Déjà vu is a complicated process that scientists do not fully understand the purpose and reason for. Along with déjà vu, there are several other similar emotions that are often associated with déjà vu known as the "dreamy state." While we do not know much about the location of déjà vu, scientists believe that this process takes place in the hippocampus, rhinal cortices, parahippocampal gyri, and the amygdala. There are four major theories as to how déjà vu occurs in the brain: the electrical malfunction theory, the neural pathway mismatch theory, and the "glitch" theory. Despite all these theories, it is incredibly difficult to study déjà vu due to the difficulty of stimulating the experience in a lab situation. As science improves, we will get closer and closer to understanding the mechanisms and purpose of déjà vu.

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Fine tuning Alzheimer's Disease (AD) treatment with Music-Based Interventions (MBI): An anatomical overview

Celeste Acosta

Abstract

Music is as universal as language itself across human culture. Music processing in the human brain is a dynamic and complex interplay of sensory, cognitive, and emotional functions that promotes healthy amounts of brain activity. The use of music as a nonpharmacological treatment is actively being researched for its potential in treating and managing symptoms associated with neurological disorders Parkinson's disease (PD), Alzheimer's disease (AD), and Alzheimer's disease-related dementias (ADRD), or sudden brain injury such as a stroke. This paper will discuss the anatomical hallmarks of music processing, which sets the foundation for discussing the dynamic activation of other brain regions notably affected by Alzheimer's disease. We will discuss the imaging studies that engaged multiple brain regions that allowed researchers to conclude how Music-Based Interventions (MBIs) potentially contribute to the enhancement of networks and pathways involved in sensory and motor processes and AD patient psychopathological outcomes.

Music Processing in the Brain

Music, a ubiquitous aspect of the human experience, can transport us through a multitude of physical sensations in milliseconds, yet it begins as something we can't see, touch or smell: tiny vibrations that swirl through the air. Those unique vibrations form notes, which merge into something more complex. It starts as a tune, then a melody, and before you know it, you're humming along to a song you first listened to at a cafe one afternoon many years ago. But your brain is tricked into thinking it's back in that moment once again, reanimating the neurons that sparked vividly while the song kept playing, even giving you the same goosebumps that had emerged on your skin back then. Music processing begins its journey in the inner ears, where acoustic data transforms into an electric signal via the cochlea. This signal travels through the auditory nerve to the brain stem, specifically to the inferior colliculus– the main area where fundamental sound features like periodicity and intensity undergo initial processing. Then, auditory information is sent to the thalamus, where all sensory information is relayed except smell, to finally arrive at the auditory cortex (AC). The AC directly projects to limbic structures, i.e., amygdala and medial orbitofrontal cortex (LeDoux, 2000). The primary AC also interacts with the superior temporal areas which further analyze acoustic cues, frequency, pitch, sound level, tempo changes, motion, and spatial locations. The left AC is more attuned to process temporal information, while the right AC in spectral resolution, contributing to the lateralization of speech in the left hemisphere and music right hemisphere (Hall et al., 2003). These fundamental structures of the auditory cortex work are what make the most basic sound processing possible.

However, music processing and further perception involves regions that go a bit beyond basic sound processing. Neuroimaging, primarily fMRI studies, have shown that music engages a larger network of cortical regions including the inferior and medial prefrontal cortex, premotor cortex, anterior and posterior parts of the superior temporal gyrus, and the inferior parietal lobe (Janata et al., 2002) (Patel, 2003).

An emotion-inducing piece of music also activates the regions deep in the limbic system–such as the midbrain, the basal ganglia (primarily the nucleus accumbens of the striatum), the amygdala, and the aforementioned hippocampus and cingulate cortex which are also involved in the processing of memory. The group of researchers led by Blood et al. in 2001, were the first to publish results that showed evidence of music producing intense pleasure via PET scans. The scans showed increased blood flow to the areas ventral striatum, midbrain, amygdala, orbitofrontal cortex, and ventral medial prefrontal cortex (also involved in music memory), which were previously known to be activated during in response to "euphoria-inducing stimuli" (Blood et al., 2001). Moreover, the perception of music rhythm, synchronized movement to its beat, and music production via singing or playing an instrument engage the sensory-motor networks of the brain (Grahn et al. 2009). These encompass regions in the cerebellum, basal ganglia, and the motor and somatosensory cortices (Zatorre et al., 2007).

Based on comprehensive imaging data, researchers have developed an anatomical delineation of pivotal brain regions implicated in music processing, as illustrated in Figure 1. This foundational knowledge is crucial to know in order to grasp the potential therapeutic advantages and outcomes of Music-Based Interventions.

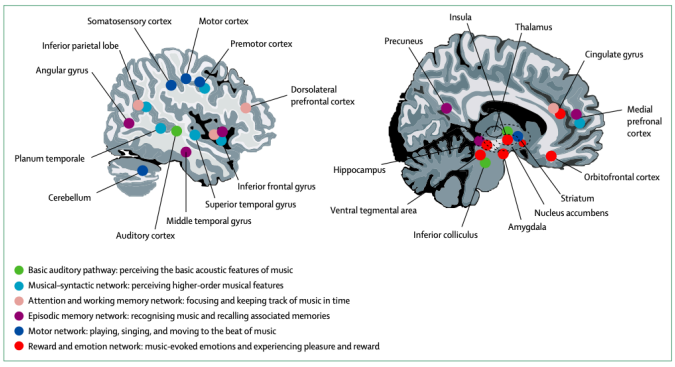

Figure 1. Key brain areas associated with music processing. Adapted from Särkämö and colleagues (Sihvonen et al., 2017)

Structures Affected by Alzheimer's Disease

As we delve into the complexities of Alzheimer's Disease (AD), it's important to keep in mind our ultimate focus: understanding how Music-Based Interventions (MBIs) can offer new pathways in AD treatment. The progression of AD, marked by distinct neuropathological stages, sheds light on why and how MBIs might be uniquely poised to mitigate some of the cognitive and emotional deficits caused by this disease. Alzheimer's disease (AD) unfolds in distinctive neuropathological stages which start with the early accumulation of beta-amyloid plaques and the formation of tau tangles within the cell. In the mild cognitive impairment (MCI) stage, cognitive decline becomes noticeable, signaling dysfunction at the neuronal level. Progressing to the moderate stage, tau pathology spreads, which eventually impacts deep limbic and cortical regions involved in memory processing, ensuing widespread neuronal cell death (Ardent, 2009). At this point of AD, major deficits in memory, behavior, and emotions are noticeable and the major cause of decline in not just overall health but also quality of life (Alzheimer's Association, 2023). With modern imaging techniques, researchers are now able to accurately map the structures of the brain that are affected by AD– which can aid the further development of therapeutic treatment options that can target these areas.

Using quantitative in vivo MRI techniques comparing healthy and AD brains, researchers noted initial structural changes in the medial temporal lobe, specifically the entorhinal cortex (deToledo, 2000). Further MRI studies combined with a series of linear regression showed that dysfunction in the entorhinal cortex disrupts communication between hippocampus and the prefrontal cortex (PFC) of the medial temporal lobe, which leads to more noticeable loss of function in memory, behavior, and emotional regulation (Killany et al., 2002). Connecting what we know about the areas uniquely activated by music processing and the areas affected in the progression of AD, the use of MBI's has potential to more directly stimulate areas deep within the cortex. More recent evidence also points to the limbic system regions–which include the amygdala, ventral striatum, and insular cortex–as playing a crucial role in the development of loss of memory and emotional regulation (Peck, 2016). The amygdala, a crucial structure for emotional processing in the medial temporal lobe, is affected even in the early stages of AD according to Poulin et al. in 2011. Previous research shows that music can evoke a strong emotional response because it activates these areas of the limbic system as well. There are major overlaps between structures affected in AD and structures that involve music processing– this simple observation is what has propelled the development of MBIs as a plausible form of therapeutic intervention for patients affected by AD and other dementias.

Music Based Interventions

Music Based Interventions (MBI's) were first developed in a series of workshops sponsored by the NIH in 2022 and have since published the NIH Music Based Intervention Toolkit (Edwards et al. 2023) which is a comprehensive paper delineating the main pillars of MBI's and how to best integrate it as a non-pharmacological treatment for AD and other neurologic disorders. There is no current standard definition of an MBI because they are unique to each patient in regard to the music style, listening mode, cultural background, and personal significance.

It is also important to recognize the current model of care for dementia and where MBI's fit into the current "standard". According to the Alzheimer's Association in 2018, there are a set of recommendations for each category of patient centered treatment models. The integration of MBI's would be most appropriate under Care of Behavioral and Psychological Symptoms of Dementia (BPSD), more specifically under the second recommendation of care developed by Scales et al. in 2018, which states to "implement nonpharmacological practices that are person-centered, evidence-based, and feasible in the care setting" (Fazio et al., 2018)

Despite the novelty of MBIs, there is research from the past decade that has already explored the potential therapeutic effect of music that provides insight on the efficacy of MBIs. Särkämö et al. completed three different studies over the course of 2014-2016 regarding music listening versus music singing compared to standard care for dementia and AD. Both music listening and singing groups showed improvements in behavioral disturbances and physical signs compared to the control group. While these effects weren't sustained after 6 months, singing notably enhanced working memory in mild dementia and maintained executive function and orientation in young people with dementia. Music listening supported general cognition, working memory, and quality of life, particularly in moderate dementia without Alzheimer's in institutional care. Both interventions alleviated depression, regardless of musical background. Music listening improved mood, general orientation, episodic memory, attention, executive functions, overall cognitive performance, and quality of life.This was a decently sized, single blind study with a total of 83 participants. A slightly larger study (n=100) investigated the effects of group music therapy versus standard care alone, and these results showed group music therapy not only decreased depression but also delayed the deterioration of cognitive functions, especially recall. More importantly, these effects persisted 1 month after they stopped the intervention (Chu et al., 2014). Interestingly, music familiar to the listener distinctly activates the anterior cingulate and medial prefrontal cortex in a healthy brain, indicating their significance in musical memory (Jacobsen et al., 2015). In AD individuals, the medial prefrontal cortex experiences a slower degeneration compared to other cortical areas. Moreover, the regions responsible for encoding musical memory exhibit minimal atrophy or decline in glucose metabolism, despite similar amyloid-β deposition when compared to other cortical regions. These findings potentially explain why Alzheimer's patients can still recognize and emotionally respond to familiar songs, even in advanced stages of the disease (Jacobsen et al., 2015).

Conclusion

Music, in its simplest form, dynamically engages sensory, cognitive, and emotional functions in the human brain. Understanding the neurological pathways of music processing in the brain is one of many facets that involve the further development of Music-Based Interventions as a nonpharmacological treatment for neurological disorders. MBIs show promise in enhancing networks crucial for sensory, motor processes, emotions, and memory. While there are still major improvements to be made in terms of further data collection process and understanding of the molecular dynamics of music processing in the human brain, the current exploration of music's therapeutic benefits represents a progressive shift toward addressing the complexities of brain disorders associated with different types of dementia. Other limitations of MBIs that could be addressed pertain to the duration of the effects of treatment and the factors that most influence the effects of the treatments to be sustained. Overall, MBIs emerge as an accessible and non-invasive treatment option in addition to traditional therapies, offering potential improvements in AD patient outcomes.

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How Do “Walk-Up” Songs Work: Links Between Music and Athletic Performance

Isabelle Afshari

Abstract

Baseball players have “walk-up” songs, Olympians make “pump-up” playlists, and Super Bowl player listen to “hype music” playlists before going on to score game-winning touchdowns. However, this habit may not be a mere placebo; music has been shown to have a neurological effect that allows athletes to improve their performance. Music works with the brain to create a heightened level of arousal, which is reflected through improvements in athletic performance. These improvements are also influenced by specific aspects of music, including tempo and personal connection. Therefore, music is used by athletes every day to truly push themselves to have influential effects on their performance.

Tempo and Athletic Performance

At surface level, music can improve athletic performance by making the exercises more enjoyable. With endless options of personalization playlists, individuals can tailor their workout soundtrack to fit their personal taste. However, the composition of songs that athletes listen to make a sizable difference in their performance. The tempo, or speed, of a song influences the physical speed of athletes. Songs with tempos between 120 and 130 beats per minute (BPM) ignite a high level of neurological arousal in athletes, whereas songs with tempos between 70 and 90 BPM evoke lower levels of arousal (Adams, 2022).

Neurological arousal refers to how the brain biologically responds to the music, and how these reactions are mirrored by improvements in physical performance. The brain’s arousal system affects the spinal cord; this activity ultimately results in the stimulation of muscle tone in addition to sensory-motor responsiveness and activity (Jones, 2003). These physical effects heighten the responsiveness of the body, which in turn would optimize conditions for movement and improve physical performance. In addition, higher arousal levels are associated with faster performance times and longer endurance; lower levels of arousal indicate stagnancy or a decrease in athletic performance.

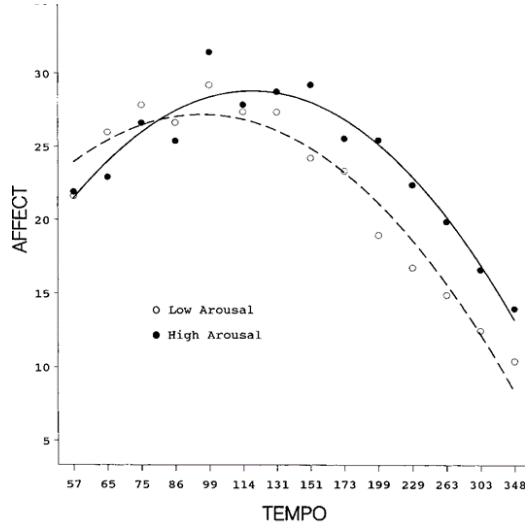

Figure 1. Optimal tempos of music to increase arousal level (M. Holbrook and Punam Anand, 1990).

However, choosing specific tempos to evoke varied levels of arousal is only beneficial if the effect of the tempo matches the intended effect of the exercise. For example, sprints would be benefitted by music with a faster BPM, but would be negatively affected by a slower BPM. Athletes tend to synchronize their movements with the beats of the music they are listening to; therefore, an increased tempo, or number of BPM, would result in an increased rate of motion in exercise (Pope, 2023).

Music and Brain Activity

More so than just increasing the speed of movements, listening to music while exercising results in the activation of various portions of the brain. Corianne Rogalsky, an assistant professor of speech and hearing science at Arizona State University, used fMRIs to track the blood flow of the brain as athletes listen to music and found that the amygdala, a center of emotions, is stimulated, which increases the consolidation of memory (White, 2019). Therefore, the music athletes listen to can trigger emotional memories that are associated with the music they choose, and these memories can bring athletes into a focused headspace for their games or competitions.

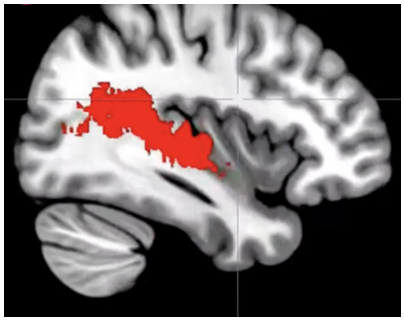

Figure 2. Functional MRI scan tracking blood flow of an individual listening to music (Kirk, 2019).

Furthermore, listening to music decreases the movement of cortisol, the main stress hormone of the human body, from the temporal lobe and impacts coordination by allowing the motor cortex to synchronize the physical movements of an athlete with the music that is presented (Strum, 2016). By decreasing cortisol levels in the bloodstream, music also decreases the stress of athletes. The synchronicity of physical movements and music allow for athletes to execute

more controlled motions which could benefit their performance. Various types of music also have a physiological impact on performance, with more invigorating music increasing levels of adrenaline and more relaxing music decreasing these levels (Kinesiol, 2021). When athletes listen to music while working out, their performance is likely to improve because of a rise in adrenaline levels. These increases in adrenaline have undoubtedly positive effects. Higher adrenaline levels lead to increased alertness, faster heart rate and breathing, and the reallocation of blood from digestive organs. There is no risk for having raised adrenaline levels unless they come from a source other than the adrenal gland, such as a pheochromocytoma, a type of tumor (Cleveland Clinic, n.d.). Increases in adrenaline levels have a positive impact on the performance of athletes because they lead to physical effects that are desirable when performing physical activity, and there are no physiological consequences of these increases if they are solely due to music that is presented. This makes upbeat music a source of improvement for athletes that has no risk involved.

Conclusion

Athletes that listen to music have improved physical performance, particularly if the music is upbeat or carries sentimental value. However, the power of music can be shared beyond Olympians and professional baseball players. With proven physiological effects, including neurological arousal, increased motor synchronicity, and raised adrenaline levels, music can make a sizable difference in the way a person's body functions when engaging in physical activity. Although the exploration of the connection between music and physical performance is still new, research will continue to explore new avenues of the connection, which may include if specific genres of music are proven to be most effective for certain workouts or if the use of music while exercising long-term can build up to lead to greater improvements in physical performance. As baseball players use their "walk-up" songs, Olympians make "pump-up" playlists, and Super Bowl winners listen to "hype music" playlists, music can just as easily help individuals embark on improving physical performance in their everyday lives, using playlists to hit a new personal record at the gym, to push through in the last five minutes of a run, or even get the adrenaline rush that will lead to motivation for the day.

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Revolutionizing Treatment: Gene Therapy Offers Hope for Hurler Syndrome

Krisha Agarwal

Abstract

Hurler Syndrome, also known as mucopolysaccharidosis type I (MPS I), is a rare lysosomal disorder wherein genetic mutations prevent the synthesis of enzyme IDUA, disrupting the breakdown of sugar molecules. This autosomal recessive condition targets newborns and causes physical and cognitive abnormalities, potentially resulting in brain damage (Cleveland Clinic, 2022). Current treatments include bone marrow transplants, which are not only dangerous but also an unfavorable solution for progressive brain damage. Recently, a new form of gene therapy, Proprietary System (PS) gene editing, has shown promising results in mice as a treatment method, as concluded by researchers at the University of Minnesota. Using high-resolution resting-state functional MRI (rs-fMRI) technology, researchers could support normal neural connections using liver enzymes. This advanced approach also helps monitor brain connectivity in other lysosomal disorders affecting brain function (University of Minnesota, 2023).

Lysosomal Storage Diseases

Lysosomes, integral to cellular function, are specialized membrane-bound organelles that house digestive enzymes. These organelles consist of luminal proteins, membrane-integral proteins, and associated proteins, which all play a crucial role in cellular processes. However, when these components are affected by congenital metabolic single-gene errors, known as lysosomal storage diseases (LSDs), the intricate balance within lysosomes is disrupted. This disruption arises from mutations in lysosome-encoding genes located on a specific chromosome locus, leading to the transcription of defective lysosomes.

The consequences of these disorders extend beyond the molecular level, manifesting as cell swelling and eventual organ dysfunction at the sites of substrate accumulation. This, in turn, significantly contributes to morbidity and mortality. Notably, the impact is more pronounced in infants and children, as their developing brains exhibit heightened vulnerability to dysfunction (Rajkumar, Dumpa, 2023).

Hurler Syndrome

Hurler Syndrome (MPS I), discovered by German pediatrician Gertrud Hurler in 1919, stands among the 11 disorders of mucopolysaccharidoses (MPS), impacting roughly 1 in 100,000 births. This neurodegenerative condition arises from a mutation in a gene on chromosome 4, tasked with encoding the lysosomal enzyme α-L-iduronidase (IDUA). IDUA plays a pivotal role in breaking down glycosaminoglycans (GAG), such as dermatan sulfate and heparin sulfate. The overaccumulation of GAG leads to the enlargement and thickening of organs like the heart, spleen, and muscles, while also impairing synapses within the central nervous system.

Typically, symptoms of Hurler Syndrome manifest in the first year of a child's life. Unfortunately, the average age of mortality is five years, with the majority of patients not surviving beyond ten years. Indications of the disorder progressive developmental delay, respiratory infections, and cardiac manifestations. Diagnosis involves clinical examinations of urinary GAG levels and DNA analysis. To expand upon the latter point, gene sequencing aids in identifying inheritable mutations and facilitates improved family planning. In contrast, treatments primarily target symptoms of the disorder rather than their underlying abnormalities. Options like enzyme replacement therapy (ERT) through intravenous injections of recombinant IDUA and hematopoietic stem cell transplants (HSCT) offer some relief. HSCT gradually substitutes donor-derived, enzyme-competent cells for hematopoietic cells lacking enzymes (Sakuru, Bollu, 2023). However, it is important to note that ERT cannot cross the blood-brain barrier, limiting its efficacy in curing the central nervous system, a critical concern for severe MPS I patients (Concolino et al., 2018). Additional interventions may include surgical procedures such as cardiac valve replacement and spinal decompression to address specific symptoms (Sakuru, Bollu, 2023). Therefore, it is imperative to seek alternative therapies that are less risky.

Gene Therapy

Gene therapy is a dynamic field in biomedical science, orchestrating the modulation of gene expression to reshape the biological function of living cells. This versatile approach offers the capacity to replace defective genes with healthy counterparts, inactivate disease-causing genes, or introduce modified genes to treat specific diseases. Therefore, it presents effective applications in conditions like cancer, cystic fibrosis, and diabetes.

The procedural aspect involves the introduction of genes into the body via carriers known as vectors, with viruses being the primary vehicles due to their ability to recognize target cells and facilitate genetic transfer. Figure 1 portrays a simplified diagram of the method. However, amidst the promises of gene therapy lie inherent risks.

As the body encounters the introduced viral vectors, an undesired immune response may ensue, potentially resulting in inflammation and, in severe cases, organ failure. Precision errors with the vectors may lead to unintended targeting, affecting healthy cells, or causing infections. Missteps in gene insertions hold the potential for tumor formation (Mayo Clinic, 2017).

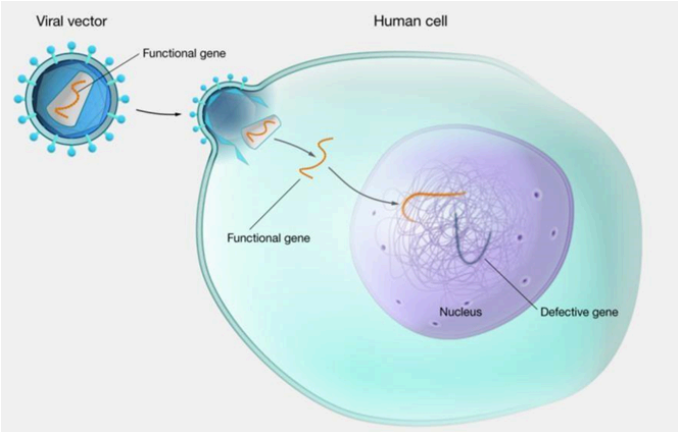

Figure 1. Diagrammatic representation of gene therapy technique (National Human Genome Research Institute, 2024)

Proprietary System Gene Editing to Treat Hurler Syndrome

Researchers at the University of Minnesota have pioneered a Proprietary System (PS) for gene editing aimed at treating Hurler Syndrome in neonatal mice. This innovative technique, represented in Figure 2, involves the action of Cas9, which induces a double-stranded break at the intron 1 locus of liver protein albumin. Simultaneously, the guide RNA (gRNA) synthesizes therapeutic transgene promoterless IDUA cDNA.

The method employs homology-directed repair to introduce the splicing acceptor, IDUA cDNA, and poly(A) sequence into the target, forming a cohesive genetic structure. Alternatively, nonhomologous end-joining pathways come into play, incorporating the donor template at the double-stranded break. This results in the creation of a hybrid sequence of albumin exon 1 and IDUA sequence. Therefore, PS gene editing is versatile, seamlessly functioning in both dividing and nondividing pathways.

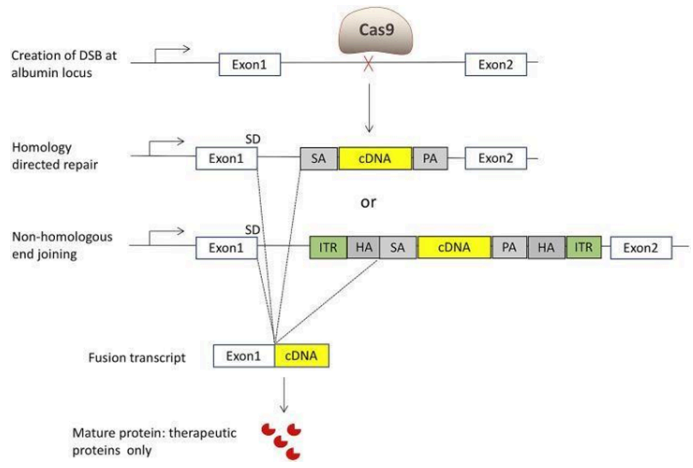

Figure 2. A diagrammatic representation of the molecular mechanism of PS gene editing (Ou et al. 2020)

The highly expressed endogenous albumin promoter assumes a pivotal role in governing the transgene's expression, with its benefits harnessed through a mechanism known as cross-correction. In this process, a lysosomal enzyme produced by one cell is released and subsequently internalized by another cell. This facilitates the degradation of stored materials, culminating in metabolic correction. To prevent transgene expression in the central nervous system, the researchers strategically employed liver-specific human IDUA.

The technique showed positive results, as evidenced by elevated IDUA activity and reduced GAG levels in both the liver and brain. The findings suggest that maintaining a consistently elevated level of IDUA in the bloodstream leads to a modest yet sufficient entry of IDUA into the brain. Notably, a particular gRNA,5′-GTATCTTTGATGACAATAATGGGGGAT-3′, demonstrated the highest efficiency in driving therapeutic effects.

The inherent advantage of PS gene editing lies in its potential to yield elevated enzyme levels with a single administration. This efficiency arises from the increased likelihood of successfully edited hepatocytes. Consequently, the application of PS gene editing opens avenues for administering reduced doses of the adeno-associated virus (AAV) vector for the treatment of LSDs. This not only mitigates toxicity but also streamlines vector production, thereby reducing overall costs.

The significance of this approach becomes pronounced in the context of LSD patients, particularly children, where uninterrupted cell division is essential for normal growth. Traditional AAV gene therapy encounters a significant hurdle in the form of vector dilution as children undergo growth and maturation. The primary merit of PS lies in its potential to confer sustained therapeutic benefits throughout an individual's life, ensuring ongoing efficacy beyond the initial post-treatment years (Ou et al., 2020).

Using resting state functional MRI (rs-fMRI) to Map MPS I

High-resolution resting state functional MRI (rs-fMRI) emerges as a non-invasive and whole-brain activity imaging technique for the diagnosis and post-treatment evaluation of MPS I. This tool examines the spontaneous blood oxygenation level-dependent fluctuations across various brain regions without stimulation. Clinically, rs-fMRI has successfully identified multiple resting state networks (RSNs) in conditions such as Alzheimer's disease, major depression, and schizophrenia. These results emphasize the foundational role of neural network deficits and interconnectivity in certain neurological disorders.

Scientists at the University of Minnesota hypothesized that the observed deficits in learning memory and spatial navigation in MPS I are influenced by alterations in limbic network connectivity. Hence, rs-fMRI is proposed as a sensitive imaging tool to assess compromised RSNs in the

MPS I brain and track their restoration following gene treatment.

As seen in Figure 3, in the realm of rs-fMRI, the examination of wild-type mice highlighted robust functional connectivity throughout the brain. Conversely, MPS I mice exhibited weakened and altered connections in crucial cortical and subcortical regions associated with learning, memory, and sensorimotor behavior. Notably, researchers observed a significant loss of functional connectivity in default mode networks, including the retrosplenial cortex, thalamus, and hippocampus. However, MPS I mice treated with gene therapy displayed a restoration of functional connections between the anterior cingulate and motor cortex, dorsal striatum, and hippocampus.

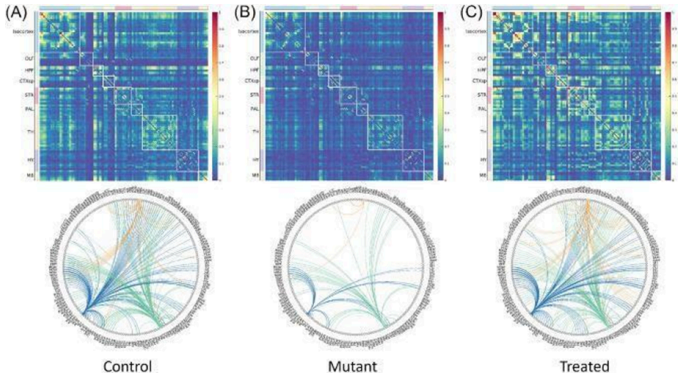

Figure 3. Correlation matrices and circular graphs of functional brain connections between (**A**) control, (**B**) MPS I, and (**C**) MPS I treated mice. Blue-connectome with connections at anterior cingulate area, green-connectome with connections at Ammon's horn, and yellow-connectome with connections at mediodorsal nucleus of thalamus. Brain connectome is sporadic for mutant but recovers after treatment. (Zhu et al., 2023)

The rs-fMRI findings reinforce the notion that Hurler Syndrome impacts synapse formation, leading to diminished neural connectivity. The observed dysfunction in hippocampal connectivity with the retrosplenial cortex holds implications for spatial navigation performance. These results bear clinical relevance for the diagnosis, monitoring, and treatment of Hurler Syndrome.

Furthermore, rs-fMRI's translational potential extends to the clinical analysis of other human neurological disorders and gene therapy outcomes (Zhu et al., 2023).

Conclusion

This comprehensive exploration provides valuable insights into Hurler Syndrome and underscores the promising avenues offered by gene therapy, particularly through PS gene editing. Traditional treatments for Hurler Syndrome emphasize the necessity for more targeted interventions addressing the root cause, and gene therapy, a burgeoning field with transformative potential, emerges as a beacon of hope.

PS gene editing marks a significant stride in pursuing effective and sustainable treatments for Hurler Syndrome. The insights gained from rs-fMRI not only enhance our understanding of the neurological deficits associated with Hurler Syndrome but position rs-fMRI as a promising diagnostic and therapeutic imaging technique. As scientists navigate this frontier of knowledge, the potential for transformative breakthroughs in treating Hurler Syndrome and related disorders becomes increasingly tangible.

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Unraveling the Links Between Synesthesia and Autism

Sarah Masud

Abstract

While synesthesia and autism may not appear to be related at the surface level, they share common features such as hypersensitivity and enhanced perception, increased attention to detail, and atypical neural connectivity. Synesthesia was found to be more common in autism and oddly not schizophrenia, another disorder of altered perception; however, this increased prevalence does not generalize to all forms of synesthesia and autism, and studies suggest that synesthesia is more common when autism co-occurs with savant skills. Although more research needs to be conducted on whether there is a biological link, similarities between the two conditions could be explained by similar underlying neural mechanisms. As synesthesia and autism share similar theoretical models in terms of hyperexcitability and perception of the world, there may be a link between the two that makes them often co-occur.

Introduction

Do you often associate sounds with different colors? Or perhaps different textures trigger different tastes? If an association is strong enough between inducing stimuli and concurrent sensations and exhibits high consistency throughout life, you may be described as a synesthete. Synesthesia is a neurodevelopmental condition in which specific sensory inputs such as letters, sounds, tastes, or smells automatically and involuntarily trigger additional sensations such as texture, color, or shape (van Leeuwen et al., 2020). Although any combination of inducing inputs and concurrent sensations is hypothetically possible, the most common inducers are linguistic while the most common concurrents are visual, such as colors or shapes; overall, the most common type is grapheme-color synesthesia, where letters or numbers trigger color sensations (Simner et al., 2006).

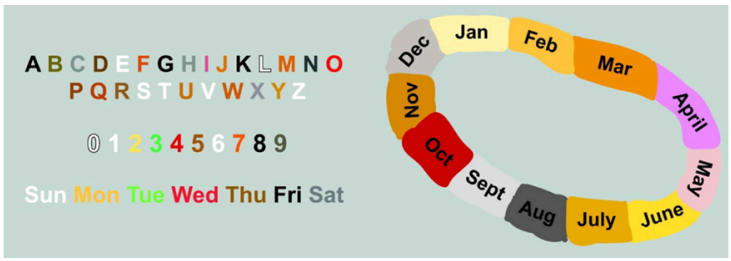

Figure 1. Examples of how letters, numbers, days of the week, and months may induce different color sensations in synesthetes (van Leeuwen et al., 2020).

Although synesthesia is a relatively rare condition, research has shown that it is more prevalent in individuals with autism spectrum disorder. Autism is a neurodevelopmental condition characterized by difficulties in social interaction and communication as well as patterns of restricted and repetitive behaviors, interests, or activities (van Leeuwen et al., 2021). 10% of autistic individuals also have savant abilities or skills that are exceptionally above average, and 50% of those with savant skills have autism (Treffert, 2009). While the relation of autism to synesthesia may not be clear at first, another diagnostic criterion for autism is altered sensory perception—which can be either hyposensitivity or hypersensitivity—and many autistic individuals pay increased attention to details. Hypersensitivity and enhanced perception are also traits of synesthesia, and there are similarities between autism and synesthesia regarding atypical neural connectivity and preference for local (detail-oriented) over global (big picture) visual processing (van Leeuwen et al., 2020). It is also hypothesized that the presence of savant skills plays an important role in determining the presence of synesthesia in autistic individuals (Hughes et al., 2017).

Though further research needs to be conducted to confirm whether there are underlying biological mechanisms connecting synesthesia and autism, the shared features and increased co-occurrence of the two conditions indicate that there may be a link between them. This paper will discuss precisely how much overlap there is between synesthesia and autism, theories as to why this overlap occurs, and the implications of these findings.

Is Synesthesia More Prevalent in Autism?

As a general estimate, synesthesia occurs in 4% of the population and autism occurs in 1% of the population. If these two neurodevelopmental conditions were to be independent of each other, the chance of them co-occurring would be about 0.04% or 4 in 10,000 people. Given how incredibly rare that is, it would be unlikely to ever meet someone with both synesthesia and autism. Baron-Cohen et al. (2013) conducted a study to investigate whether this base rate is accurate or if synesthesia is more common in autism.

After exclusions, 164 adults with professionally-diagnosed autism and 97 controls completed a synesthesia questionnaire, the Autism Spectrum Quotient (AQ), and the Test of Genuineness-Revised (ToG-R), which is used to validate self-reported synesthesia. It was found that the rate of synesthesia in autistic adults is 18.9%, almost three times greater than the rate of 7.22% in the control sample.

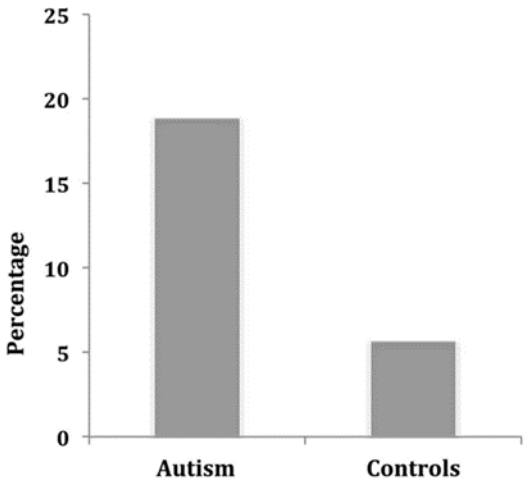

Figure 2. The percentage of people with synesthesia in the autism and control groups (Baron-Cohen et al., 2013).

The significant difference between the rate of synesthesia in autistic adults and the general population indicates that something is linking these two conditions and making them interdependent. This could perhaps be because they share underlying biological factors, such as enhanced local visual processing and hypersensitivity. There is also evidence that suggests synesthesia and autism are connected at multiple levels. A study by Gregerson et al. (2013) found a significant phenotypic and genotypic overlap between synesthesia and absolute pitch, which is the ability to identify or re-create a note on demand. This trait also has a higher prevalence in people with autism, suggesting that synesthesia and autism share several characteristics that result in the two often co-occurring.

However, there are issues of reliability and validity to be considered with any finding based on self-reported measures. The increased presence of synesthesia in autistic adults may be explained by individuals with autism being more likely to report abnormal sensory and perceptual experiences than those without autism. There were also three autistic participants who claimed not to have synesthesia, yet they were determined to be synesthetes based on their results on the synesthesia questionnaire; however, they were considered as non-synesthetes because they reported themselves as such. Because these participants declared they did not have synesthesia because they were unsure if their experiences counted, it is possible that the resulting rate was not an over-estimate, but instead an under-estimate. This study also has several limitations, the most critical one being that researchers were unable to collect complete consistency tests to validate the results. The sample also only included high-functioning autistic adults, and it would be interesting to see if these findings generalized to autistic children and more impaired autistic individuals.

Comparing Synesthesia in Autism and Schizophrenia

It is also worth questioning whether this increased prevalence of synesthesia is observed in other neurodevelopmental disorders or if it is specific to autism. One way to study this is by looking at relatives of synesthetes and whether certain disorders have a significantly higher chance of running in the family. Nugent & Ward (2022) investigated whether there is a familial aggregation between synesthesia and two disorders —autism and schizophrenia—as well as Type 1 diabetes as a control predicted to have no link to synesthesia. Both autism and schizophrenia were hypothesized to have a familial connection to synesthesia due to their shared features of altered sensory perception. After exclusions, 282 synesthetes and 281 non-synesthetes completed an online questionnaire, which resulted in collecting information about 1114 first-degree relatives of synesthetes and 1130 controls. Individuals were subsequently sorted into one of three groups: diagnosed autism, probable autism, and possible autism. Among participants, it was found that autism was more common in synesthetes (3.93% diagnosed, 3.57% probable, 2.14% possible) than in non-synesthetes (0.38% diagnosed, 0.38% probable, 1.91% possible). Among relatives, autism was also more common in first-degree relatives of synesthetes (2.98% diagnosed, 1.08% probable, 0.72% possible) than first-degree relatives of non-synaesthetes (1.68% diagnosed, 0.18% probable, 0.71% possible).

While an association between synesthesia and autism was observed, the results failed to indicate any link between synesthesia and schizophrenia at the individual or familial level. This finding was surprising considering that altered neural connectivity is also a characteristic of schizophrenia, like autism and synesthesia, and schizophrenic hallucinations and synesthetic experiences may both be explained by inflexible frameworks of sensory perception; that is, both groups are likely to distort sensory input to fit their internal models of the world even when faced with contradictory evidence. The key difference here may be that synesthetes are aware their sensory experiences are false.

However, this study has certain limitations, the most significant one being that there is no way to verify the truthfulness of the responses. The inclusion of a “prefer not to respond” option may be masking positive cases as well. Even assuming that all participants responded truthfully, there may still be intergroup variability in diagnosis-seeking behavior: synesthetes and their relatives may be more proactive in seeking an autism diagnosis than non-synesthetes. However, other evidence shows that high levels of autism are observed in synesthetes even without a formal autism diagnosis (van Leeuwen et al., 2019).

Considering Savant Skills’ Role in Synesthesia

One final thing to consider when measuring this co-occurrence is that it does not generalize to all types of synesthesia and autism. Considering that both conditions are conceptualized to lie on a spectrum with different characteristics across individuals, there may be an increased prevalence of certain types of synesthesia among certain types of autism. A study on this investigated whether synesthesia is indeed more common in autism or only when autism co-occurs with savant skills (Hughes et al., 2017).

Researchers tested three groups: 40 autism-savants, 34 autism-non-savants, and 29 controls without autism. Participants were asked whether they had a formal diagnosis of autism and completed a questionnaire on savant skills. Then, they were tested for grapheme-color synesthetes in total: one was a control, one was an autism-non-savant, and four were autism-savants. The prevalence of synesthesia in the autism-savant group (10%) was over seven times higher than the general population (1.4%) and held statistical significance, while no significant difference was observed for the control and autism-non-savant groups.

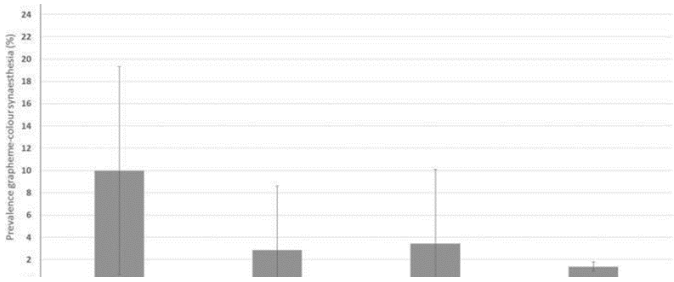

Figure 3. The prevalence of grapheme-color synesthesia in autism-savants, autism-non-savants, the control group, and the general population (Hughes et al., 2017).

A primary limitation of this study was that there is no objective test to assess for savant skills and the questionnaire involved self-reporting savant skills. It is likely that participants vary in how they perceive their own talents compared to the general population without an objective standard. Factors such as overestimating and under-estimating one's abilities as well as personality traits like modesty come into play. However, it is still worth questioning why synesthesia was more common in autism-savants and what the implications of these results are.

The first possible explanation is that synesthesia leads to savant skills because synesthetes are known to have improved memory. For example, if digits are encoded as both numbers and colors, they will have richer memory representations. This improved memory could then reach savant levels. Another possible explanation is that hyper-systemizing and veridical mapping are common in autism. Systemizing is the drive to identify patterns in rule-based information, and veridical mapping is the related ability to match two systems by their shared traits. In synesthesia and types of savant skills that require mapping two things, veridical mapping may then independently lead to both conditions, explaining why the two often co-occur with autism.

Shared Traits Between Synesthesia and Autism

Now that it is clear that synesthesia is more prevalent in autism, the next step is to ask why. What are the underlying mechanisms and shared characteristics that lead to this increased prevalence? Van Leeuwen et al. (2019) conducted a study to test the hypothesis that synesthesia and autism share atypical sensory sensitivity and perception. 76 synesthetes and 43 non-synesthetes completed a synesthesia screening questionnaire, the Autism Spectrum Quotient (AQ), and the Glasgow Sensory Questionnaire (GSQ), which assesses hypersensitivity and hyposensitivity across seven sensory modalities. Individuals with autism typically score higher on the GSQ than the general population, and it was hypothesized that synesthetes would score higher as well. Participants also completed a motion coherence task to assess for global motion processing and an embedded figures task to assess for local visual processing. The hypothesis was partially confirmed. Synesthetes scored higher than non-synesthetes on AQ-attention-to-detail, but not AQ-total. Synesthetes also showed GSQ scores positively correlated with AQ-attention-to-detail and higher scores on hypersensitivity subscales, but not hyposensitivity. Lastly, synesthetes performed poorer on detecting the global motion of direction in the motion coherence task and performed better on the most difficult level of local processing in the embedded figures task. High attention to detail, hypersensitivity, and bias towards local perception are all common characteristics of autism, and these findings suggest that synesthetes share these atypicalities.

These similarities between the two conditions could be explained by a shared underlying neural mechanism. There is evidence of local hyperconnectivity and reduced long-range connectivity in both synesthesia and autism, which would explain why both excel at tasks where global context, including long-range feedback, must be ignored. Another similarity lies in both groups showing atypical responses in the parvocellular system, which is the system responsible for processing spatial details and colors. This would explain why synesthetes and autistic individuals both exhibit enhanced perception of details and colors at the cost of reduced global motion processing.

Similar Theoretical Models of Synesthesia and Autism

Though little research has been done to conclude whether there is a clear biological explanation, Van Leeuwen suggests that there are possible theoretical models of perception in synesthesia and autism that account for their similarities (Van Leeuwen et al., (2020)). In autism, there is an imbalance between excitation and inhibition in the brain that leads to excitation not being met with sufficient inhibition (Orekhova et al., 2007). In synesthesia, the balance between excitation and inhibition has not been specifically measured, but there is evidence for hyperexcitability in the visual cortex for individuals with grapheme-color synesthesia (Terhune et al., 2011).

Predictive processing models of perception involve comparing "priors", or top-down knowledge based on one's past experiences, against incoming sensory information. A prior can be any knowledge structure that influences how sensory input is perceived, such as associating red with danger. If one has an over-reliance on priors, they may wrongly interpret every red item they see as dangerous. One version of this model proposes that people with autism have weaker priors and are therefore more likely to see the world as it is. This is especially interesting because synesthesia resembles the antithesis of this.

Rather than the hyper-real perception of the world in autism, synesthesia appears to be an over-reliance on priors similar to hallucinations in schizophrenia. So, how is it that synesthesia and autism co-occur so commonly? There is an alternative model of perception in autism that suggests that their priors are specific, narrow, and inflexible; therefore, a lot of incoming sensory information that contradicts their worldview is treated as surprising and unpredictable. This model is potentially more compatible with synesthesia, as autism and synesthesia may be similar in demonstrating excessively strong priors that lead to altered perception. Specific and inflexible priors are consistent with the imbalance between excitation and inhibition as well. If priors are too narrow to accurately predict incoming sensory signals, the brain will make more errors in predicting them. So, the different theoretical models of synesthesia and autism converge in this sense.

Conclusion

The shared features of hypersensitivity, enhanced perception, heightened attention to detail, and atypical neural connectivity suggest a link between synesthesia and autism. While studies indicate higher rates of synesthesia in individuals with autism, there are nuanced distinctions to be made when considering different manifestations of the two conditions, one particularly being the presence of autism with savant skills. However, the absence of a similar association with schizophrenia underscores the specificity of synesthesia and autism frequently co-occurring.

Evidence for a definitive biological link between synesthesia and autism still remains elusive, and these preliminary findings prompt a call for more research. As the complexities of neurodiversity are further explored, unraveling the links between synesthesia and autism will hopefully allow for deeper insights into the intricacies of the human brain and the diverse ways in which it perceives and interacts with the world.

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Mesenchymal Stem Cell Regenerative Therapy in the Spine - Recent Advancements and Possible Applications: A Review

Harrison Kennedy

Abstract

A spinal cord injury (SCI) is an injury which damages the central nervous system, particularly the neurons and structures located in the spine. Treatment options involving mesenchymal stem cells (MSCs) have recently been recognized as possible repair solutions to an SCI. MSCs have multifaceted functionality which allows for a wide range of applications; and, specifically for usage in the spine, MSCs do not contain immunogenic response agents, which makes them suitable for treatment involving the central nervous system. Clinical usage of MSCs has been proven successful in other facets of medicine, but the exact mechanisms by which they repair SCIs is not fully understood (Xia et al., 2023). Recent research, however, suggests MSC involvement in reducing neuronal inflammation, regenerating axons, and repairing spinal blood vessels (Staff, 2022). These new findings anticipate future advancements in the usage of MSCs conjunctively with neurorehabilitation therapies (Xia et al., 2023). Further speculations could even involve treatment for reversing paralysis, inhibiting glial scarring, and reducing neurological symptoms of SCIs all within the spine.

Introduction

As strides in medical advancements occur across the frontier between health and illness, one area continues to elude reliable treatment: the nervous system. Particularly concerning substantial injuries to the spinal cord, modes by which to reverse and heal damage are currently underdeveloped. One possible solution to this "last frontier" of medicine is regenerative spinal cord injury (SCI) therapy using mesenchymal stem cells (MSCs). This novel development is currently the focus of a multitude of reviews, trials, and examinations; its efficacy in treatment is being revealed as having great promise. This is a relevant issue considering that treating the nervous system is considered to be one of the final areas of medicine for humans to conquer. Additionally, SCIs are life-altering injuries, often disabling those who sustain them. In the United States alone, "there were 17,810 new SCI cases reported in 2020, with a total of 294,000 Americans living with SCI," a number that could significantly decrease with MSC therapy (Ma et al., 2022). MSCs have shown efficacy in aiding in the regeneration of neuronal tissue in many clinical trials and have evidence backing their properties that allow for them to be a prime candidate for SCI treatment. Such properties include "neuroprotection, immunomodulation, axon sprouting and/or regeneration, neuronal relay formation, and myelin regeneration, among other mechanisms," which reinforce the assertion that MSC therapy is among the best approaches for treating the complex pathophysiology of SCIs (Shang et al., 2022). Furthermore, the use of MSC therapy in conjunction with other neurodegenerative-focused therapies is being explored due to the multimodal facets of an SCI and their complex pathological conditions.

Timing and the Immune System

Mesenchymal stem cells (MSCs) are cells harvested from various tissues and contain the ability to proliferate into different types of specialized cells, including neurons. In the realm of the nervous tissue within the spine, MSCs have the distinct ability of aiding in overall regeneration thanks to their high proliferation abilities. This is fostered by their ability to release chemical factors that can influence cell interactions within the spinal cord, which is a useful tool in treating SCIs. Among cytokines and exosomes with anti-inflammatory abilities, MSCs also release "vascular endothelial growth factor (VEGF), nerve growth factor (NGF), glia-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF)", which not only allow for expedited nerve cell regeneration but also work to eliminate the effects of glial scarring, a major motor-inhibiting issue following SCI which can result in inflammation that stifles neuronal repairing and formation (Xia et al., 2023). Additionally, in major SCIs, the upregulation of endogenous neurotrophic factors often is not significant enough to produce meaningful regeneration or recovery in the trauma-affected areas. The need for an exogenous neurotrophic factor explains the effectiveness of GDNF and BDNF administered externally through MSC therapy.

Another important factor, VEGF, works in a different way to repair neuronal tissue through its vascularity; as an angiogenic factor, it promotes pericyte recruitment, which allows vascular tissues to mature and regenerate. Within the central nervous system (CNS), neurons and blood vessels work in units considered neurovascular units. These units allow VEGF to promote neuronal regeneration by enhancing the nutrient flow (Pan et al., 2013). Furthermore, VEGF mediates "vascular endothelial cell proliferation and migration, angiogenesis, and vascular permeability and leakage," enhancing the function of neuronal vascularity while appropriating the beneficial capacities of vascular components (Pan et al., 2013). Within the nervous system, vascular health is crucial due to the importance of blood supply for neuronal function and repairing sequences. Other growth factors such as NGF aid in the survival retention of neurons by enabling increased axonic regeneration.

NGF overproduction has been shown to improve functional recovery in a mouse model when administered following a SCI (Wang et al., 2021). After chemically modifying neural stem cells (NSCs) to overproduce NGF following a SCI, researchers found the motor functions of the affected limbs were generally improved, and, at the site of the trauma, the affected cells did not retain extreme pathological states over a prolonged timeline. This can be observed in Figure 1, which displays data showing the regenerative properties of NGF-modified NSCs. The introduction of NGFs appears to have shrunk the affected area of an SCI lesion and improved the motor function of the hindlimbs. This reinforces the assertion that NGF can regulate the neuronal environment and increase endogenous responses from certain neurons such as NSCs (Wang et al., 2021).

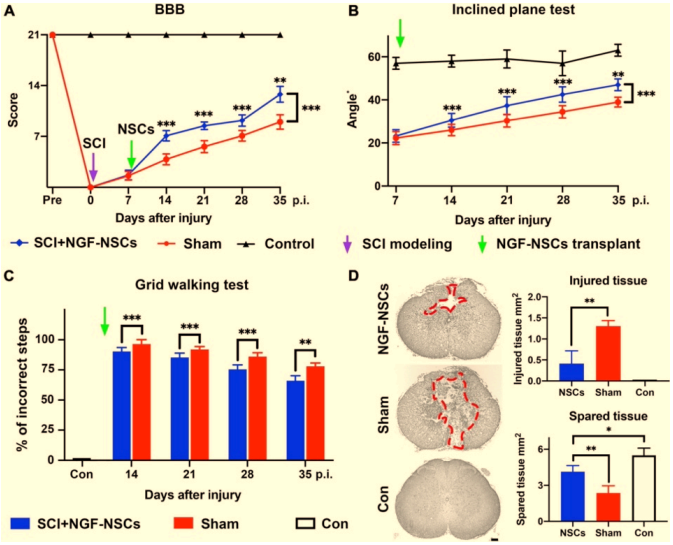

Figure 1. NGF-Modified NSCs

Figures A-C highlight the benefits of NGF-modified neural stem cells (NSCs) on "functional recovery of hindlimbs and alleviated histopathological damage after SCI" by analyzing the angular and quantitative improvements. Figure D shows the area of injured tissue 4 weeks after initial injury, circled by red dotted lines. This shows the minimized histopathological damage contained within the epicenter of the lesion when utilizing NGF-NSCs. After transplantation, rats with significant SCIs regained improved function of hindlimbs once they received treatment from NGF-NSCs.

Exogenous factors of the same chemical makeup have similar effects in regulating microenvironments and increasing regenerative ability. GDNF and BDNF are often linked with "β III tubulin, enolase 2, and microtubule associated protein 1b" (Xia et al., 2023). These neuromarkers have been shown to encourage microtubule health, axon regeneration, appropriate neuronal aging, and overall maintenance of synaptic areas. High level dosages of BDNF may also improve motor function, help maintain the recovering blood spinal cord barrier after SCIs, and improve neuronal regeneration (Muheremu et al., 2021). Sequentially, when GDNF is introduced to the SCI site, nerve cell density and motor function can increase. These neurotrophic factors, when paired with "recombinant proteins such as osmotic pumps, nanoparticles, viral vectors, as well as polymer scaffolds," can encourage the regeneration of the SCI-affected area of the spine by providing it with ample neurotrophic support (Muheremu et al., 2021). These various factors secreted by MSCs within the microenvironments of the neural tissue in the spinal cord chemically support regenerative capabilities and are therapeutic in the case of SCIs. Each factor in combination can change the effects of a SCI and be applied to regenerative therapies in humans. And, when paired with other therapeutic methods of inter-neural intervention, their positive effects can be amplified.

Clinical Applications and Recent Advancements

When an SCI occurs, endogenous repair is induced and cells, such as Schwann, myelinating, and regenerative cells, migrate to the trauma site to repair damaged tissue. There are positive benefits to this process, but the main problem stemming from endogenous repair is that axon growth is inhibited, and glial scarring often occurs due to oligodendrocyte myelin debris from the trauma (Nandoe Tewarie et al., 2009). Logistically, the introduction of MSCs to treat SCIs and combat the negative endogenous effects appears legitimate, but the methodology behind achieving similar results to the expected outcome in clinical trials is actually much more complicated. There are multiple factors to address regarding the introduction and transplantation of MSCs to an area of trauma including "mode of transplantation, dose and frequency of MSCs, timing of SCI, and type of SCI," which complicate the process of clinical research and require further studies to apply MSCs to SCI treatment effectively(Xia et al., 2023). This is due to the diversity in proliferation and differentiation that MSCs contain, as illustrated by Figure 2. With the exponential number of possibilities that MSCs contain, the implicating factors, such as the mode and timing of transplantation, complicate this even further. The standard mode of transplantation is a local injection within the site of a SCI, but MSC transplant injections into the subarachnoid space and intravenously are also common in clinical trials (Xia et al., 2023).

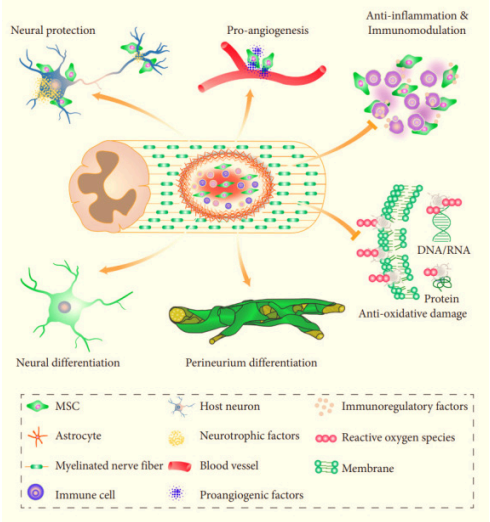

Figure 2. Properties of MSCs

A figure illustrating the multifaceted properties of MSCs, showing their ability to target various pathological conditions within a SCI (Ma et al., 2022). This emphasizes the proliferation abilities of MSCs to differentiate and offer support to various aspects of the neuronal and spinal tissues. Each image stemming off the initial stem cell source represents a unique use that they can serve within the human body.

The idea of enhancing MSCs through additive therapy and procedures is also being explored clinically. Methods such as pre-conditioning, three-dimensional cultures, genetic modifications, and pairing with neurorehabilitation show promise in enhancing capabilities of MSCs (Ma et al., 2022). One example of pre-conditioning, IFN-γ pretreatment, has been observed to aid in the release of chemical factors that give MSCs their immunosuppressive and immunomodulatory abilities (Ma et al., 2022). This is an important aspect within the spinal cord due to immunogenic complications common in the neural system, like glial scarring and microglia activity, as immunogens retroactively damage the neural tissue following an SCI. Alterations with oxygen levels of MSCs, such as hypoxic treatment followed by reoxygenation, seem to improve proliferative abilities and migratory actions of MSCs, allowing them to regenerate numbers and relocate to affected areas. Additionally, similar preliminary oxygen treatments have proved to enhance survival rates of MSCs, a common downfall when examining prolonged timelines and chronic SCIs. It is believed that within the spine, these benefits are due to an “up-regulation of cytokines,” like VEGF, which promote neuronal regeneration among other therapeutic effects (Ma et al., 2022). Similarly, using certain types of tissue engineering, the proliferation and survival of MSCs can be altered; one mode by which to achieve this is biomaterialistic scaffolding. Biomaterials within scaffolding can aid in cell survival, intercellular interactions, proliferation, and protection (Blando et al., 2022). By using certain gels, as well as synthetic and biological materials, the microenvironments in which MSCs are comfortable reproducing and releasing chemical factors in can be replicated (Xia et al., 2023). These “neurotrophic factor co-delivery” assisters can increase production of cytokines, promoting the regeneration of targeted areas of the spinal cord (Xia et al., 2023). Biomaterial scaffolds, such as “block copolymer of PLGA and poly-l-lysine (PLL) with a highly interconnected porous structure (approximately 250–500-μm-diameter pores),” when paired with MSC therapy, have clinically been proven to regenerate nerve tissue in rat models with SCIs as well as restore motor function (Ashammakhi et al., 2019). Additionally, Figure 3 shows the wide range of scaffolding methods available, and what benefits might come with each. The combinations of what materials to use and how to assemble them are numerous. This offers a view on how beneficial this method could be and how adaptable the possibilities are to address many distinct types of SCIs and lesions. A large factor in the dangers of spinal cord lesions and trauma is the loss of cells in the affected area and the following necrosis of tissue. This environment makes it hard to encourage cell-proliferation, and neuronal microenvironments of cell necrosis-affected tissues do not make suitable areas to introduce new cells. So, scaffolding MSCs with biomaterial can promote proliferation and tissue regeneration whilst inhibiting glial scarring and inflammation (Blando et al., 2022). The creation of a habitable extracellular matrix (ECM) can support “regenerative environment, differentiation, and trophic support” in the form of releasing factors that can regenerate tissues (Blando et al., 2022).

Clinically these assertions have shown merit as well. In a clinical trial involving patients with advanced SCIs, Yannan Zhao et al. found that biomaterial scaffolding paired with MSCs regenerated motor function of spinal cord transmission through the peripheral nervous system (PNS) (Blando et al., 2022). One patient, with a major thoracic SCI eventually regained the ability to walk after experiencing MSC scaffolding therapy, and another regained lower body control after losing it to a major cervical SCI. By using electrophysiology, researchers were able to determine that following treatment, the patients were able to conduct electrical transmission through the spinal cord more effectively than when paralysis was sustained.

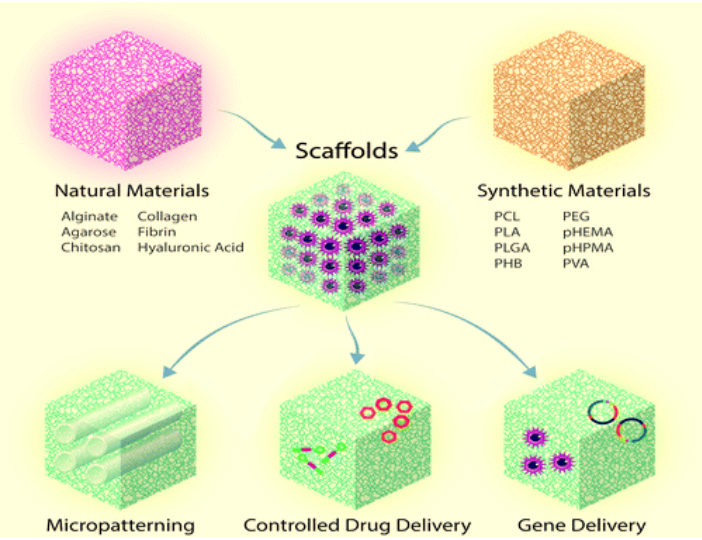

Figure 3. MSC Scaffolding

A figure displaying the ways by which scaffolds could be used to enhance the functionality of MSCs and allow for positive implications (Ashammakhi et al., 2019). Additionally, it illustrates the ways other therapy options like gene or controlled drug delivery can be utilized to enhance these effects. The three images following the arrows below the Scaffolds figure in the middle represent implementations of scaffolding. The two images above the middle image represent the materials (both synthetic and natural) used in scaffolding.

Another mode by which to influence the effectiveness of MSCs in treating SCIs is through pre-injection gene modification. After genetically modifying rat MSCs to express MNTS1, “a multineurotrophin that binds TrkA, TrkB and TrkC, and p75(NTR) receptors or MSC-MNTS1/p75(-) that binds mainly to the Trk receptors,” Gentaro Kumagai et al. injected the genetically modified MSCs to the central affected area of a contusive SCI (Kumagai et al., 2013). This resulted in promotion of angiogenesis, enhanced axonal growth, reduced inflammation and glial scarring, and various other positive factors after regenerative SCI therapy (Kumagai et al., 2013). Additionally, MSCs genetically modified to release growth-factor-1, an insulin-like factor, exhibit better survival and capacity to improve myelination (Xia et al., 2023). As found by Yuan-haun Ma et al., the use of genetic modifications and tissue engineering like biomaterial scaffolding, produced greater functionality and motor rehabilitation in animal spine models (Xia et al., 2023). Additionally, related to the secretions of MSCs that give them regenerative properties, three-dimensional scaffolding and tissue engineering can increase the expression of specialized neurotrophic factors like BDNF and GDNF, which expedite

nerve cell axonal regeneration and minimize the effects of glial scarring. Furthermore, neurorehabilitation can be paired with these modes by which to transplant MSCs to enhance their regenerative capabilities. Studies have shown that physical and mental activities such as “treadmill training, electrical stimulation, electroacupuncture, transcranial magnetic stimulation (TMS), ultrashort wave therapy, and swimming training,” enhance the effects of MSC transplant therapy after a SCI (Xia et al., 2023). The hypothesis that CNS controls aspects of the PNS can promote rehabilitation within the neural tissue of the spine that controls muscle motor activity. Another important aspect of understanding the importance of the mode by which to transplant MSCs is the form of injection. The most used is intravenous (IV), intrathecal (IT), and intralesional (IL) injections, each with their own benefits and drawbacks (Xia et al., 2023). While IL injections have been observed to be effective in locating MSCs to the site of the initial SCI trauma, it is normally an intricate procedure with a lot of room for error, especially when dealing with already damaged cell tissue. The risks of further damage or contamination of spinal tissue outweigh the efficacy of an IL injection of MSCs, pushing for the exploration of other injection modes. IT and IV injections are not only less invasive but also easier operations to perform. Furthermore, IT injections are generally more effective “in terms of cell engraftment and safety” (17). Additionally, it has been established that IT injections can be a noninvasive and safe therapy when trying to improve neuronal functioning and motor capabilities in humans, including the general rehabilitation of spinal cord tissue (Bydon et al., 2019). According to Mohamad Bydon et al., IT injections improved both objective and subjective measures of recovery in patients, as established in a human clinical trial involving 14 patients suffering from SCIs (Bydon et al., 2019). With each MSC transplantation method having different benefits and drawbacks, there is no end-all, best method. Each method can be utilized in many ways, and through clinical research, the consensus is in favor of the idea that in cases of SCIs, it is more advantageous to utilize multiple different injection methods to transplant MSCs.

Clinical Applications and Recent Advancements

While there are plentiful examples of clinical studies, not many are standardized or contain large enough sample sizes to draw supported conclusions. One study, however, unified a large quantity of results regarding MSC therapy in SCIs into a single meta-analysis using data from 62 clinical trials. To address “how much scientific evidence there is to support the sufficiency of stem cell therapy in preclinical and clinical studies of SCIs”, Zhinzhong Shang et al. analyzed 62 clinical trials involving 2,439 patients (Shang et al., 2022). After extracting data, it was observed that in 48.9% of patients receiving MSC therapy, their American Spinal Injury Association (ASIA) impairment scale score, a neurological assessment that takes sensory and motor ability of the spinal cord into account, improved by at least one grade. There are mechanisms by which MSCs work that are not understood due to the discrepancy between expected success and actual success of the treatment.

Additionally, Zhinzhong et al. found that side effects such as “neuropathic pain, abnormal feeling, muscle spasms, vomiting, and urinary tract infection were (the most) common, with an incidence of > 20%.” The likelihood and inexplicable nature of these side effects are most concerning (Shang et al., 2022). This demonstrates the premature excitement regarding MSC transplantation therapy, as there is still so much more to address and understand, especially regarding the effectiveness and risks. Currently, the main problem in analyzing contemporary data is its scarcity. This highlights the importance of promoting research; with time, sufficient data will become available to make accurate conclusions without doubts.

Overall, these current clinical applications make integration of MSCs in the cases of SCIs, more realistic and feasible when regenerating tissue and restoring function. However, the exact mechanisms are not fully understood. Additionally, while the clinical data sounds promising, it is still debatable whether certain data is conclusive due to controversial methods or studies that take novel approaches. Furthermore, certain risks should not be ignored concerning MSC therapy. Serious effects have been observed in patients, like a “large tumor-like mass inside the spinal cord after 8 years of olfactory mucosa cell transplantation,” due to the MSC therapy the patient was receiving (Lukomska et al., 2019). Moreover, in neurological applications of MSCs, there have been even further negative side-effects observed. After injection, unintended symptoms consisting of fevers, headaches, and pain were common, while definitive positive results were quite rare (Lukomska et al., 2019).

Adversities and Current Limiting Factors

While the attractiveness of mesenchymal stem cell therapy, specifically in neural systems, has led to many valuable studies, there seems to be an overstatement regarding the actual applicability and current understanding of MSC therapy. As a novel topic, there has been a recent influx in interest regarding MSC therapy in combating SCIs, but the conclusions made are not in support with each other. There also seems to be a degree of confirmation bias in the current state of public opinion. With the recent increase of interest in stem cell therapies, many Phase I studies, reports, and reviews have been published; however, significant clinical data is yet to be attained. A large-scale meta-analysis focused on adverse events (AEs) or negative side effects of a MSC treatment of a SCI. Zhizhong Shang et al. discovered that clinical trials and research have produced approximately 28 possible AEs (Shang et al., 2022). Additionally, it was also found that the development of viable SCI treatment using stem cells is still in the early, infantile, stages. Not only do the ideal parameters for injection and treatment need to be established, but the exogenous effects of MSC introduction to a site of trauma also need to be better understood. Better clinical trials, research on large mammals, and early-stage human trials need to be further studied for the advancement of the stem cell field. Currently, knowledge is limited on both the interactions between neuronal tissue and MSCs as well as the optimal operations on a SCI trauma site.

In addition, clinical trials are not closely regulated. Therefore, more research on MSCs and their functions is needed for the current interest and excitement surrounding this topic to be justifiable and within reason.

Ethical Concerns of Stem Cell Therapy

While the ethics of using MSCs, cells often derived from tissues like adipose, bone marrow, or other general tissue groups, is not disputed, there have been concerns raised in the scientific community surrounding stem cell research and its morality. This conversation is often centered around the idea of scientific misuse of stem cells, immoral genetic manipulation, and human cloning. An example of scientific misuse of stem cells can be seen with Rishi S. Nandoe Tewarie et al.'s research done in the field of human asexual or same-sex reproduction through the use of oocytes proliferated from male stem cells, which can enable one male or two males to produce a human embryo (Nandoe Tewarie et al., 2009). While this is entirely possible and within the realms of scientific reason, it has been debated whether this would be an ethical action. There is no way of knowing the detrimental effects this could have on a child due to the pairing of strictly male DNA. This leap, while scientifically relevant, would be concerning ethically and could eventually lead to the degradation of human moral laws. Additionally, cloning human cells follows the same line of reasoning: while scientifically possible, it is still ethically questionable. Many believe that there needs to be a line drawn in how deeply science interferes with natural human development and evolution over time. The implications of cloning open doors that generate additional issues. Another ethical concern regarding stem cell research is genetic modification and human germline engineering. By utilizing stem cells to produce artificial gametes, the expression of certain genes can possibly be altered, thus allowing human intervention within the genomic sequence of embryos (Nandoe Tewarie et al., 2009). This is ethically concerning because it would essentially enable humans to design the type of child they wish to bear, eliminate all genetically expressed diseases, and change the physical appearance of their future child. This is concerning on various levels and would lead to the dissolution of countless social, economic, and cultural values.

Conclusion

As a novel method of approaching SCI regenerative therapy, MSC transplantation is a promising and exciting solution. Not only are the factors secreted by MSCs beneficial for neuronal repair and regrowth, but their effectiveness is amplified when paired with other enhancing. Multiple studies and clinical trials have shown that the factors secreted by MSCs can enable tissue repair and neuronal regeneration in the spine. However, MSC therapy can also come with concerning side effects. The promise of MSC therapy is offset by its inconsistency, risks, and ineffectiveness in current clinical trials. It is hard to find substantial and valid research supporting large-scale MSC transplantation in the human spine that does not include many failures and low success-rates. This puts into check the current excitement surrounding MSC therapy and applications within the nervous system of the spine. While there are obviously possibilities in the future, at the current state of research and clinical trials, the effectiveness of MSC therapy is questionable at best. There are still many factors that need to be addressed as progress is made, such as standardizing methods, developing lower-risk results, and exploring the mechanism of MSC therapy. With a better understanding of these intricate modes by which MSCs work to regenerate neurons and enhance the microenvironments within tissues following a SCI, future trials in humans could be seen as safer and more realistic.

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Inside Out: A Brain's Tale of Introverts and Extraverts

Krisha Agarwal

Introduction

What makes us who we are? According to the American Psychological Association, personality is the 'the enduring configuration of characteristics and behavior that comprises an individual's unique adjustment to life, including major traits, interests, drives, values, self-concept, abilities, and emotional patterns.' (Detloff, 1972) Two primary types of human personality are introversion and extraversion.

Psychologist Carl Gustav Jung differentiated introversion and extraversion based on the "direction of flow of psychic energy". An extravert places importance on an external object (another person, place, or thing) based on his qualities (Detloff, 1972). On the other hand, introverts are loyal to an inner point of reference that takes precedence over the external object (Detloff, 1972). The object becomes important if it aligns with the inner self. Therefore, the differential feature between introverts and extraverts is how the person arrives at this perspective rather than the actual relationship between the object and subject (Detloff, 1972).

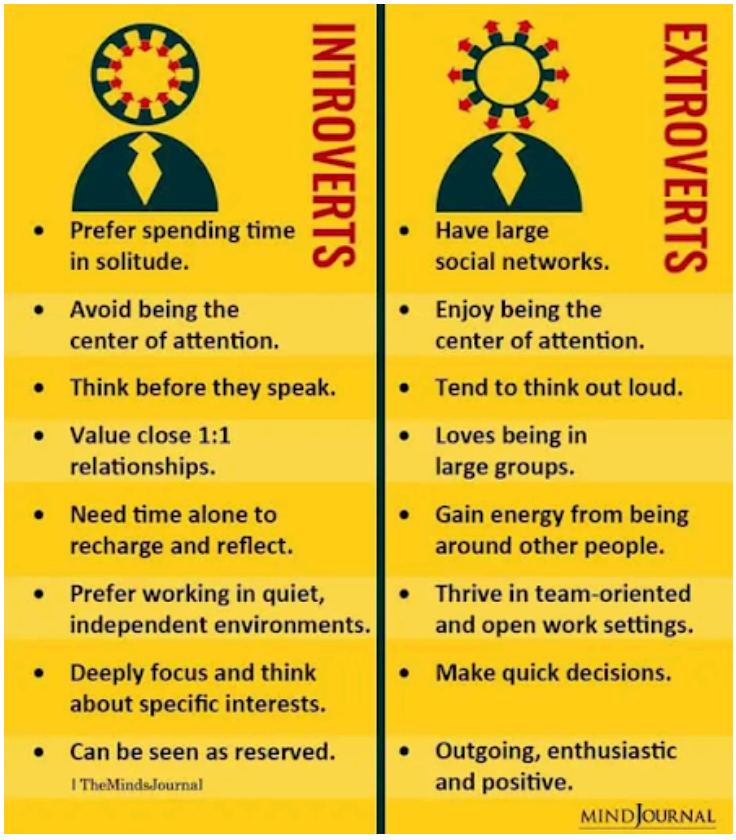

Figure 1. Personality differences between introverts and extraverts (The Minds Journal, 2022)

Physical Structure

Psychologist Hans Eysenck suggests that the behavioral differences in extraverts are due to an inherent drive to compensate for underactive reticulo-thalamo-cortical pathways. As a result, extraverts have lower activity in their behavioral inhibition system, a functional loop including the ascending reticular activating system, the frontal lobes, septal regions, and hippocampus. A positive correlation has also been found between extraversion and gray matter concentration in the left amygdala (Omura et al., 2005). The thinner cortical gray matter ribbon in the dorsolateral prefrontal cortex (DLPFC) emphasizes its importance in extraversion (Wright et al., 2006). The DLPFC strategically controls an individual's thoughts and actions based on goal-oriented behavior and positive affective states (Macdonald et al., 2000). Its dysfunction has been associated with depression and anxiety, which may also explain why low levels of extraversion lead to increased vulnerability (Grimm et al., 2011).

Neurotransmitters

In some people's brains, enhanced release of neurotransmitter dopamine, part of the brain's reward system, leads to greater excitement and engagement with the world (Watson, 2021). This release is linked to the sympathetic nervous system, responsible for the 'fight, flight, or freeze' response, which makes the brain alert and hyper-focused on its environment (Granneman, 2016). A study by researchers at Cornell University observed that rewards like food, sex, and money trigger dopamine release, producing positive emotions and increased drive for these goals (Depue & Fu, 2013). In the study, it was noted that extraverts have a more robust dopamine response system, making them experience strong positive emotions more frequently. Moreover, with time, extraverts develop a more extensive network of reward-context memories to activate the brain's reward system, further increasing the feeling of positivity and excitement. On the other hand, it was noted that acetylcholine, which is linked to introspection, was more prevalent in introverts. This neurotransmitter is integral in the ability to think deeply and to concentrate. This idea is reinforced by the fact that Acetylcholine is associated with the parasympathetic nervous system, responsible for the 'rest and digest' response, due to its features of energy conservation, muscle relaxation, and decreased blood pressure–necessary for periods of intense study (Granneman, 2016).

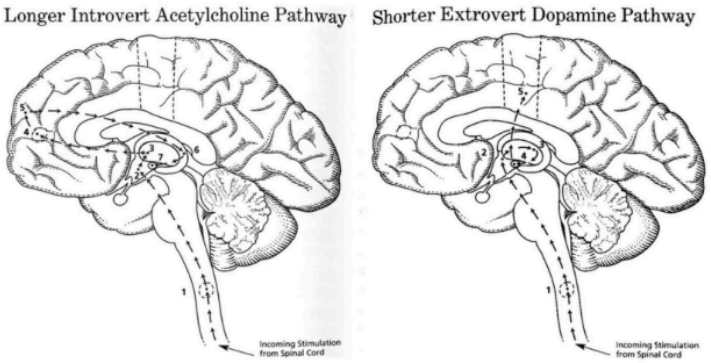

Figure 2. Neurotransmitter pathways between introverts and extraverts (Medium, 2016)

Environmental Influences

Introversion and extraversion hold a genetic component, but environmental factors also play a role. Results from identical twin studies suggest that one's surroundings greatly influence personality, with a 40% genetic and 60% environmental variance (Loehlin & Nichols, 2012). In another study, Professor Brian Little developed the free trait theory, which states, "...introverts may temporarily act as extraverts in order to advance projects requiring expressions of enthusiastic assertiveness." (Little, 2008). In conclusion, introversion and extraversion are flexible, complex blends of genetic components and environmental factors. These personality types of extraversion and intraversion arise from neurological and biochemical processes, influencing our behavioral and emotional responses. Understanding this dynamic can provide valuable insights into human behavior.

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Optical Illusions: What Are They, and Why Do They Occur?

Ananya Sampathkumar

Abstract

Optical illusions are commonly used in psychology classes in order to show how the brain can be easily manipulated. These illusions all target different parts of the visual pathway. As a result, researchers are able to find the specific reasons for some illusions, such as the Hermann Grid. However, scientists currently have no specific reason that all illusions trick us. As further research is done, optical illusions will be better understood, and scientists will be able to use them to further understand the visual pathway.

Introduction

Very often, people will claim to see things that do not exist. Whether that could be witnessing a mythical creature or losing track of a bug, our brain and eyes can often play tricks on us. One common trick played on our senses are optical illusions. Optical illusions, also called visual illusions, are a phenomenon that occurs when the perception of something differs from the actual reality of it (Yoshimoto, et al. 2021). Some commonly discussed optical illusions are the Hermann Grid Illusion, the Kanizsa Triangle, and the Lilac Chaser. These visual illusions play differing tricks on your mind, making you see motion and shapes where there are neither.

There are a multitude of possible reasons why optical illusions continue to play tricks on our mind. While each optical illusion is different in its effects on the brain, there are a few theories as to why these images fool our brains into seeing such differences from reality.

Visual Cue Pathway

The visual processing system is an incredibly complex pathway with many different parts of the brain and the eye involved. It begins when light enters the eye. From the iris and lens, light will be projected onto the retina. The retina is a very important part of the visual system as it determines the type of image that will be seen.

Inside of the retina, there are two different types of photoreceptors: rods and cones. Rods are located on the periphery of the retina, and assist in the processing of images in low light and in black and white. On the contrary, cones are found in the center of the retina and process images in higher light with different colors.

From the retina, a cranial nerve known as the optic nerve receives the information. This information is passed through until it reaches the optic chiasm. The optic chiasm is the intersection between the two optic nerves that allows for information from the left eye field and right eye field to be sent to both sides of the brain. Without it, our brain would only receive half of our visual information and would not be able to function as properly.

Once the information passes the optic chiasm, it continues to the lateral geniculate nucleus, which is a part of the thalamus. All sensory information passes through the thalamus, and then visual information is finally passed to the visual cortex. The visual cortex is where the images from the retina finally begin to be processed and are recognized by our brain (Baskin 2021). The complexity of the visual processing pathway leads to the possibility of error at any point. Different optical illusions target different parts of the pathway in order to have the effect that they do.

Hermann Grid Illusion

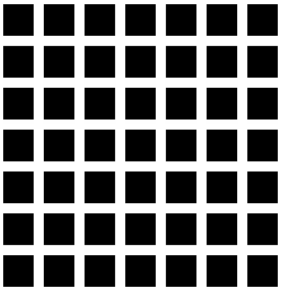

Figure 1. Hermann Grid Illusion. Black squares are separated by white lines. When staring at white lines, there seem to be gray circles in the intersection of the white lines where there are not (University of Pittsburgh, 2019).

One famous example of an optical illusion is the Hermann Grid Illusion. As seen in Figure 1, this illusion tricks the brain into believing there are gray circles located in the intersections of white lines. These circles are seen due to the posterior and anterior neuron connection.

Posterior neurons convert light stimuli into electrochemical messages. These messages are then sent to the anterior neurons, also known as ganglion cells. These ganglion cells are tasked with deciphering all the information they receive; the inputs that these ganglion cells receive are either excitatory or inhibitory. From there, they decide how best to transfer the information to other parts of the brain. Their decisions result in the unique organization of ganglion cells, which is often known as center surround.

When one views the Hermann Grid Illusion, ganglion cells are activated. The first ganglion cell (referred to as ganglion one) has 10 out of 16 of its inputs exposed to light.

Of these 10 inputs, eight of them are excitatory and two are inhibitory. The two inhibitory inputs are canceled out by the excitatory inputs, leading to a net gain of six excitatory inputs. Due to the increased amount of excitatory inputs in comparison to inhibitory inputs, the white line seems very bright.

The second ganglion cell (referred to as ganglion two) has no excitement at all. Due to not having any inhibitory inputs or excitatory inputs, the surround is repressed, and the center is not excited. As a result, the black background is shown as very dark.

Finally, the third ganglion cell (referred to as ganglion three) has 12 out of 16 inputs exposed to light. Out of these 12, eight are excitatory and four are inhibitory. As a result, the net result is four excitatory inputs, so the intersections between the white lines seem darker than the lines themselves. As a result, they are processed as a light gray color, tricking our brains into believing that the intersections are a darker color than the rest of the lines (University of Pittsburgh, 2019).

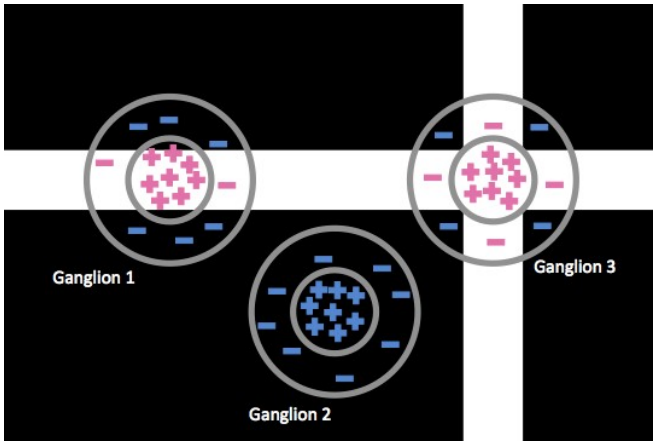

Figure 2. Hermann Grid Illusion. Black squares are separated by white lines. When staring at white lines, there seem to be gray circles in the intersection of the white lines where there are not (University of Pittsburgh, 2019).

While the Hermann Grid Illusion is easily explainable, this is simply one example of an optical illusion. There are many different types of illusions that all affect different parts of the brain. Despite this example, scientists still do not have specific answers as to why all optical illusions occur in the way that they do.

Theories on Optical Illusions

While there is information regarding specific illusions, scientists do not know what truly causes optical illusions (van der Berg 2019). However, scientists have a few theories. One reigning theory is the backward processing theory. This theory states that information travels through circuits of neurons. Usually, all this information is processed through the visual pathway and then passed on to the prefrontal cortex for decision-making. However, scientists believe that not all the information stays on this path, and some neurons change course by sending information back to the first stage of processing. This theory accounts for the processing of the Kanizsa Triangle, specifically (Duffy, 2016).

Another popular theory is that our brain simply misunderstands the signals it is being given by the eyes. Sometimes the visual cues are not enough to provide the necessary information for the brain to function properly, so some assumptions are made in order to maintain normal processing. As a result, some scientists believe that optical illusions are caused by a lack of information or a misinterpretation of the visual cues by the brain (van der Berg 2019).

Summary

Optical illusions occur when the brain incorrectly perceives images. These illusions manipulate different parts of the visual information pathway, and as a result, scientists are unable to figure out why exactly optical illusions occur. While researchers know how and where specific illusions like the Hermann Grid Illusion occur, they have two reigning theories as to why these occur on a broader scale: the backwards processing theory and the misunderstanding theory. Understanding optical illusions is crucial to the understanding of the visual pathway and all the issues that can occur during processing. With time, we will be able to better understand how the body perceives visual signals.

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The Interplay of Cognitive and Emotional Control in Autism Spectrum Disorder

Kaitlyn Tuvilleja

Abstract

Autism Spectrum Disorder (ASD) is a condition that affects how an individual interacts, communicates, learns, and behaves (National Institute of Mental Health). This can significantly impact two crucial areas for navigating our daily lives: cognitive and emotional control. The cognitive side aids decision-making and clear communication. They allow us to weigh various options logistically and predict the potential consequences of those decisions. The emotional side helps manage healthy relationships as these controls allow for attentive listening, clear communication, and disagreement navigation. Multiple studies delve into the interplay between cognitive and emotional control between individuals with ASD and typical adults (TYP) without ASD. By understanding how cognitive and emotional control affects individuals with ASD, we can create a society that is more accessible and enthusiastic to help.

Cognitive Control in ASD

Cognitive control is managing your thoughts, feelings, and actions to adapt to various situations (Miller and Cohen 2001). In terms of attention and planning, cognitive control aids an individual's mental organization of information. It also contributes to decision-making and how to make logistical choices and predict the consequences. For example, most individuals can switch between tasks or even multi-task. However, these controls can be inhibited by physiological and psychological factors. Brain structure and function abnormalities, such as neuroinflammation, oxidative stress, and gut-brain axis dysfunction are correlated to cognitive problems in ASD, such as depression and aggression. Even deficiencies in sensory perception, specifically visual processing, can contribute to the deficits of cognitive control in ASD (Al-Mazidi, 2023).

While TYP individuals use cognitive control subconsciously, individuals with ASD may find difficulties in using cognitive control abilities efficiently. Most individuals with ASD struggle with task-switching problems, which are theorized to be in coordination with a lack of behavioral control. To observe this, researcher Marjorie Solomon at the University of California, Davis conducts a study observing whether cognitive and emotional controls work together.

The study included children both younger and older than twelve years old. To examine cognitive control in ASD, participants were given the “Preparing to Overcome Prepotency” (POP) task. The POP task consisted of two easier and harder trials (i.e. requirement to inhibit a habitual response). Reaction times were slowed throughout each task for both ASD and TYP groups regardless of age. As more attempts were made, the TYP group eventually had more efficient performances. In contrast, the ASD group showed more difficulty in suppressing habitual responses as tasks continued (Fig. 1). These results suggest that children with ASD may have deficits in cognitive control, particularly in predicting responses. Further analysis shows that ASD children under 12, though a small difference, tend to make more inaccuracies than TYP children. This suggests a lack of cognitive control for ASD individuals may be more pronounced at earlier ages (Solomon et. al, 2008).

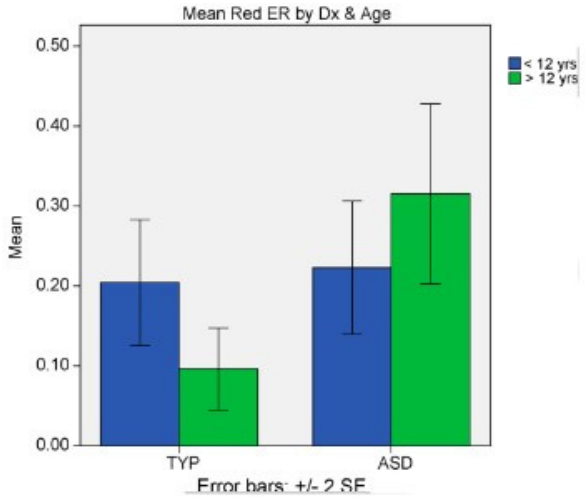

Figure 1. Inaccuracies with harder trials between ASD and TYP group across participants younger than 12 (blue) and older than 12 (green) by age range (Solomon et al.)

Emotional Control in ASD

Emotional control refers to the management of an individual's emotions. People with ASD often have strong emotions and struggle to control them, this is often referred to as emotional dysregulation. To put it into perspective, when placed in an overwhelming environment, TYP individuals may try to calm down, while individuals with ASD tend to react without a clear goal in mind (Ghanouni and Quirke., 2022). ASD individuals usually have trouble understanding their own emotions and struggle to adjust their behavior depending on the situation. Other factors such as bright lights and sounds can make it even more difficult for ASD individuals to handle their emotions, leading to potential shutting down or avoidance of certain situations (Mazefsky et al., 2013). This highlights the challenges individuals with ASD face. With the difficulty of comprehending emotions coupled with heightened sensitivities, interventions or therapies are crucial to support ASD individuals with navigating social situations and developing efficient coping mechanisms.

The Interplay Between Cognitive and Emotional Control

Researchers acknowledge that there may be interactions between systems managing cognitive and emotional control. The study involved a TYP group and an ASD group, both trained in cognitive reappraisal. Individuals with ASD are known to have trouble controlling their emotions. Researcher Richey and his team compared brains of ASD and TYP brain responses when they try to reinterpret situations in a more positive light to help regulate emotions, also known as reappraisal. During the fMRI brain scan, participants were shown pictures of faces and asked to develop positive or negative thoughts about those faces.

What the researchers found was that the ASD group had weaker activity in two regions of the dorsolateral prefrontal cortex (DLPFC) and the amygdala. The dorsolateral prefrontal cortex (DLPFC) was involved more with motivation and reward, especially for social stimuli (Fig. 2).

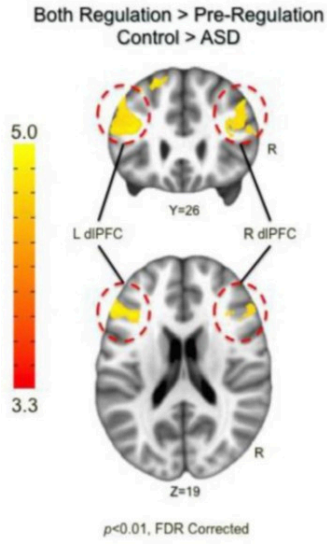

Figure 2. Highlighted right and left dorsolateral prefrontal cortex (dlPFC) in ASD participants (Richey et al.).

This explains why ASD individuals do not find social interactions or events as exciting or as rewarding as other people would since social events don't feel as rewarding to them. The amygdala, which was involved with suppressing negative emotions, isn't as active in ASD individuals. TYP individuals are shown to activate the amygdala more when presented with tasks that require suppressing negative emotions. This would explain why ASD individuals usually have difficulty calming down as the amygdala isn't as active as typical individuals (Richey et al., 2015). Despite the different brain region strengths, both groups had similar changes in their emotional responses, suggesting people with ASD might use different brain mechanisms to achieve emotional regulation (Richey et al., 2015).

Conclusions and Future Implications

Understanding how cognitive and emotional controls affect individuals with ASD is essential for developing effective interventions and fostering a more inclusive society. ASD individuals struggle with social interactions due to their differences in brain activity. Despite the challenges in cognitive and emotional control, individuals with ASD possess unique strengths and capabilities. Researchers can use this data to create techniques and therapies to support individuals with ASD. By acknowledging these differences and fostering an environment of support, we can empower individuals with ASD to thrive in all aspects of society.

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Glioblastoma Multiforme: Challenges and Advancements in Treatment

Casey Meskovich

Abstract

Glioblastoma multiforme (GBM) is a tumor that is initiated in glial cells, usually astrocytes. GBM presents difficulties in treatment due to the delocalization of tumor cells, inherent resistance to most cancer drugs, and the limited capacity of the brain to repair itself. Although most cancers have demonstrated an increase in treatment efficacy associated with recent technologies, the recovery rate of GBM has remained stagnant over the years. Recent research, focusing on the immune response of the brain, has sparked hope for better treatments. This paper discusses why previous treatments have been ineffective and describes the recent advancements in treatment.

Introduction

One afternoon in September of 2018, Henry Leonard's office hummed with the clacking of computer keys and quiet chatter between coworkers–and, Henry's snoring. He had been asleep at his desk for approximately fifteen minutes before a concerned colleague shook him awake. Taking a sip of his coffee, Henry dismissed his lethargy as a symptom of aging; he had always been healthy and didn't see any other explanation. He squinted at his computer, unsure of what he'd been working on before falling asleep, and sighed. It was open to an extensively chaotic weekly calendar. Typically, Henry took pride in being well-organized, but had recently found himself struggling to keep track of projects.

A dull ache throbbed in his temples as Henry considered the work he had to finish that day. Preferring to avoid medication when possible, Henry ignored the pain. As the day progressed, his headache developed into nauseating pain. For the first time in fifteen years, Henry swallowed an aspirin tablet.

The day trudged on, and Henry was happy to go home. Later that night, he called a close friend to discuss his overtiredness, but was met with anger rather than sympathy. Henry was shocked to learn that he had spoken to his friend the day before, and had been aggressive and barely lucid. He had no recollection of this conversation, and apologized profusely.

Later that month, Henry was diagnosed with glioblastoma multiforme, an advanced form of brain cancer. In hindsight, these were his first symptoms–disorganization, headaches, memory loss, and inexplicable aggression. It was a bleak prognosis for Henry; very little is known about the causes of the disease, and it is highly incurable. Despite being the most common type of brain tumor, treatments for GBM have shown minimal advancements compared to treatments for other types of brain cancer. GBM carries an average five-year survival rate of 7.2%, significantly lower than the overall five-year survival rate for all types of brain cancer, which stands at 13% (Nuffield Trust, 2023).

What is GBM?

GBM is a type of glioma. Gliomas originate from genetic mutations in glial cells, which provide physical and chemical support for neurons (NORD, n.d.). According to the World Health Organization, gliomas are divided into grades I-IV, depending on the degree of malignancy.

Grade I gliomas are typically benign and slow-growing, often associated with mutations in the neurofibromin I (NF I) gene, responsible for growth regulation (Roswell Park Comprehensive Cancer Center, n.d.).

Grade II and grade III gliomas, characterized by rapid growth, most often arise from mutations in the TP53 gene. This gene is responsible for the production of a tumor suppressor protein. Grades II and III are rare in children, but commonly manifest in young adults.

Grade IV gliomas are GBM, and are the most common and malignant (Roswell Park Comprehensive Cancer Center, n.d.). GBM is commonly seen in patients over 50 years of age. However, there is growing evidence that GBM can also develop in children, adolescents, and young adults. Tumors found in younger individuals, though, are genetically unique from those found in older adults (MDPI, n.d.).

GBM, in particular, develops from astrocytes (Fig. 1).

Figure 1. An astrocyte (Ferri, 2023).

Astrocytes have a multitude of functions within the brain, ranging from clearing excess neurotransmitters, to stabilizing and regulating the blood-brain barrier (BBB) (NCBI, 2023). Astrocytes make up the majority of cells in the central nervous system; this is unsurprising, considering their versatility.

Astrocytes also have a wide variety of locations within the central nervous system; as a result, GBM can start anywhere in the brain. However, it most commonly forms in the frontal and temporal lobes, which play roles in speech, movement, behavior, and memory. Resulting symptoms, then, coincide with these functions; headaches, drowsiness, personality changes, and memory loss are among the most common (Moffitt Cancer Center, n.d.).

The intensity of these symptoms is influenced by genetic, epigenetic, and microenvironmental factors. Uniquely, family history is not a factor; the majority of patients have no family history of cancerous brain tumors. There is, however, a correlation between GBM patients and the diagnosis of close family members–individuals with immediate relatives afflicted with GBM are twice as likely to develop the disease. The disease is linked to age, with a median age of 64, and is slightly more common in men. The only controllable risk factor for GBM is exposure to ionizing radiation therapy, as this can contribute to genetic mutations (Moffitt Cancer Center, n.d.).

In most cases, the exact cause of GBM is unknown. However, there are a few similarities between characteristics of patients; many harbor mutations in the IDHI, EGFR, PTEN, TP53, PI3K, and TERT genes, which are coincidentally among the most commonly mutated genes in human beings (NCBI, 2023). Although functions of these genes are generally different, they all play a role in cellular pathway signaling. In rare cases, GBM can be linked to certain genetic syndromes, such as Turcot syndrome and neurofibrosis type 1 (NCBI, 2023).

Current Therapies and Their Success Rates

For GBM patients, options are extremely limited, as GBM presents distinct challenges. Localization of brain tumors, the presence of the BBB, and the limited capacity of the brain to repair itself are among these challenges. Arguably the most, however, is the inherent resistance to conventional treatments (American Association of Neurological Surgeons, n.d.).

GBM cells have stem cell properties. They're able to self-renew and differentiate into different cell types. This means that tumors are often made of a number of different types of cells, a phenomenon referred to as heterogeneity (MDPI, n.d.). Additionally, cells are able to take on different functions or roles within any one tumor, and change these roles as needed. Cells in a tumor are able to interact dynamically, forming a flexible tumor environment (MDPI, n.d.). As a result, GBM is able to adapt quickly and effectively to external conditions (like, the presence of a new drug in the system). The plasticity (ability of tumors to change and adapt) of GBM, combined with the recurring nature of the tumors, presents a difficulty in treatment.

GBM is most commonly treated with surgery, followed by chemotherapy. Radiation therapy is also used, often after a surgery to destroy inaccessible cancerous cells. Each of these treatments are uniquely unsuccessful. In surgery, for example, the delocalization of the tumor presents a problem–GBM diffusely invades the brain, unlike tumors in other parts of the body. As a result, it's difficult to remove the entire tumor with surgery (NCBI, 2020).

The presence of barriers presents a challenge for chemotherapy. Both the blood-brain barrier (BBB) (Fig. 2) and the blood-tumor barrier (BTB) are in effect when treating GBM.

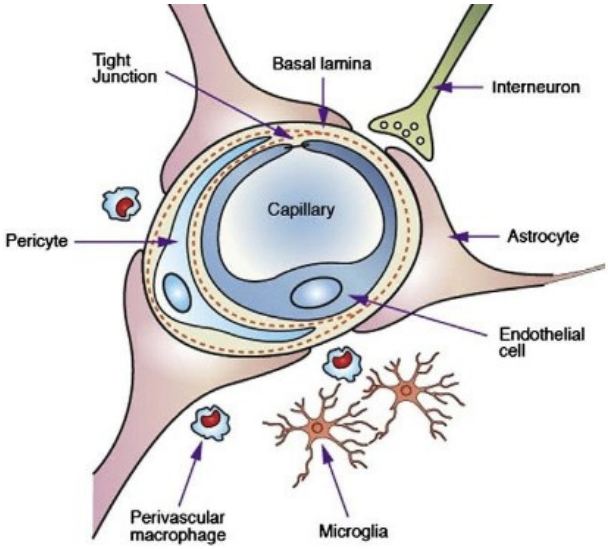

Figure 2. Diagram of the blood brain barrier (Parashar, 2012)

The blood vessels that vascularize in the CNS are highly selective, and function to regulate the movement of molecules between the blood and the brain, resulting in a membrane known as the blood-brain barrier (BBB) (NCBI, 2020). Tumors are known to compromise the BBB, resulting in vasculature called the BTB. The BTB is characterized by a non-uniform permeability, resulting from high heterogeneity (NCBI, 2019), and forms during the development of metastasis. As the tumor progresses, vasculature becomes increasingly heterogeneous. Normal vasculature is neatly arranged in a hierarchy of evenly spaced and well-differentiated arteries, capillaries, venules, and veins. Vessels supplying tumors (those that compromise the BTB) are increasingly chaotic, often following an irregular serpentine path (NCBI, 2010).

Selectively permeable barriers have been shown to reduce the effectiveness of cancer therapies for GBM. Current therapeutics have similar sizes to molecules that will not cross the BBB, such as recombinant proteins and peptides, antibodies, and viral vectors. This makes it difficult, if not impossible, to find therapeutics that cross into the brain.

Additionally, endothelial cells of vessels limit intercellular support of large hydrophilic drugs, a category many cancer drugs fall into (NCBI, 2023). These factors make many therapeutics ineffective in treating GBM.

GBM also exhibits interesting resistance patterns that make it difficult to treat. Resistance is most commonly acquired through the mechanism of DNA enzyme repair. Some cancer drugs (most notably temozolomide) create methyl adducts, which inhibit normal functions, on DNA. This modification is toxic to the cell's DNA and can trigger cell death. However, the repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) is capable of reversing this methyl adduct, effectively repairing the damaged DNA before it leads to cell death (NCBI, 2020). This repair process prevents cell death and allows cancer cells to survive the chemotherapy's intended effects (NCBI, 2020).

Immunotherapies In Treating Cancer

While there are a few options available for GBM patients, immunotherapy is not one of them. Immunotherapy has been proven to be effective for various other cancers, including some that frequently metastasize to the brain. Melanoma, kidney cancer, and breast cancer are among these. However, as GBM does originate in the brain, immunotherapy has not been seen to be effective.

In tumors that don't originate in the brain (but may potentially metastasize to the brain), drugs called immune checkpoint inhibitors are used. Human immune systems have several checkpoints to regulate immune responses and prevent the immune system from attacking healthy cells. However, cancer cells can often take advantage of these checkpoints to avoid being attacked by the immune system. Immune checkpoint inhibitors are drugs that block these checkpoints, allowing it to recognize and attack cancer cells more effectively. These drugs have been found to elicit a significant increase in both active and exhausted T cells—signs that the T cells have been triggered to fight the cancer (Heady & Sun, 2023).

When the checkpoints are blocked, the immune system's killer T-cells become more active and capable of recognizing cancer cells as threats. T-cells are activated in lymph nodes. During this process, antigen presenting cells are recruited to the tumor, where they phagocytose dead or dying tumor cells (Heady & Sun, 2023). Receptors on the dead cells activate the antigen-presenting cells and these cells then migrate to the nearest lymph node and prime naïve T cells moving through there, allowing the immune system to continue to target the tumor (Branca, 2023).

In GBM, and other tumors originating in the brain, however, this T cell priming process isn't effective–leading to the lack of response to immunotherapy treatments. Researchers have found a significant difference in the way the two types of tumors (those that originate in the brain, and those that don't) respond to immunotherapy. In a study by UCLA, researchers aimed to specifically examine the effect of immune checkpoint inhibitors to explain the higher response of tumors originating outside of the brain to immunotherapy.

It was found that T cells in tumors that did not originate in the brain had characteristics that implied tumors were blocked from entering the brain (Heady & Sun, 2023). Immunotherapy led to a significant increase in T cell lymphocytes in brain metastases, but this increase was much smaller in patients with GBM (Heady & Sun, 2023). This data suggests that the priming circuit is not as effective in GBM, as T cells are best primed in draining lymph nodes outside of the brain–a process that is not possible for tumors originating inside of the brain. In the context of tumors, draining lymph nodes refer to lymph nodes that receive lymphatic drainage from the area surrounding a tumor. Tumors often stimulate the growth of new blood vessels and lymphatic vessels to support their growth and spread. As a result, tumor cells and antigens can enter the lymphatic system and be transported to nearby lymph nodes (Koukourakis & Giatromanolaki, 2022).

From these findings, researchers have suggested that dendritic cells are a potential therapeutic strategy. Dendritic cells are able to reach T cells in the brain, which lymph nodes cannot do. This process would include generating dendritic cells from patients in the lab, pulsing them with tumor-specific proteins, and then re-injecting them back into the same patient (Heady & Sun, 2023). By recreating the priming process in dendritic cells, the effects of lymph node activation can be re-created as well.

This poses exciting possibilities for the field of neuro-oncology. Currently, the UCLA researchers are attempting which immune cells are changing in the more responsive tumors to help better explain the higher response rate to the treatment. No study has comprehensively examined the differential effect of immune checkpoint blockade treatment on these two types of brain tumors (those that originate in the brain, and those that metastasize to it) before. In future studies, the researchers plan to analyze data from a larger, more uniform group of people who were diagnosed with melanoma that had spread to the brain (Branca, 2023).

Conclusion

Glioblastoma arises due to genetic mutations in these cells, causing uncontrolled growth. Unlike many brain tumors, treating glioblastoma presents specific hurdles. Challenges include the brain tumor's location, the BBB, and the brain's limited self-repair capacity. However, the most significant challenge is its inherent resistance to standard treatments.

While GBM has been generally difficult to treat, immunotherapy (which activates T-cells to target cancer cells) has proven to be particularly unhelpful. New studies show that this could potentially be due to a T-cell priming step that occurs outside of the brain, whereas GBM originates in the brain. Ongoing research into T-cell activation by dendritic cells offers hope for patients like Henry Leonard.

Moving forward, many scientists suggest a holistic approach that combines innovative therapies, personalized medicine, and current chemotherapies. This collective momentum in research not only aims to improve survival rates but also prioritizes enhancing the quality of life for individuals facing this challenging diagnosis.

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Practical Applications of The Circadian Rhythm

Erin Ford

Abstract

The Circadian Rhythm is a cycle within the body that controls multiple biological processes such as the sleep-wake cycle, body temperature, hormone releasing, and digestive system. The circadian rhythm is widely theorized and understood to be developed because of the daily cycle of light and dark. This can be attributed to sunlight serving as the primary source of food for photosynthetic organisms, causing a cycle within the organism that causes food to be processed during the hours of daylight and a period of fasting during the night. Recent research has suggested that disruptions in this rhythm can lead to various issues within the body. However, there have been advancements in the applications of the circadian rhythm in the areas of the immune system and infection; exercise and sleep; digestion and food-processing; and cancer and treatments. This paper explores the fundamental mechanisms of the circadian rhythm and the impact on human health in various areas, advocating for practical applications of this profound biological cycle.

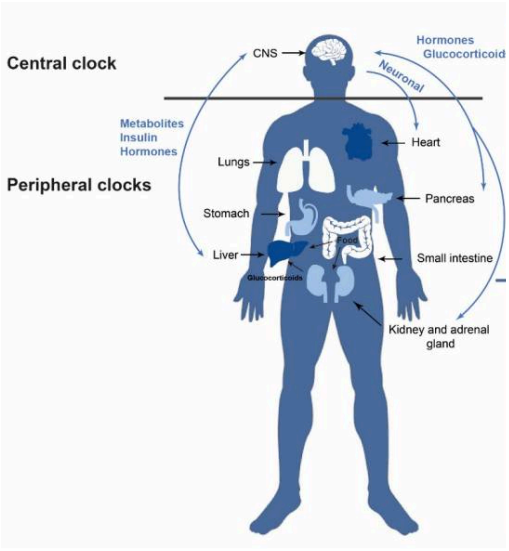
Introduction to the Circadian Rhythm and Its Importance

The circadian rhythm can be defined as the internal clock that controls feelings of awakeness and sleepiness in response to the 24 hour cycles of light and dark from the environment. The importance of the circadian rhythm cannot be understated, as the proper functioning of this cycle is crucial for everything from memory consolidation, eating habits, and digestion to body healing, temperature, and hormone release (Reddy, 2023). These processes ensure that your body is able to function normally.

An example emphasizing the importance of the circadian rhythm is the release of melatonin and cortisol, a process necessary for the proper functioning of the sleep wake cycle and even further, the proper functioning of the brain. Melatonin is a hormone that is released from the pineal gland to induce sleepiness in response to a lack of light while cortisol is a hormone that promotes alertness in response to the presence of light (Reddy, 2023). This occurs because of the suprachiasmatic nucleus (SCN) of the hypothalamus, the region of your brain that controls homeostasis. In the presence of light, the retinal cells within the eyes will perceive this light and transmit this information via the optic nerve. The optic nerve then activates the SCN, producing a signaling molecule called GABA (gamma-amino-butyric acid), inhibiting the release of melatonin. In essence, the light perceived by the optic nerve causes the body to send out signals through the SCN, preventing the release of melatonin so that the feeling of sleepiness goes away during the day. The opposite occurs when there is no longer light: the retinal cells recognize the lack of light and inhibit the SCN, preventing the release of GABA and initiating the production of melatonin and inducing sleepiness (Reddy, 2023).The proper functioning of the circadian rhythm for this process is essential because a lack of/excess melatonin could cause the body to not be able to sleep at night or a feeling of tiredness during the day. Lack of sleep can even affect mood, learning ability, and social cognisance (Sleep Deprivation, 2022).

A lack of properly functioning circadian rhythm can lead to various sleeping disorders, as well as issues related to the absence of zeitgebers—environmental signals like light, temperature, or food that cue the body to adapt its processes accordingly (Chaix, 2016). For example, “While blind individuals do have a pathway in the brain that functions as their body clock, roughly half of blind individuals experience non-24-hour sleep-wake rhythm disorder, during which their sleep cycles get later every night, jumps around, or results in waking up later in the day” (Reddy, 2023).

This process is just one of many that is controlled by the circadian rhythm, stressing its importance. The circadian rhythm is able to function because of the influence of zeitgebers. Because of the many bodily processes influenced by the circadian rhythm, the manipulation of zeitgebers and timing of treatments along with them is being researched as a method of treatment for various illnesses and infections via the immune system. Additionally, lifestyle changes that utilize the timing of the circadian rhythm can lead to better overall health; the circadian rhythm is even being taken into consideration for cancer treatment in a practice called “circadian medicine or chronotherapy” (Dose, 2023). The importance of the circadian rhythm and its ability to be manipulated through zeitgebers has led discoveries about its influence over immune response efficiency.



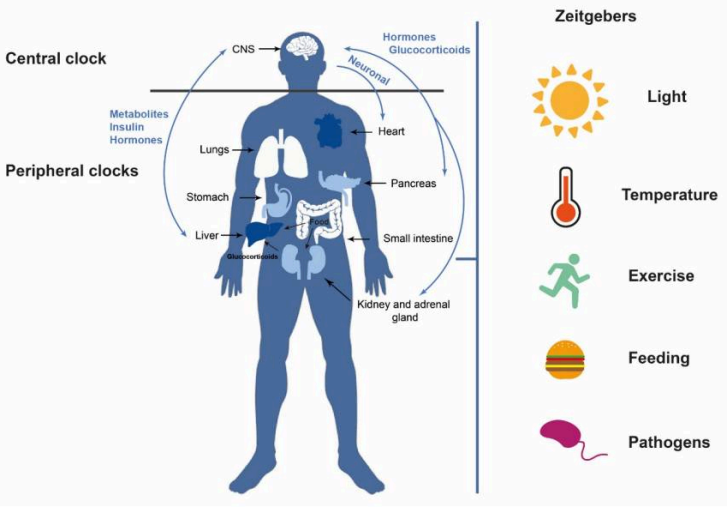


Figure 1. A diagram explaining the processes controlled by the circadian rhythm as well as the factors controlling it. Cycle zoomed in on previous page. Obtained from an overview article by Ana Amiama-Roig and others.

Timing and the Immune System

One of the systems the circadian rhythm can be used to control and improve is the immune system. The circadian rhythm is responsible for the timing of expression of many proteins; some of these are important for the initial response for the immune system. One such protein is REV-ERBα: this protein is a key part of the immune system because it "regulates transcription of inflammatory genes in macrophages" (Ruan, 2021). These macrophages are the lymphocytes that are responsible for removing unfamiliar and potentially harmful entities in the body. Another example is Nuclear receptor RORγt which is "a master regulator for the development of IL-17-producing T helper cells (TH17 cells), an important immune cell type for autoimmunity" (Ruan, 2021). T helper cells are essential for activating other cells within the immune system, such as those required to eliminate infected cells and foreign bodies. Additionally, the circadian rhythm controls the acquisition of lymphocytes. For example, the amount of B and T lymphocytes in circulation oscillates along with the rest and activity cycle, with increased numbers in the rest phase. The more lymphocytes in circulation, the more effective the immune response will be and the faster the recovery. The control the circadian rhythm has over these processes make the manipulation of zeitgebers a viable option for the treatment of infections. For example, light and dark cycles are used to increase T and B cells within a patient because of their peak during the rest phase. The lack of light acts as a zeitgeber to initiate the rest phase, leading to the increase in production of these cells. This leads to an increased immune response from the patient and a better chance of recovery from the infection (Ruan, 2021). By placing the patient in a room with low light and initiating this rest phase of the circadian rhythm, more white blood cells can be produced. This timing along with the circadian rhythm can contribute to the immune system's ability to fight off an infection.

Exercise and the Circadian Rhythm

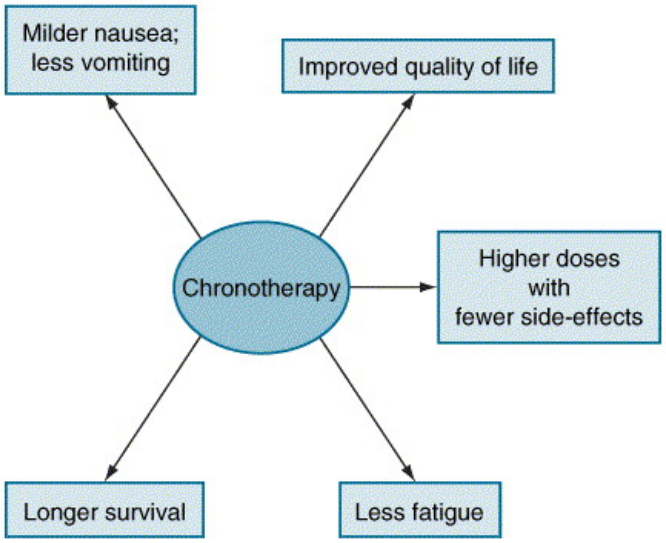
The timing of daily activities such as eating and exercise along with the circadian rhythm can result in more efficient bodily processes such as exercise and digestion. As light and dark cycles are important in the moderation of lymphocytes, the timing of daily activities--like eating or exercising--can improve the effectiveness of various bodily processes. Research has demonstrated that blood pressure, body temperature, hormone levels, and heart rate variability are all controlled by circadian variation (Dose, 2023). With these physiological features being integral to sport performance, timing exercise with the optimal levels of these factors can increase effectiveness of exercise and peak performance during periods of exercise. Conversely, misalignment can be detrimental to effectiveness of sleep cycles: "Night exercise causes a phase delay of the onset of dim-light melatonin" (Wang, 2022). As a result, exercise before bed is not recommended because it can block the production of the hormone that induces the feeling of tiredness and it is advised that physical activity take place slightly earlier in the day. Therefore, a better sleep schedule can be obtained based on the timing of exercise with consideration of the circadian rhythm. This better sleep schedule leads to all of the benefits associated with more sleep, such as improved immune response to possible pathogens (Ruan 2021). This indicates that consideration of the circadian rhythm in the timing of exercise can not only improve the quality of the exercise but also improve other necessary functions such as sleep and digestion.

Effective Digestion and The Circadian Rhythm

Similar to the timing of exercise, the timing of meals with consideration of the circadian rhythm can also result in a healthier lifestyle. For example, "insulin mediates the phase adjustment of the circadian rhythm of the tissues related to food in mice" (Wang, 2022). This process is important for tissue function which, in turn, assists in digestion and absorption of nutrients and aligning the stomach's circadian rhythm with meal times. Hence, the timing of meals with respect to the circadian rhythm can affect the efficiency of meal processing. Recent research supports this idea: in a study describing how the circadian rhythm controls pathways related to metabolic processing, researchers found that these pathways begin to increase when eating is anticipated. This is a temporary effect that declines after a few hours (Chaix. A, 2019). These results indicate that having a scheduled eating time every day can assist in the absorption of nutrients because the body will always be prepared to process food during that time. Furthermore, deviating from this schedule would mean consuming a large amount of nutrients when the body is not prepared to process it, and, as a result, leads to a less efficient digestive process. This supports the argument that "the consumption of a larger portion of caloric intake during the first half of wakeful hours may be preferred for better blood glucose regulation and weight control" (Dose, 2023). Essentially, after a large period of fasting, or sleep, the body has had a long period of time to prepare for the next meal and because of this, the circadian rhythm has ensured that the proper pathways are prepared. Cumulatively, the timing of meals alongside the circadian rhythm results in more efficient digestion and leads to better absorption of the nutrients necessary for other processes within the body.

Chronotherapy and Cancer Treatment

The circadian rhythm's applications are not only exclusive to day to day life but also have significance within the medical field. The timing of the circadian rhythm can be used to increase effectiveness of cancer treatments and the overall quality of life in cancer patients. The time of day when cancer treatments are administered can affect how much of the dose can be tolerated and the side effects experienced by the patient. An example of this was a study done with mice that found "the same dose of an anticancer drug became lethally toxic only when administered at certain times of day, whereas at other times of day, a 10-fold increase in dose was tolerated"(Ancoli-Israel, 2005). These results seem logical when considering the amount of processes that are controlled by the timing of the circadian rhythm. Certain proteins being made at specific times may help the body process the drugs or could cause unpleasant interactions leading to side effects of the drug. If the circadian rhythm dependent proteins that cause unpleasant interactions are made mostly within the first hours of waking, then the majority of this interaction can be avoided by taking the drug treating the cancer later in the day. Other research focusing on cancer patients has shown that the quality of life of the patient increases significantly when chronotherapy is used. Administration of the drug during the morning was compared with administration during the evening and it was found that during the morning hours patients experienced "milder nausea, and less vomiting in those receiving the chemotherapy in the evening" (Ancoli-Israel, 2005). The reduction of these unpleasant side effects leads to the patient feeling better physically, which in turn leads to "better psychosocial adaptation (including better social relations, less feeling of loss of independence, less anxiety, less depression, and less somatic discomfort) than patients receiving traditional therapy" (Ancoli-Israel, 2005). It is then likely that chronotherapy plays a part in the patient having fewer side effects and better quality of life during treatment.



Chronotherapy is an effective treatment method because of the difference between the circadian rhythms followed by cancerous and noncancerous cells. According to Benjamin Dose "Chronotherapy aims to exploit these differences in circadian rhythms by administering treatments at times when cancer cells are most vulnerable, and healthy cells are least vulnerable, thereby reducing toxicity and enhancing efficacy" (Dose, 2023). This strategy ensures that the cancer treatment can be administered at a time when it will be the most effective and when the healthy cells will be least affected which is what causes the minimized side effects. This kind of thinking may extend beyond cancer treatment and to other more common medications with adverse side effects. If other medications can be found to be more effective or have reduced side effects at certain periods of the circadian rhythm, then the same benefits as those from chronotherapy can be obtained.

Conclusion

To summarize, the circadian rhythm is a very powerful process in the human body that has a great deal of control over the different processes in the body; therefore, it is important to consider the circadian rhythm when carrying out certain processes, such as fighting off an infection. For example, more lymphocytes are produced during the rest phase which is initiated by a lack of light. The use of light and dark cycles can then be used to increase the amount of lymphocytes in circulation, which could increase the immune response to an infection. It is also important to consider the circadian rhythm in everyday habits such as when to eat or exercise. Exercising before bed can delay the release of melatonin and can lead to a worse night of sleep. Additionally, eating at the same time everyday can help the body process the caloric intake better because the circadian rhythm causes the proper digestive proteins to be produced at that same time each day. Furthermore, because the circadian rhythms of cancerous and noncancerous cells differ, the timing of cancer treatments to when cancerous cells are most vulnerable and noncancerous cells will be least affected by the treatment. This can lead to a decrease in unpleasant side effects, increase in effectiveness and overall better treatment experience for the patient. These applications emphasize how important the circadian rhythm truly is and further research may reveal even more applications of this complex system leading to new treatments and even more ways to live a healthier lifestyle.

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Understanding Common Personality Disorders: the Neurological Basis of OCD, NPD, and BPD

Isabelle Afshari

Abstract

Historically, the complexity of personality disorders has posed challenges to both diagnosis and treatment; however, with advances in technology, various studies have begun making new developments to elucidate the neurobiological causes of many of the most common personality disorders, such as obsessive-compulsive disorder (OCD), narcissistic personality disorder (NPD), and borderline personality disorder (BPD). By understanding the neurobiological causes of these disorders, further therapeutic and pharmaceutical treatment options can be developed, and information about these disorders can become widespread.

What is a personality disorder?

According to the Diagnostic and Statistical Manual of Mental Disorders: 5th Edition (DSM-5), a personality disorder is defined by the disruption in at least two of the areas of cognition, affectivity, interpersonal control, and impulse control, with these behaviors carrying throughout a variety of situations and being tracked back to adolescence or early adulthood (5th ed.; DSM–5; American Psychiatric Association, 2013). The three most prevalent personality disorders in the United States include obsessive-compulsive disorder, borderline personality disorder, and narcissistic personality disorder; however, the broader diagnosis that encompasses all personality disorders is general personality disorder.

General personality disorder follows a broad pattern of behaviors for a diagnosis, which as the DSM-5 defines, is "when personality traits are inflexible and maladaptive and cause significant functional impairment or subjective distress" (5th ed.; DSM–5; American Psychiatric Association, 2013). Because of the vast range of behaviors that can be characterized as general personality disorders, symptoms are sorted into three clusters, labeled Cluster A, Cluster B, and Cluster C. Cluster A personality disorders are considered the more "severe" types of personality disorders, with symptoms including "odd beliefs, unusual perceptual experiences, odd thinking and speech, paranoid ideation, and odd or eccentric appearance or behavior" (Esterberg, Goulding, & Walker, 2010). Cluster B personality disorders are characterized as "dramatic, emotional, or erratic," and often have connotations of a lack of empathy (Kraus & Reynolds, 2001). Cluster C personality disorders consist of three personality disorders: avoidant personality disorder, dependent personality disorder, and obsessive-compulsive personality disorder, with all of the disorders including avoidance and control as coping strategies and an inability to form close relationships with others (Bachrach & Artnz, 2021).

Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder is the most common Cluster C personality disorder, as well as the most common personality disorder in the United States, with 2.3% of American individuals having diagnoses of lifetime OCD, and 1.2% of Americans having diagnoses of 12-month OCD (Ruscio, Stein, Chiu, & Kessler, 2010). OCD is diagnosed based on the presence of obsessions, which are manifested by intrusive thoughts or images that increase anxiety, and by compulsions, which are performed to reduce this anxiety (Stein, 2002).

Although the diagnosis of obsessive-compulsive disorder is made based on behaviors, research has established neurobiological and genetic factors as key underlying causes. In a Cambridge University neuroimaging study, researchers found that patients with OCD tend to have hyperactivity of the ventral cognitive circuit, specifically in the basal ganglia and thalamus, which control sensory function, executive functions, and behaviors (Westenberg, Fineberg, & Denys 2014). Additionally, patients with OCD have been found to have elevated glutamate and glycine levels in their cerebrospinal fluid as compared to controls, meaning that these patients had an increase in excitatory neurotransmitters, which produce alerting signals to be transmitted throughout the nervous system. There have also been increased findings of serotonin, a modulator of glutamate, in OCD patients (Bhattacharyya, Khanna, Chakrabarty, Mahadevan, Christopher, & Shankar, 2009). These findings suggest that the symptoms of OCD are produced by a framework in which more excitatory neurotransmitters are released, leading to increased activity within the ventral cognitive circuit, thus contributing to the elevated feelings of anxiety and obsessions that are only subdued by engaging in compulsions. Furthermore, researchers have found potential genetic ties to OCD: a study with monozygotic (identical) as compared to dizygotic (fraternal) twins found that it is more common for both the monozygotic twins, with identical DNA to have an onset of OCD if at least one twin does, with a rate of 80-87% than for both the dizygotic twins, which have a 47-50% rate of both having OCD if one twin has it. The study concluded that these findings serve as evidence of a dominant or codominant mode of transmission of OCD; however, the particular allele that this would affect has not been found (Jenike, 2004).

Though obsessive-compulsive disorder has been linked to neural activity, the most common methods of treatment are behavioral interventions. However, pharmacologic approaches–including neuroleptic augmentation of antidepressants, and neuromodulation, including deep-brain stimulation–have found positive outcomes (Hirschtritt, Bloch, & Mathews 2017).

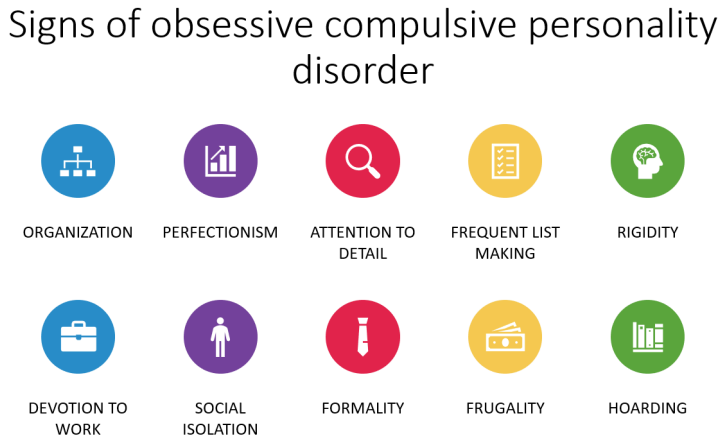

Figure 1. Signs of OCD
Some common characteristics of OCD include organization, perfectionism, and attention to detail (Wikimedia Commons, 2022).

Narcissistic Personality Disorder (NPD)

Narcissistic personality disorder is the most common Cluster B personality disorder in the United States, with a lifetime prevalence rate of 6% in the general population, as found by the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions (Ronningstam, 2010). Diagnosis of narcissistic personality disorder is based on behaviors of one of two subtypes: overt or covert. The overt subtype is characterized by "grandiosity, attention seeking, entitlement, arrogance, and little observable anxiety," whereas the covert subtype is characterized by being "inhibited, manifestly distressed… shy, outwardly self-effacing, and hypersensitive to slights" (Caligor, Levy, & Yeomans, 2015).

Similar to other personality disorders, narcissistic personality disorder is diagnosed based on a pattern of behaviors, yet it does have a neurological basis. Although not much research has been conducted on the effect of neurotransmitters on NPD, some studies have found links of narcissism to lower levels of serotonin. In a German study conducted by Paraskevi Mavrogiorgou, 74 healthy control patients and 74 patients with depressive disorders completed two personality assessments and an EEG for analysis of serotonergic transmissions (Mavrogiorgou, Seltsam, Kiefner, Flashback, & Juckel, 2022). The results dictated that individuals from either group that tested positive for narcissism tended to have lower serotonergic neurotransmissions.

For NPD, no psychotherapy nor pharmacotherapy treatments have been found to be effective, with a 63-64% drop-out rate for psychotherapy and no current approved pharmacological approaches to increase the number of serotonergic neurotransmissions in narcissistic personality disorder patients (Weinberg & Ronningstam, 2022).

Borderline Personality Disorder (BPD)

Borderline Personality Disorder is another Cluster B personality disorder, which has a prevalence of 0.5-5.9% in the general United States population (Leichsenring, Leibing, Kruse, New, & Leweke, 2011). Clinical signs of borderline personality disorder include emotional dysregulation, repeated self-injury, and chronic suicidal tendencies (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004).

According to the DSM-5, while the root cause of BPD is not confirmed, genetic factors and adverse events during childhood, such as abuse, contribute to the onset of the disorder. However, recent studies have begun to prove the significance of serotonin in BPD. In particular, a study conducted at the Mount Sinai School of Medicine found that dysfunction of the serotonin (5-HT) system has been linked with borderline personality disorder (Gurvits, Koenigsberg, & Siever, 2005). This connects to the behavioral traits of those with the disorder, as this type of dysfunction has been associated with both self-directed and non-self-directed impulse aggression. Additionally, it has been found that the instability found in individuals with BPD may be affected by dysregulations in cholinergic, noradrenergic (NE) or gamma-aminobutyric acid (GABA)-minergic systems. These systems regulate inhibitory pathways, which suppress signals; therefore, if these are dysfunctional, patients will be much more alert and reactive to stimuli (Gurvits, Koenigsberg, & Siever, 2005).

BPD has no effective pharmaceutical treatment to combat symptoms because there is so little known about it. However, common alternatives include psychotherapy, which includes dialectical behavioral therapy and cognitive behavioral therapy, in addition to family therapy (NIMH, 2023).

Figure 2. Signs of BPD
Some common characteristics of BPD include fear of abandonment, unstable relationships, and unstable sense of identity (Wikimedia Commons, 2024).

Conclusion

Neurotransmitters prove to be crucial in determining the symptoms of the three most commonly diagnosed personality disorders, obsessive-compulsive disorder, narcissistic personality disorder, and borderline personality disorder. In particular, serotonin plays a significant role in determining behavioral tendencies, with higher levels leading to greater sources of anxiety, and lower levels leading to increased apathy. Although the DSM-5 has yet to validate the link between neurotransmitters and these personality disorders, new studies continue to suggest that serotonin does have an impact on behaviors. If the impact of serotonin is eventually validated by the DSM-5, the detection of these disorders would become much more objective, as it would be dependent on serotonergic levels rather than a psychologist or physician's perception of behaviors. Additionally, the production of medications to alleviate the symptoms of these disorders and normalize serotonin levels could prove impactful for the large percentages of Americans impacted by these disorders. Affected individuals will have new means of receiving treatments and diagnostic methods for these disorders will evolve as the observed role of neurotransmitters in these disorders increases.

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Can Expressing Gratitude Make You Happier & Healthier?

Vani Sharma

Abstract

The human brain consistently receives stimuli and adjusts accordingly. From social cues and emotions to memory consolidation for your studies, the brain is a moving part that is shaped by the environment and its inputs. One of these inputs is gratitude which can lead to changes in the brain's molecular and chemical structure leading to outcomes such as increased confidence, less anxiety and depression, increased resilience, motivation, and productivity. This paper focuses on the power of gratitude and positive self-talk and how that can be harnessed in applications in the real world and to improve overall mental health.

Introduction

Gratitude: the quality of being thankful and showing appreciation. From learning as little children to practicing saying "thank you," to the popular holiday celebration, Thanksgiving, to the high sale of gratitude journals, there is no doubt that showing appreciation for what we have is a cornerstone ideal of society. Showing gratitude in society is considered a marker of social and emotional intelligence, but what if it also impacts our neural plasticity? Expressing gratitude could help us boost our brain health, motivation pathways, productivity, happiness levels, resilience, and more. The objective of this paper is to delve deeper into the neurochemical and structural changes our brain undergoes when we express gratitude and how humans can harness this to improve mental health.

Power of Gratitude

Gratitude not only impacts central nervous system functioning but also changes the brain's molecular structure. Firstly, according to UCLA's mindfulness awareness research center, gratitude keeps the gray matter functioning, making us healthier and happier (Moran, 2013). Gray matter plays a large role in emotional functioning in addition to memory as well as movement. With that being said, even just a few minutes of daily recognition of gratitude can create an environment of positivity and boost your mental state. On a more rudimentary neuroscience level, when we express gratitude or receive it, the brain releases dopamine and serotonin (Chowdhury, 2019). Both are considered 'feel good' neurotransmitters that play key roles in our emotions, mood enhancement, and extending happiness as shown in Figure 1. When gratitude is practiced consistently and daily, these neural pathways that release these neurotransmitters can be strengthened to create a stable sense of positivity within us.

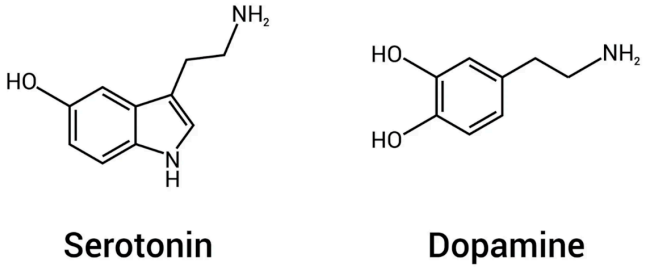

Fig 1. Serotonin & Dopamine Chemical Structures (Guy-Evans, 2023)

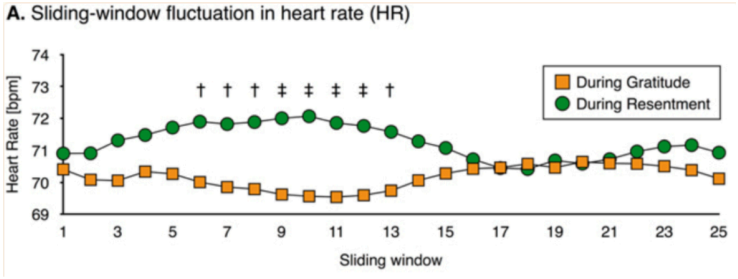

Fig 2. Heart Rate Fluctuations (Kyeong et al., 2017**)**

There are many studies and scenarios that can be examined to see this in action. One study from the National Library of Medicine demonstrated that those who showed gratitude as opposed to resentment had lower heart rates, as shown in Figure 2 (Kyeong et al., 2017). This response is due to the parasympathetic and sympathetic systems respectively. Previous studies have shown that heart rate is decreased among those with high self-esteem and increased in those with high stress and anxiety. The results of this study suggest that gratitude changes heart rhythms in a way that enhances mental health as well as self-confidence. Another study published in the Brain, Behavior, and Immunity Journal looked at gratitude among women in an online six-week program. They were instructed to do a gratitude writing intervention with a control group present to see if there were effects on neural activity (Hazlett et al., 2021). It was observed at the end that gratitude reduces inflammatory responses and increases support-giving. With that being said, gratitude is not just a social-moral emotion but is a neural correlate with cognitive implications.

Positive Self-Talk & Cognition

Language can impact how we think, feel, and behave under social stress. It can also improve cognition performance (Kim et al., 2021). Prior research has confirmed that self-talk has positive effects on attention, emotional regulation, performance enhancement in sports, academic engagement, and regulating anxiety and depression. When we engage in positive self-talk, it promotes positive psychological states, and the reverse is true with negative self-talk. Furthermore, neuroscience studies have found that positive self-talk promotes functional connectivity in the reward-motivation network ("Clinical Depression, n.d.").

The reward motivation network is responsible for pleasure, motivation, and learning. The basis of the reward pathway is that neurons release dopamine to allow you to feel pleasure. The brain makes associations between the source of pleasure and the pleasurable feeling. Then, the brain continues to make this connection stronger over time and encourages the repetition of behaviors that bring pleasure.The pathway is outlined in Figure 3. Positive self-talk increases motivation, cognitive fatigue-related inattention, and self-respect. Additionally, it can help individuals cope with difficult situations. A real-life example of this is people who use self-talk before a presentation are less anxious than those who say negative words to themselves. It can also help athletes as they compete.

Real-World Applications & Improved Mental Health Benefits

There are many practical applications of the aforementioned teachings and ways we can harness gratitude, positivity, and positive self-talk to increase neural plasticity as well as improve our mental health and productivity. Firstly, we can use these principles to help neutralize self-talk, which has poor effects on cognition, self-esteem, and goals (Raina, 2021). When we self-criticize and engage in negative self-talk, this has a high correlation with stress and anxiety as well as subsequent clinical diagnoses such as depression. When our brains criticize, emotional systems related to punishment and behavioral inhibition are activated. The brain sees this as a threat and creates a hyperfocus to not let something repeat. This leads to physical and mental stress and leads to mental exhaustion from overthinking. Some strategies we can take to mitigate this based on the practice of gratitude are to notice negative self-talk, reassure ourselves, and show compassion. By practicing self-kindness, normalizing the experience, and being mindful, we can motivate ourselves to improve and do better while being cognizant of our well-being and happiness.

In the same way, positive self-talk can also make you feel better and raise your productivity levels ("How Positive"). Experts at Mayo Clinic, ranked as one of the top hospitals in the country, say to harness these effects we must not say anything to ourselves that we wouldn't say to someone else. Mayo Clinic further states that redirecting negative thoughts to a positive manner may lead to increased life span,

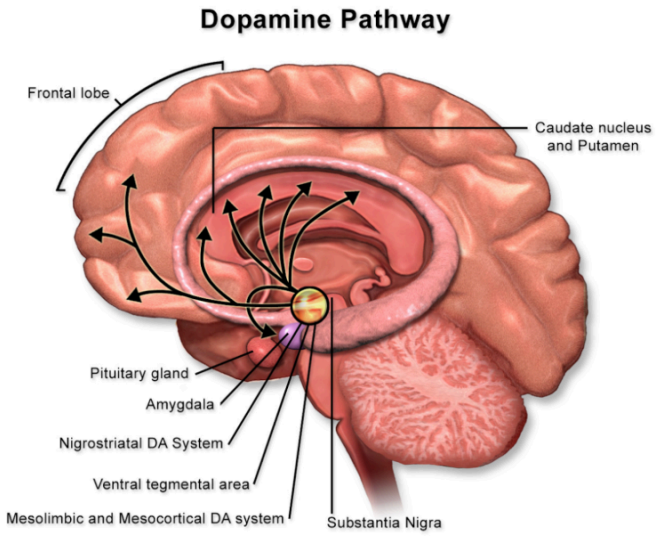

Fig. 3. Dopamine Reward Pathway (Guy-Evans. 2023)

lower depression rates, lower levels of distress, better psychological and physical well-being, better cardiovascular health and reduced cardiovascular disease, and better coping skills during hardship and stressful times. One technique that can be tried is changing the self-talk point of view. A Harvard Business Review recently shared that referring to yourself in the second or third person can make a grand difference and lead to being calmer and more confident as opposed to using 'I' or 'me.'

Limitations & Future Directions

It is important to note that research in this field is quite new, and there is much that is left to be further known, especially in conducting studies and looking at the nervous system response. There is no doubt that bigger studies can be funded with a greater sample size and looking at diverse patient populations. There are so many limitations as it is difficult to just pinpoint gratitude as the sole source for some of these changes. The brain is stimulated by a multitude of factors and many things can cause the release of "feel-good" neurotransmitters. With that being said, some future directions for this area of study would be to do larger-scale studies that are able to limit confounding factors to study the effects of gratitude and positive self-talk.

Concluding Statements

Gratitude is not only a social and emotional component of our lives but remains integrated with our neural systems. Over time, practicing gratitude can alter the circuitry of our brain to become more resilient, and productive, and dampen demotivating negative sentiments. Humans can harness the powerful effects of gratitude such as neurotransmitter release and the calming effects of positive self-talk to live happier and healthier lives. Even just small acts of gratitude a day can tremendously improve brain health.

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Swearing and the Brain: A Cultural and Emotional Experience

Vraj Patel

Abstract

Swearing stems from functions involved in the brain, specifically automatic and emotional swearing. The process excludes regions involved in conscious thought, like the prefrontal cortex and language processing centers, typically active in deliberate speech. It is important to note that this exclusion does not imply that these language areas are completely uninvolved; rather, automatic swearing relies more heavily on emotional circuitry such as the amygdala and basal ganglia. Research has focused on exploring the right hemisphere and its involvement with the automatic processing of emotional information, which is crucial in spontaneous swearing. Evidence and imaging tests from cases including damage to the left hemisphere point to significant activity in the right hemisphere during instances of automatic swearing. Additionally, the concept of swearing also involves the idea of "taboo," and the brain responds to expletives in a manner similar to when responding to threats to safety, indicating a deep-rooted emotional and survival mechanism at play.

Introduction

Swears are everywhere. Expletive words are prominent in everyday discussions and environments, including family gatherings, schools, campuses, workplaces, and social settings. Given this extensive exposure, an intriguing question arises: how do these spontaneous expressions relate to the brain's wiring? According to Stapleton, a prominent researcher at Ulster University, "swearing" refers to the act of using words and phrases that stem from a negative emotional reaction and can produce an equivalent reaction in the listeners. Swear words are also categorized within a language as "taboo" words, leading the listener to experience increased physical and emotional reactivity towards them when used (Byrne, 2019; Stapleton et al., 2022). Due to the prevalence of expletives in language, the act of swearing can result from two different origins: a consciously decided path and an automatic, involuntary path (Stapleton et al., 2022). These separate pathways suggest that intentional or spontaneous swearing engages complex brain networks, contributing to a multifaceted output. Adding to the complexity, the use of swear words then incorporates a neural process from multiple pathways, including language and speech production, somatosensory processes, and the limbic system for emotional responses (Finkelstein, 2018). The emotional pathways related to automatic swearing are the focus of this discussion.

The Emotional Pathway of Swearing

Though swearing leaves the mouth in the form of speech and language, the neural process of swearing is highly connected to emotional pathways. Swearing activates parts of the limbic system such as the basal ganglia and amygdala, which respectively process memory and emotions. Based on studies done with individuals with aphasia – disorders concerning limited capabilities of language processes – their ability to swear does not lessen, suggesting that reflexive and spontaneous swearing originates from regions in the brain unrelated to the language processing centers (Stapleton et al., 2022).

With regulating emotions, extensive connections exist between the amygdala and the prefrontal cortex (PFC), the brain region that regulates executive functions such as planning, judgment, and behaviors. The amygdala sends emotional information to the PFC to process the information and respond accordingly. The medial prefrontal cortex (mPFC) in particular plays a role in emotion regulation, including swearing. It focuses on judging appropriate social behavior, including inhibiting the use of obscene language. However, in the case of automatic swearing, the mPFC does not perform at its highest capabilities, and "the performance of the inhibitory guards deteriorates and the automatic swearing wins over" (Finkelstein, 2018). Thus, while the prefrontal cortex typically regulates speech for an appropriate response, this control is lessened in instances of automatic swearing, and our deep, emotional responses manifest verbally.

The Right Hemisphere and Swearing

Broca's area, the region of the frontal cortex focused on language production, exists in the left hemisphere of the brain for most individuals. However, cases have occurred where damage to the left hemisphere leads to the inability to talk, but the ability to swear remains intact. These situations lead to the idea that the right hemisphere plays a prominent role in the production of automatic speech, including swearing. The differences in the right and left hemispheres extend to the basal ganglia, where its right portion enables swearing. Studies where the right basal ganglia was removed demonstrated the absence of automatic speech (Finkelstein, 2018).

The right hemisphere has been studied as a path for unconscious emotional processing. Behavioral studies, brain imaging, and studies focused on brain pathologies have found that the right hemisphere activates during situations involving automatic emotional responses, specifically subcortical regions such as the right amygdala and thalamus, and visual areas such as the superior colliculus and pulvinar

(Gainotti, 2012). Automatic swearing as a response to stimuli is an example of such an unconscious emotional response, following the same right hemispheric activation as explored by Gainotti.

The Taboo of Swearing

The brain activates not only when one swears, but also when one hears swearing. The "taboo" aspect of swearing is connected to the limbic system. Jeffrey Bowers and Christopher Pleydell-Pearce explored the link in their experiment which studied the idea that "the phonological form of a word can directly evoke a negative emotional response" (Bowers and Pleydell-Pearce, 2011). The researchers conducted an experiment where participants were exposed to swear words and "neutral" words, and their physical responses were recorded. Neutral words included terms not categorized as "taboo" in a language, such as "glue" and "drum." The participants read aloud words that appeared on a screen, including swear words, euphemisms referring to certain swears (i.e. "f-word"), and neutral words. The researchers recorded the participants' skin conductance levels while they read out the words, a measure of activation of the sympathetic nervous system. The results showed a drastic increase in skin conductance when swear words appeared on the screen compared to euphemisms and neutral words. The researchers concluded that "people find it more stressful to say aloud a swear word than its corresponding euphemism" (Bowers and Pleydell-Pearce, 2011). The physical responses when hearing expletives are similar to when a threat is perceived, activating the sympathetic nervous system – "increased heart rate, sweating, faster breathing" (Stapleton et al., 2022) – and reinforcing the taboo aspect of swearing.

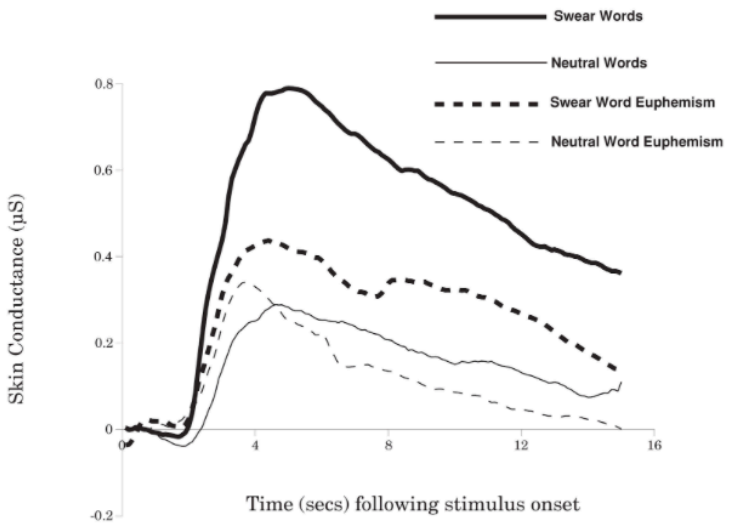

Fig. 1. Skin conductance (µS) as a variable of time (seconds) following stimulus onset. Stimuli: swear words, neutral words, swear word euphemism, neutral word euphemism (Bowers and Pleydell-Pearce, 2011).

Conclusion

The brain's functions involved with swearing highlight the complexity of its abilities. Whether the expletives originate internally or externally, the brain activates the emotional pathways when responding, limiting conscious speech typically in control via the medial prefrontal cortex. The right hemisphere of the brain in particular demonstrates high activity during emotional responses and continues the production of swears independent from the left hemisphere. This lateralization reveals the necessity of both hemispheres to allow for proper human behavior in response to one's environment. Future research may explore specific features of the right hemisphere that connect it to automatic emotional responses and details on why the right and left hemispheres are lateralized in terms of conscious versus emotional response.

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The Use of MRI for the Early Prevention of Alzheimer's Disease

Joy Akindulureni

Abstract

Alzheimer's Disease (AD) is a neurodegenerative disorder that affects the cells in the brain which results in dementia. AD is caused by the accumulation of Amyloid Beta (Aβ)peptides made from protein forms an accumulation in the brain that leads to plaques and tangles that affects the medial temporal lobes and neocortical structures. Early detection of AD is very important for intervention and early treatment to prevent the further progression of the disease in individuals. Magnetic Resonance Imaging (MRI) is a neuroimaging tool that can be used to help study brain changes. MRI can help to detect biomarkers that are associated with AD which could be white matter hyperintensities, hippocampal volume loss, and tau phosphorylation. Tau phosphorylation is due to cerebral atrophy which leads to neurodegeneration. The application of MRI in the early detection of AD could help in the progressive treatment and preventative methods for individuals who have AD or are at risk of developing the disease. This paper will discuss the use of neuroimaging, specifically MRI on the early detection of Alzheimer's in people which can be used in clinical settings and lead to better prevention methods.

Introduction

Alzheimer's Disease (AD) is characterized by decline in cognition, memory loss which in turn alters behavior and interferes with activities of daily living (Breijyeh& Karaman., 2020). It is more defined as an interaction of amyloid βeta protein with glial cells and neurons, which results in neuritic plaques and neurofibrillary tangles in the cerebral cortex mostly in the medial temporal lobes and neocortical structures (Srivastava & Ahmad, 2021). AD is shown by cognitive decline, language capabilities, and loss of memory all of which can later affect behavior of the individual. Some structural symptoms would be progressive loss of neurons, neuronal network destruction and atrophy of the hippocampus (Blennow, 2006). AD symptoms are categorized based on early, moderate or late stages.

AD is a very complicated disease that could be caused by very different factors and there is no precise cause of the disease. For the early stage, the symptoms like misplacement of items, mood changes and memory loss are easily dismissed . The moderate stage is when the symptoms become more severe with difficulty in communication and spatial navigation which can interfere with personal life. In the late stage, symptoms are more severe with no remedy like inability to recognize familiar faces, physical capabilities (Khan et al., 2020)

Previous studies have also shown that atrophy and volume loss in the hippocampus are an early characteristics of AD as they can be associated with cognitive and memory decline (Eskildsen et al., 2015).Therefore, AD is the leading cause of dementia in the world; its prevalence continues to increase with the numbers doubling every 20 years. AD constitutes challenges for the healthcare system and signifies the need for strategies that could lead to early detection.

Early detection of AD is very important for the development of preventive measures and progressive treatment methods for individuals at risk. With neuroimaging tools today, MRI and PET are the most common for their ability to detect brain abnormalities that could lead to a risk in developing AD (Mosconi et al., 2007). Witb these neuroimaging tools, we can be able to further prevent the development of AD in individuals.

Alzheimer's Disease

AD is a neurodegenerative disorder and a common cause of dementia that is caused by cell death due to neuritic plaques and neurofibrillary tangles in the cerebral cortex. It is the sixth most leading cause of death in the United States and is caused by neuronal cell death which starts in the entorhinal cortex of the hippocampus. AD's etiology involves the combination of genetic predisposition, environmental factors and lifestyle choices. Even though AD is known to affect people who are older, it is necessary to know that the symptoms do not progress with age (Zvěřová, M., 2019). Many studies have shown that aging is associated with AD as they have been with approximately 90% of the cases. AD usually affects people from ages 65 and older but it is also possible that the disorder could show up earlier due to other factors like genetic mutations or even underlying health risks like heart diseases or stroke (Blennow., 2006). AD prevalence has been known to be increasing for each year and could keep increasing with the amount of cases each year.

The biomarkers for AD are mostly with blood and the structural brain changes due to the neuroimaging tool that is being used like MRI as it is more accessible and can be better used for diagnosis of the disease.(Altuna-Azkargorta & Mendioroz-Iriarte, 2021). Biomarkers are very essential for the diagnosis of the disease and also help with the use in treatment methods as well. Pathology of AD stems from the plaques and tangles in the brain due to tau phosphorylation. Another biomarker for diagnosing AD could be due to the lessening of hippocampal volume and hyperintensities of white matter in the brain (Schapiro et al., 2009). Early detection of AD would lead to better preventative methods that can be used in clinical settings for individuals.

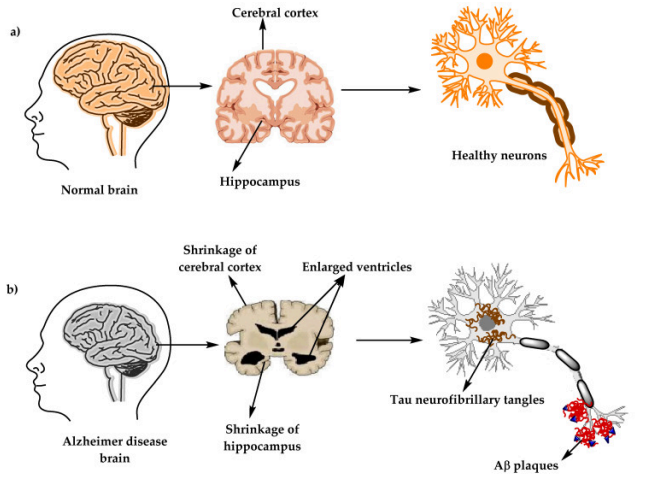

Figure 1. a) Structure of the brain when a healthy with the neurons and hippocampus with b) Alzheimer's showing the plaques in neurons and shrinkage of hippocampus (Breijyeh& Karaman., 2020)

The Role of MRI in the Detection of Alzheimer's Disease

MRI, an innovative and non-invasive tool plays an important role in identifying brain changes earlier that are associated with AD leading to progressive interventions. With MRI, neurodegeneration which is present in cerebral atrophy can be captured by MRI imaging. While not being specific to cerebral atrophy, this biomarker of neurodegeneration along with neuronal injury serves as an important biomarker in the diagnosis of AD.

are also another type of biomarkers that can be used in the diagnosis of AD. Cerebral atrophy is caused by neurodegeneration which can be captured by MRI. Optimization of MRI to diagnose AD can be very valuable in the early detection of the disease. Progression of the atrophy is also later seen in the Medial Temporal Lobe (MTL) and entorhinal cortex which later results in deficits in executive functioning and memory loss for AD patients. MRI can also be used to detect white matter hyperintensities which show demyelination and axonal loss. With the use of MRI, it can play a huge role in the early detection of the disease which could lead to better treatment methods for individuals at risk before it progresses further.

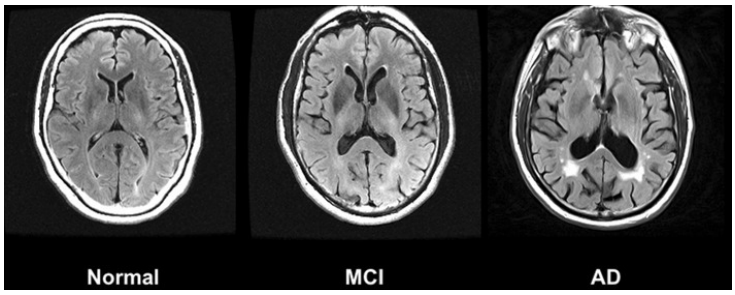

Figure 2. Increased White Matter Hyperintensities in an Alzheimer's patient compared to a healthy normal control and a patient with Mild Cognitive Impairment (MCI) (Chandra et al., 2018).

The focus of the use of MRI can help in detecting the biomarkers associated with AD. The biomarkers associated with AD that could be detected would be cerebral atrophy, which is the loss of neurons and synapses that leads to brain shrinkage from neurodegeneration. Atrophy and volume loss of the hippocampus also show the characteristic of AD that is associated with cognitive decline. This could spread to other regions which leads to worse progression of the disease. When the atrophy spreads to the cortical regions like frontal, parietal and temporal brain regions, the disease worsens which can be captured with MRI (Chandra et al., 2018).White matter hyperintensities is another biomarker that could be detected by MRI as they show the demyelination and loss of axons in the brain. The application of MRI in early detection of AD could make for better treatment methods that can help individuals with the disease or who could be at risk (Chandra et al., 2018).

Challenges and Directions

While MRI can be used in the detection of AD, it also faces limitations due to sensitivity of being able to differentiate AD from either normal aging or other neurological diseases. This limitation showcases the importance for research and refinement. Another limitation would be that there could be an overlap of the imaging characteristics with other disorders that could make the results more complex. Another limitation would be the accessibility and cost that comes with using the MRI due to the equipment, which could limit its use and availability in certain settings.

MRI in the early detection of AD can be useful for the progression of treatment methods of the disease. MRI can be used to capture the alterations in brain structure like the hippocampal volume, white matter loss, and atrophy, which can give a quick insight on the development and progression of the disease before it worsens. MRI can also help clinicians and researchers be able to understand better about the brain structures affected and how they impact function so that there could be more methods for treatment which might eventually lead to a decrease in the prevalence.

Conclusion

AD is a neurodegenerative disorder that affects millions of people worldwide and is known for being associated with aging as it mostly affects the elderly. It is caused by tangles and plaques due to tau phosphorylation which leads to neuronal cell death that affects the cerebral cortex. It is characterized by memory loss, brain structure atrophy, language capabilities and behavioral alterations. Although there is no known cause, there could also be a lot of factors that contribute to the disease which could be genetic or environmental. There are no preventive measures but there are protective measures like maintaining a healthy lifestyle and being physically active which could help.

MRI being a non-invasive tool in neuroimaging could play an important role in the detection of AD that could potentially lead to the further progress of treatment methods. There are some limitations and challenges which could come with the use of the neuroimaging tool like the cost, complexity of the detecting for the disease, and the overlap in imaging features although it can still be an innovative tool to be able to detect for the disease earlier that could lead to better methods for treatment.

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How the Brain Creates Predictive Models of the Environment

Kaitlyn Tuvilleja

Abstract

Researchers, utilizing technologies like fNIRS (functional near-infrared spectroscopy) on 6-month-olds and EEG (electroencephalography) on infants viewing image sequences, can uncover how young brains craft and apply predictive models to react to events. Adult brain learning is also examined through two types: model-free learning (trial and error) and model-based learning (implementing predictive models). By analyzing data from various age groups, researchers can examine how brains craft predictive models of the environment and leverage those findings for future implications. Dissecting the way the brain constructs predictive models of the environment at distinct ages is crucial for developing enhanced educational practices: this paper examines the development of predictive cognitive models from infancy through adulthood using neurological studies, highlighting their implications for enhancing educational strategies and adaptive behaviors.

Introduction

The way that we react or the choices we make in certain situations is hypothesized to be guided by internal models. This can trigger the body's flight-or-fight response, curiosity, and even hunger. For example, when going to the doctor, the doctor will hit an individual's knee to check their reflexes. What may seem like a knee-jerk reaction is a realization of the brain's predictions about immediate danger, analogous to how a pianist's fingers can predict where the next note is through repetitive practice and auditory exposure to their piece. The brain actively constructs a "call for action" that drives us to continuously shape the brain's internal models (Kayhan et al., 2019). This way, the internal map that the brain has created can guide future actions and decisions. The brain's activation process for predictive models can even be thought of as a construction zone: a place where it actively repairs and reshapes the mental map in response to unexpected changes. To support this theory, O'Reilly's team from Oxford University selected a handful of adults and presented a target object that would change positions. The positions included both predictable locations, learned through repeated exposure and unexpected ones. The study revealed that "Activation in the parietal cortex when an immediate motor response was programmed as participants had to update their internal models to accommodate the change of target locations" (O'Reilly, 2013). When the change was predictable, the parietal cortex, a region of the brain responsible for processing sensory information and coordinating motor responses, quickly adjusted the planned motor commands. However, a surprise triggers the brain's anterior cingulate cortex–an area responsible for updating internal models based on error detection–to activate. Essentially, when unexpected movements occur, they trigger specific brain regions in charge of movement planning and adaptation, evidence to the hypothesis of the brain creating internal models. This factors into the ability to create internal predictive models, and how individuals learn and react to the world through these models, starting from infancy.

Predictive Model Creation in Infants

Current research explores how infants develop the capacity to construct mental maps. As of 2015, a functional near-infrared spectroscopy (fNIRS) study was conducted on infants (Gallagher, 2023). An additional study conducted by E. Kayhan at the University of Potsdam demonstrated that at 6 months old human brains already create a predictive model of the environment. More specifically, "after a learning period, when images were unexpectedly omitted, infants showed activation in the occipital cortex, as if an image was presented, suggesting that they generated predictions about the visual input"(Kayhan et al., 2019).

Researchers were interested in how babies process and adapt to change when prompted by unfamiliar environments. To explore this, they conducted a study with sixty 9-month-old infants. Dr. Kayhan and his team had predicted that "if participants formed predictions based on the repeated observations of the predictable stimuli, they would show a prediction error response when their predictions were violated by the unexpected appearance of the cues" (Kayhan et al., 2019). The study involved showing pictures to the babies and would utilize a system that combined sound and brainwave monitoring (audio-visual EEG). The pictures featured a bee, but the sequence changed to test the babies' predictions. First, the babies were shown repetitive images of a bee (expected sequence). This established a control data set for the scientists. Next, the babies were then shown a predictable surprise which included a bee image followed by an image that could be associated with the bee (i.e. a flower). Finally, the babies were shown an unexpected sequence where the bee image was followed by an image that wouldn't make sense (i.e. a truck). Scientists expected that babies' brains would be more surprised if a pattern was not followed, inducing a stronger electrical response called an Nc wave.

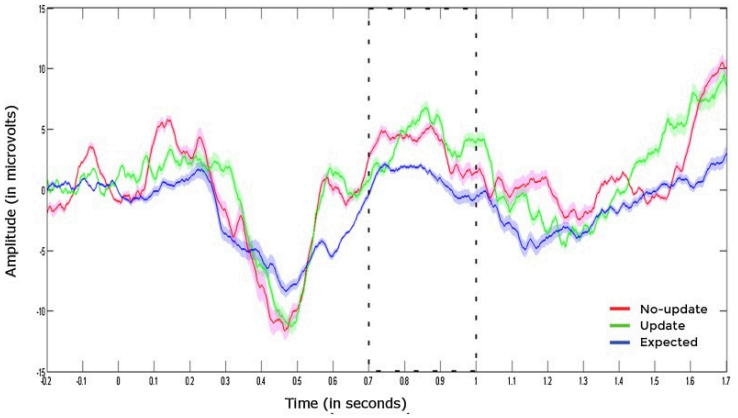

Figure 1. Shows the brain signal from the vertex of the head for the different trial types. The update line shows the highest amplitude meaning the brain produced a stronger Nc wave with the update trial than no-update and expected (Kayhan et al., 2019).

Before the experiment, researchers had predicted that babies would portray a weaker Nc wave (less electrical activity) by seeing the repeated bee images. NC waves detected whether attention was suppressed during the trials (if infants didn't pay attention during trials). Interestingly enough, there was not a significant difference in Nc wave strength between the update and no-update trials within the enclosed section (Fig. 1). This shows that infants might be processing given information more deeply than expected, almost challenging previous knowledge on how infants create predictive models of the environment.

These results can potentially be incorporated in lower education fields, potentially setting a foundation for surprise-based learning. Teachers can implement some surprise or novelty in learning experiences that could benefit children's learning. For example, allowing for more open-ended questions can encourage students to explore different approaches to problem-solving scenarios, sparking curiosity toward unexpected results. By honing in on a child's ability to create predictive models, educators can create more effective and engaging learning practices that foster critical thinking and problem-solving skills.

Predictive Modeling in Adults

However, before revamping academic frameworks based on children's predictive models of the environment, understanding the brain's decision-making is essential. In part, adult brains can learn from reinforcement learning: model-free and model-based (Otto et al., 2015). Model-free RL directly uses past experiences to figure out what actions are rewarding, while model-based RL builds a mental map of how the world works and uses this map to decide what action to take. To further explore this phenomenon, scientist Gläscher strived to find how predictions are created through "trial-by-trial neural signals that reflect the dynamics of this learning" (Gläscher, 2023).

The study consisted of 18 Caltech adult students with normal vision) and no neurological or psychiatric conditions (20/20 and not colorblind). Within two sessions, researchers examined how participants developed optional decisions in a reward-based environment.

The first session involved participants to observe pre-determined choices without rewards. From this, researchers were able to measure state prediction errors (SPEs) – the difference between predicted and actual outcomes – and reward prediction errors (RPEs) – surprises associated with unexpected rewards. By examining the errors, researchers were able to gauge the participant's initial understanding of the system. The second session gave participants the liberty to implement their own choices with the potential of a reward. This tested whether patients could utilize the knowledge in the previous session. Researchers revealed that 13 out of the 18 participants were successfully able to employ model-based learning to execute optimal choices. Suggesting a clear preference for constructing predictive models over trial and error approaches. Participants acquired optimal decision-making through model-based learning which is illustrated through their ability to adapt to the system's modifying tasks, even when rewards were provided. This would demonstrate the idea that "participants would acquire knowledge about the transition probabilities during session 1, despite the absence of any rewarding outcomes. This state knowledge can therefore be only acquired through model-based learning, potentially updated via an SPE" (Gläscher, 2023).

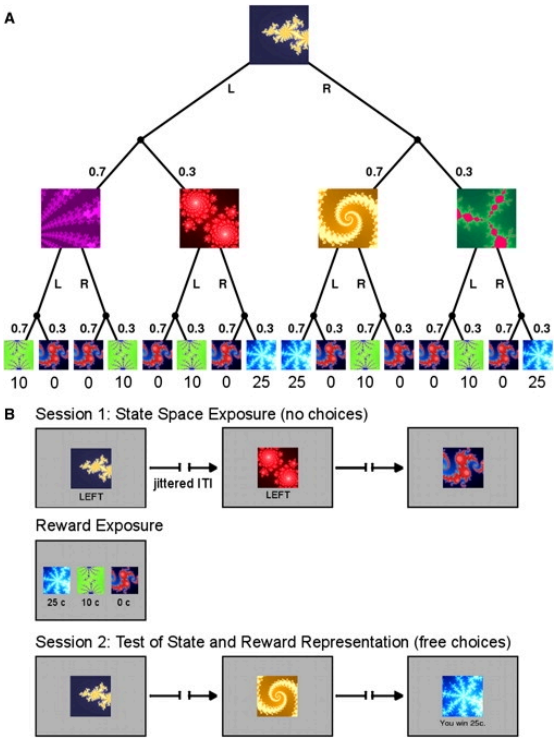

Figure 2. Illustration of the decision-making process of scientist Gläscher and his research team at CalTech's study on model-free reward learning and model-based reward learning (Gläscher)

Future Implications for Learning

Like infants, these findings can be used to configure educational plans for students. As children grow older, their brain develops. To aid these developments, it should be important to continue implementing lessons that can be designed to build upon and challenge these predictive abilities.

Brains do not inactively experience the world but actively work to construct models to predict what will happen next.

This “auto-pilot” function, through its remarkable plasticity, continues to refine its predictive models. Research on infants illustrates the ability to effectively detect unexpected events and update models accordingly. Meanwhile, in part, adults utilize model-free and model-based learning for decision-making. With knowledge of children and adult brain plasticity, educators can leverage these traits to create more engaging learning environments and foster groundwork for adult learning styles. These findings in plasticity hold the potential for unlocking new opportunities for personalized cognitive training programs for children. For example, educational practices can be designed to refine and challenge a student’s predictive models. These implications can be extended to older individuals, as well. With this new profound knowledge of brain plasticity, the possibilities are truly invigorating.

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Symphonies vs. Silence: How Does Music Affect Work Performance?

Sarah Masud

Introduction

Imagine this: you're slouching at your desk, staring at the mountain of tasks you have yet to complete, and your productivity is at a minimum. How do you combat this? Do you pull out your headphones and your favorite playlist, hoping they'll get you in the groove to work? Or do you cut out the distractions and try to focus without any bothersome background noise? The debate on whether music enhances or hinders work performance is a long one running with many studies reporting mixed results. Some individuals say that listening to music uplifts their mood and boosts their productivity, while others insist that working in silence is the key to sustaining focus. While it is difficult to make a definite claim on how music affects work, one important consideration is that different ways of listening to music can lead to different outcomes. It is worth examining how emotional, cognitive, and background use of music impact job satisfaction and performance.

Previous Findings: What's the Big Debate?

Early studies investigating the effect of music on work performance have often posed contradictory findings. Shih, Huang, and Chiang (2012) found that background music containing lyrics had a negative effect on attention and concentration. Similarly, Padmasiri and Dhammika (2014) reported that listening to relaxing music decreased work performance. However, this study didn't consider contexts where workers can choose music rather than just being exposed to it in their work environment. Lesiuk (2010) found that people listening to their preferred music reported lower stress and better mood, as well as improved performance in situations with high cognitive demands. Likewise, a study by Haake (2011) indicated that music at work evokes positive emotions, resulting in feelings of inspiration, concentration, and stress reduction. It may be that workers prefer listening to music because it makes work more enjoyable and increases satisfaction and creativity. However, it's evident that the content and context of music matter greatly.

Music Genre and its Impact

Chamorro-Premuzic and Furnham (2007) describe three ways that people use music in everyday life. The first is emotional use, which refers to evoking positive or negative moods, changing the emotional state, or expressing pleasure in experiencing an emotion that isn't necessarily positive (e.g., finding comfort in sad music). The second is cognitive use, which entails listening to music for intellectual purposes and enjoying the technical aspects. An example of this is seeking out classical or jazz music—not because it's unlikely to elicit emotions, but because its complexity allows for rational appreciation and suits those who like intellectually stimulating experiences. The last is background use, which involves listening to music while performing other tasks without getting distracted.

Using these three uses of music as a foundation, a study by Sanseverino et al. (2022) sought to understand how emotional, cognitive, and background use of music affect perceptions of job satisfaction and performance. They hypothesized that (1) emotional use has a positive relationship to job satisfaction and performance, (2) cognitive use has a positive relationship to job satisfaction and no direct relationship to performance, and (3) background music has no direct relationship to job satisfaction or performance. To test this, 424 participants were instructed to complete a questionnaire about their music listening habits while working. 57.7% reported listening to music, 26.5% reported not listening to music because they could not, and 15.8% reported not wanting to listen to music. For this study's purposes, only the 244 participants who stated that they listen to music while working were considered.

Music use was determined using fifteen questions from Chamorro-Premuzic and Furnham's 2007 study, which consisted of five questions for each use of music. Respondents rated how they use music on a Likert scale from 1 ("strongly disagree") to 5 ("strongly agree"). Job satisfaction was assessed with five questions on the same scale, and respondents rated their satisfaction in various areas such as relationships, physical conditions, and prospects. Finally, job performance was measured using four questions. Participants were asked to rate how effective they've felt regarding different aspects of their performance, such as, "How effective were you in performing without mistakes?" Altogether, these measures would uncover whether different uses of music are correlated with different work outcomes.

Results and Implications

Sanseverino's 2022 study found that both job satisfaction and performance are positively correlated with emotional use of music, which confirms the first hypothesis. Cognitive use showed non-significant relationships both with satisfaction and performance, disproving the second hypothesis. Finally, background use had a negative correlation with job satisfaction, disproving the third hypothesis, and didn't show any significant relationship with job performance. Age, interestingly, showed a negative relationship to all three uses of music, indicating that music use during work may decrease as people grow older. Another fascinating finding was that men were less likely to use background music and more likely to engage in cognitive use.

In this study, emotional use of music was the only type associated with positive effects on both job satisfaction and performance. But why is this, and what aspects of emotional use could lead to more positive outcomes than other uses of music? It may be that enjoying the emotion elicited by music enhances perceptions of work satisfaction. In turn, this combination of a charged emotional state and increased satisfaction could contribute to more positive perceptions of tasks accomplished at work.

Cognitive use of music, which was more common in men than women in this sample, is surprisingly not related to job satisfaction. However, this could be explained by the participants that were recruited; this study intentionally excluded professional musicians who engage with this type of music more frequently, resulting in a sample that had low scores on cognitive use. Another explanation for this low number could be that the positive emotions evoked from cognitive use were mistaken for emotional use, which would be far more common in this sample of non-musicians. Future studies with more representative samples—including musicians and more women engaging in cognitive use—could further investigate why cognitive use is unrelated to job satisfaction. One possibility is that appreciating the technicality of music adds an extra requirement to work, so cognitive use distracts workers from pursuing more important tasks. Therefore, this would counteract any positive activation they get from enjoying the structure of music.

Lastly, background use of music seemed to only have negative effects in this study, including a significant negative correlation with job satisfaction. However, this study cannot assume any causal relationships due to its cross-sectional design; that is, data on music habits and satisfaction was collected at a single point in time, so it's unclear which came first. It's possible that the effect is reversed and the more people feel dissatisfied with their work, the more they use music as background noise.

This general rule that correlation is not causation is important to keep in mind for all three uses of music and their reported effects. To determine any causality, it would be necessary to conduct further longitudinal studies; that is, research that repeatedly measures effects over time rather than a single instance. Future work could also apply this research to the real world and outline how organizations can use music as a resource. Even an approach as simple as implementing quiet workspaces, where employees are free to engage with their chosen music or none at all, can increase performance and satisfaction across the board while accounting for individual preferences.

Conclusion

The conversation surrounding the influence of music on work performance is nuanced, with various studies reporting different results. While some swear by the motivational power of their favorite songs to boost productivity, others find comfort in the tranquility of a silent workspace. The study conducted by Sanseverino et al. (2022) sheds light on the multifaceted relationship between different uses of music and job satisfaction and performance. Emotional use of music was found to be positively correlated with both job satisfaction and performance, suggesting that the emotions evoked by music can enhance perceptions of work satisfaction and task accomplishment. On the other hand, cognitive use of music did not show any significant relationships, and background use of music primarily demonstrated negative effects, particularly concerning job satisfaction. This suggests that excessive reliance on music as background noise could be a common reaction to feeling dissatisfied with work. However, it's important to note that reasons for listening to music and the outcomes gained vary from person to person. By recognizing the different ways music is used and its varying effects on job satisfaction and performance, organizations can tailor strategies to support their employees' well-being and productivity. From creating designated quiet spaces to offering flexibility in music choices, accommodating different preferences is key to creating a productive and enjoyable workplace.

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Dopamine: A Social Neurotransmitter

Vraj Patel

Introduction

Humans live in a social world. We constantly exercise the social aspect of the mind in our everyday lives, face-to-face with others, in large group settings, and even online. Social interactions are critical to human life; without them, we may not even be considered “human.”

Social interactions involve many parts of the brain, both in performing them and their outcomes. Dopamine plays an interesting role in the outcomes of social interactions. It is a neurotransmitter involved in pleasure, satisfaction, motivation, and body movements (Costa & Schoenbaum. 2022). Dopamine mainly functions in a brain pathway involved in motivation: the mesocorticolimbic pathway. Originating in the ventral tegmental area (VTA), dopaminergic neurons – neurons that release dopamine – project to the nucleus accumbens (NAc) and the prefrontal cortex (PFC). This pathway allows for producing and maintaining feelings of motivation and desire (Reynolds & Flores, 2021). Such feelings may arise during social situations, impacting our interactions and promoting the necessity of sociality in humans (Krach et al., 2010). The focus of the discussion is on the connection between social environments and dopamine pathways.

The Reward System and Dopamine

Research conducted by Dr. Solié Clément, Dr. Benoit Girard, and their team at the University of Geneva explored the activity of the VTA in mice during periods of social interaction. They found that the VTA dopamine firing rate increased when the mice were in social contexts, particularly in this case, when other mice were present in their view. Additionally, the physical proximity of other mice was correlated with an increase in VTA activity. This means that the closer the other mouse was to the experimental mouse, the more activity was recorded. The team concluded that being around other mice activated the “reward” pathway in the brain, increasing the mouse’s desire to remain in the social setting and driving social interaction.

The study also found that within the VTA, a subset of neurons activate only when experiencing “novel” stimuli and decrease firing when habituated to a certain stimulus. When an experimental mouse was repeatedly placed in a context with the same mouse, the VTA firing levels reduced after each subsequent round, suggesting habituation towards the social stimuli. These findings complicate the VTA and reward system of the brain.

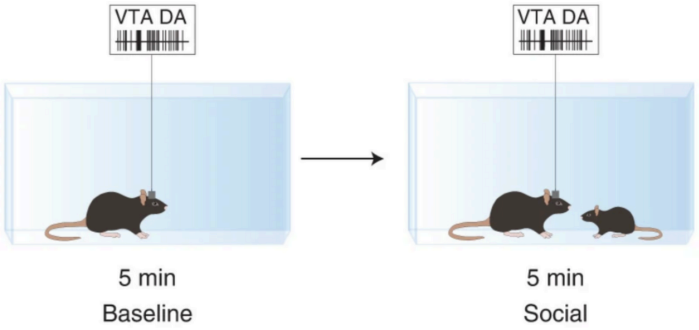

Figure 1. Important Regions Regarding Neurogenesis. In-depth view of where neural stem cells proliferate. (2023). Neural Stem Cell Culture Protocols. https://www.sigmaaldrich.com/US/en/tec hnical-documents/protocol/cell-culture-an d-cell-culture-analysis/stem-cell-culture/n eural-stem-cell-culture-protocols

Future Research with Dopamine and Social Contexts

Dopamine activity occurs during social situations, as seen in the mice in Solié’s study. This brain feature may be a reason for the necessity of social environments for certain species, including humans. The involvement is complex, though, as repeated exposure to the same individual lessens dopamine activity, demonstrating habituation. Future research could explore decreased dopamine levels, as seen in some neurological disorders, and their effect on social interactions. Such research could provide information on whether dopamine levels are a factor causing social interactions, or whether they are an output of being social.

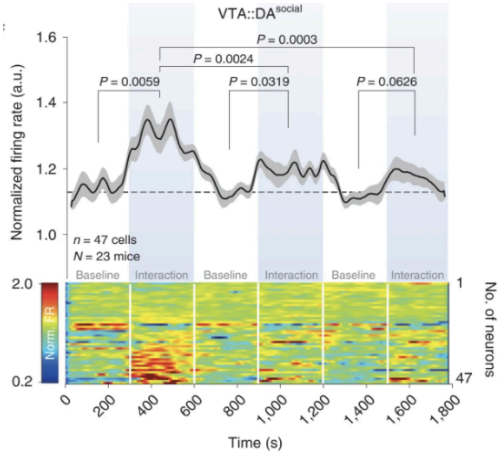

Figure 2. The activity of VTA DA neurons when the mouse was in social settings. The black line demonstrates the firing rate during the baseline and when interacting. During each subsequent interaction, the VTA firing rate decreases, as seen by the diminishing firing peaks (Solié et al. 2021).

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Impacts of Lifelong Bilingualism on Neurodegenerative Diseases

Esther Nam

Abstract

Lifelong bilingualism is the regular use of two languages throughout one's daily life. Constantly switching between languages requires more control over word selection and the ability to resolve interference from the language not in use (Abutalebi & Green, 2016). Because bilinguals face these conflicts on a regular basis more often than monolinguals, there has been evidence of structural changes and increased connectivity from overuse of certain areas and networks of the brain associated with carrying out these executive control tasks. This article aims to provide insight into how bilingualism and reserve works together, and how that relationship can manifest improvement in cognitive functioning in individuals with neurodegenerative diseases.

Introduction

According to the 2021 census, 22% of the U.S. population who are older than 5 years speak another language other than English (U.S. Census Bureau, n.d.). Researchers have found that Alzheimer's disease (AD) is delayed by 4-5 years in lifelong bilinguals when compared to their monolingual counterparts (Bialystok et al., 2007; Craik et al., 2010). The exact mechanisms underlying this phenomenon are not quite known, but many interpretations of various observational results have indicated that because the bilingual experience involves constant cognitive conflict between two languages, there is a strengthening in associated networks as well as structural changes in the brain that ultimately contribute to cognitive and brain reserve. Since bilinguals face these conflicts much more often than monolinguals do, they consequently have larger reserves that serve as a neuroprotective factor against neurodegeneration or even the normal course of cognitive decline that comes with aging.

Reserve is a hypothetical construct used to explain how some individuals who have suffered brain damage maintain similar cognitive and functional ability to those with healthy undamaged brains. The amount of reserve an individual has determines the amount of damage the brain can tolerate without deterioration in functioning. Increased brain reserve allows for 'damage' to accumulate without significantly affecting cognitive ability, which may explain why bilingual individuals show less cognitive decline than monolinguals, even when their brains exhibit greater levels of deterioration (Gold, 2015; Bialystok et al., 2007; Sala et al., 2021). This then leads to the question of whether bilingualism may also help protect against expression of clinical symptoms in other neurodegenerative disorders such as Parkinson's disease (PD) and multiple sclerosis (MS). According to one literature review, this is possible as there is insufficient evidence to conclude otherwise (Voits et al., 2020).

The incidence of Alzheimer's disease in the U.S. in 2050 is projected to double, according to Alzheimer's Association (Alzheimer's Association, 2023). Therefore, it is vital to thoroughly investigate the link between neurodegeneration and the bilingual experience, which may reduce neurodegenerative disease prevalence (Bialystok et al., 2007) and improve overall quality of life. But to understand how bilingualism can delay clinical expression of neurodegenerative diseases, we must first understand the concept of reserve and the protective role it plays.

Reserve

Reserve explains how some people with brain damage demonstrate a similar level of cognitive ability to people with non-damaged brains. One case showing this is a study done by Katzman et al. where 10 patients with AD performed as well as matched controls did on cognitive tests. They also found that these patients had larger brain weights and more neurons than the controls to maintain cognitive and functional ability through mechanisms of reserve (Katzman et al., 1988). There are two types of reserve models: active and passive. These models differ in the way they are defined and may lead to different interpretations of results, but in the case of bilingualism, both are applicable.

Active Model - Cognitive Reserve and Compensation

The active model currently involves two subtypes of reserve: cognitive reserve and compensation. Cognitive reserve (CR) refers to the way an individual approaches a task in terms of the networks and resources the brain uses in the moment, hence "active." It is also active in the sense that it depends on neural activity, experiences, and exposures that the person experiences in their lifetime (Barulli & Stern, 2013). Therefore, people with higher cognitive reserve can carry out cognitive tasks in a more efficient manner (Stern, 2002). The main proxies that have been the most studied are education, occupation complexity, IQ, and, a more recently introduced yet prevalent one, bilingualism. In terms of these proxies,

higher education levels, cognitive demand by an occupation, and IQ are associated with greater levels of cognitive reserve. An example of cognitive reserve coming into play includes a study done by Poletti et al. where they found more educated patients with Parkinson's disease (mild cognitive impairment (PD-MCI)) had a slower progression towards Parkinson's disease dementia (PDD) than those who were less educated (Poletti et al., 2011). A different study by Thorvaldsson et al. investigated effects of IQ in terminal decline (TD) on motor speed, perceptual speed, spatial ability, and verbal ability in the elderly population of Gothenburg, Sweden. TD is the acceleration of cognitive decline a person experiences in their final years before death. They first measured the IQ of the participants using a simplified version of the Raven Standard Progressive Matrix called the Raven Coloured Progressive Matrix, which was more suitable for older participants. Results show that those with higher IQ tended to express later onset of cognitive declines in the variables of interest than those with lower IQ, which is in line with the cognitive reserve hypothesis (Thorvaldsson et al., 2017).

Stern describes cognitive reserve as arising from two ways of using brain networks: increased efficiency in using a network of interest and the ability to recruit alternative networks to carry out increasingly demanding tasks (Stern, 2002). According to referenced studies, the normal response to a more difficult task is to use the current brain network more actively and/or to recruit additional networks to help (Stern, 2002). Between two individuals with different levels of cognitive reserve, the person with a higher amount will recruit the same amount of neuronal activity on a difficult task as the individual with a lesser amount on an easier task. For the ability to recruit alternative networks, Stern writes that having a higher cognitive reserve enables an individual to recruit a larger array of networks to carry out a difficult task (Stern, 2002). Compensation is very similar to cognitive reserve, but it is referred to as such in the context of brain injury or brain damage (Barulli & Stern, 2013; Stern, 2002). When someone suffers brain damage that affects the normal brain network they use for a certain task, they are forced to use an alternative method to complete the same type of task. Their brain must "compensate" for the impaired or lost network. One of the proposed neurological bases for cognitive reserve is known as neural reserve, which encompasses the networks that are used during task processing (Barulli & Stern, 2013).

Passive Model - Brain Reserve (Threshold Model)

The passive model, or threshold model, is solely based on the brain's anatomical structure. This would include brain size or weight, the number of neurons it has, the number of synapses, gray matter volume, and so on. Compared to cognitive reserve, this model is much more objective as it relies on a strict structural component that determines what is called brain reserve capacity (BRC). The theory is that every person has a certain predetermined level of BRC based on their brain structure, hence why this model is "passive."

If a person suffers through an insult to the brain, the functional impairment is expressed in the amount of damage that has exceeded the amount of BRC. In other words, there is a "threshold" that must be surpassed for brain damage to express its effect on cognitive function (Barulli & Stern, 2013; Stern, 2002). This is not to say that BRC is predetermined at birth. It is based on brain structure at the time insult was received, which can account for any accumulated structural changes.

Lifelong Bilingualism and Reserve

Bilingualism can be defined as a gradient in terms of the proficiency of the second language (L2), from elementary to near-native. In this paper, bilingualism is defined as having near-native proficiency of L2 from a young age, unless specified otherwise. Bilingualism as a proxy for cognitive reserve has more recently gained prevalence in the last couple decades compared to other proxies such as occupation (Bialystok et al., 2007, Gold, 2015; Subramaniapillai et al., 2021 (review)).

This includes selecting the target language according to context, selecting vocabulary consistent with the target language, inhibiting words from the language not in use, monitoring speech for intrusions from the other language, and disengaging and engaging in language when switching back and forth (Abutalebi & Green, 2016). These processes all contribute to increasing CR because they are cognitively demanding tasks that are completed regularly, depending on the context of the language use. In terms of differential functionality, a study by Mouthon et al. (2019) demonstrates how the use of a second language increases efficiency of network use in university student translators who were moderately (LP) or highly proficient (HP) in their L2.e participant name the object in the given picture in their first language (L1) and/or L2 depending on the task conditions. The authors found that the HP group exhibited activation in the general control network whereas the LP group exhibited activation in the language control networks. The language control network is larger and responsible for linguistic-related cognitive processes while the general control network is responsible for more general processes such as planning. The findings suggest that with higher L2 proficiency, there is less reliance on the language control network as controlling the two languages can be done with the same resources as any other general cognitive task. This corresponds to what Stern wrote about efficient network use where the more difficult the task, individuals with higher reserve tended to show less activation in task-related areas (less activation in language networks for language-related tasks) compared to those with less reserve recruiting more of the task-related areas (Stern 2002).

The language control network consists of several key brain regions. These include the dACC/pre-SMA complex, left prefrontal cortex, right inferior frontal cortex, inferior parietal lobules, cerebellum, and subcortical structures like the thalamus, left caudate, and left putamen (Abutalebi & Green, 2016).

Some of these structures experience an anatomical change from continued use by bilinguals. One such case mentioned by Abutalebi and Green is the dorsal ACC (dACC) and pre-supplementary motor area (pre-SMA), which are involved with conflict resolution, language selection, and language switching. Studies reviewed by these authors have found increased gray matter density, often measured as the mass of neuronal cell bodies in grams per cubic cm, of the dACC in bilinguals (Abutalebi & Green, 2016). Borsa et al. (2018) conducted a study with older bilingual and monolingual adults that investigated the cognitive and neural hypotheses at the same time. Gray matter volume (GMV) of the ACC, one of the region of interests that were selected, showed to be a strong predictor of interference and conflict effects in the cognitive control test Attentional Network Task (ANT) in older bilingual adults, which was not the case for the monolingual group. Gray matter volume (GMV) of the ACC, one of the region of interests that were selected, showed to be a strong predictor of interference and conflict effects in the cognitive control test Attentional Network Task (ANT) in older bilingual adults, which was not the case for the monolingual group. An interesting finding from this study was that the mean GMV between the monolingual and bilingual groups had no significant difference, which contrasts with previous studies that did find a difference (Abutalebi et al., 2015). One possible explanation could be the proficiency level of the L2. It is hard to tell if proficiency levels in the L2 were close to proficiency in L1 in Borsa et al.'s study as a result. Another difference is the age of acquisition (AoA) of the L2, where in Borsa et al., 2015, the mean AoA was 6.20 years compared to 12.68 years in Abutalebi et al. (2015).

In addition to gray matter, white matter, and the amount of myelinated neuronal axons per unit volume may also be affected by a bilingual experience. In a study by Luk et al., white matter integrity was found to be higher in older bilingual people, and they also displayed stronger white matter connectivity between anterior-posterior regions of the brain. These results have been interpreted as possible explanations for previous research showing older bilinguals to have higher levels of cognitive control than their monolingual counterparts (Luk et al., 2011). Olsen et al. have also found an increase in overall brain volume, including both gray and white matter, in the frontal and temporal lobes compared to monolinguals. These differences are interpreted to enable bilingual individuals to access a larger network of brain regions and stronger connectivity (Olsen et al., 2015).

Bilingualism, as mentioned earlier, is a continuum of L2 proficiency. Higher proficiency level is associated with increasing gray matter volume (Abutalebi & Green, 2016) and the evolution of the mechanisms of language control (gradually shifting resourcing from language-specific networks to general cognitive networks) (Mouthon et al., 2019). To put it another way, the benefits of bilingualism are given in a "dose-dependent manner" (Sala et al., 2021), which emphasizes the bilingual continuum.

Bilingualism may also affect networks involved in executive function. In a literature review comparing the effects of bilingualism on memory systems and executive functioning systems, it seems that the effects of bilingualism act via the protection of executive functioning networks rather than the protection of memory circuits (Gold, 2015), which dementia mainly impacts. Continuous language switching requires a great deal of control, which with overuse, indirectly strengthens general executive control systems through old age (Gold et al., 2013; Gold, 2015). It has been hypothesized in one study that increased activity in frontoparietal and frontostriatal networks that are associated with the bilingual experience can lead to neuroprotection against the decline in the executive control circuits (which involve frontostriatal and frontoparietal networks) (Gold et al., 2013). This is supported by that study's findings comparing older adults' performance in a task-switching paradigm involving switching between colors and shapes. Older bilinguals outperformed older monolinguals with less effort, indicated by requiring less activation, suggesting that switching in language also improved the ability to switch in general areas outside of language (Gold et al., 2013).

The protective effect of bilingualism against the expression of AD symptoms has been evidenced, as well as its protective effects against age-related decline.

Bilingualism and Alzheimer's Disease

Alzheimer's disease (AD) has been consistently listed as one of the top causes of death among older adults. The main etiologic theory of AD is the Amyloid Cascade Hypothesis: the accumulation of amyloid-β peptide in the brain is a significant cause for the development of AD (Karran et al., 2011), of which the main components are amyloid plaques, neuritic plaques, and neurofibrillary tangles (NFTs) (Thal et al., 2013). Dementia is sometimes a symptom resulting from this disease, and progression to this stage can often be predicted with the presence of mild cognitive impairment (MCI). MCI is characterized by cognitive impairment that cannot be considered normal healthy cognition but is also insufficient to be diagnosed with AD (Voits et al., 2020).

With respect to reserve and the expression of AD symptoms including MCI, previous research provides evidence for brain reserve or cognitive reserve to be responsible for the delay in onset of dementia symptoms (Voits et al., 2020). To summarize, patients diagnosed with Alzheimer's who are bilingual can demonstrate similar cognition functioning to their monolingual counterparts with greater brain atrophy, or a decrease in brain tissue. It is also suggested that bilinguals are able to maintain normal cognitive processing by making up for brain atrophy by using alternative networks that do not use the atrophied brain regions. This aligns with the study by Sala et al. (2021), where despite exhibiting similar levels of cognitive impairment, bilinguals with AD showed greater levels of cerebral hypometabolism than monolinguals. Cerebral hypometabolism is when the brain is consuming less glucose than normal, and can be indicative of damage.

It has also been found that bilingual patients rely on alternative network use than normal ones that may have been affected by AD pathology. This is indicative of compensation due to the context of a brain injury, in this case damages caused by AD. A common conclusion in the study of bilingualism as a lifestyle is that it can delay the onset of Alzheimer's disease symptoms by around 4-5 years (Bialystok et al., 2007; Craik et al., 2010). Studies reviewed by Gold also find delays of 3 years for multilinguals, 4.5 years for native-born bilinguals, and 6 years for illiterate bilinguals (Gold, 2015).

While some argue that reserve slows the decline rate, others argue that both monolinguals and bilinguals experience decline at the same rate. However, bilinguals still maintain functioning for several years before they begin to experience cognitive impairment. Bialystok et al. supports the latter theory, with their study–of bilingual and monolingual patients meeting criteria for AD with dementia or other dementia-related neurodegenerative disorders–showing both groups display similar rates of cognitive descent, but bilinguals have better cognition than monolinguals despite that because they have more CR to compensate for degeneration (Bialystok et al., 2007). This is also in agreement with the study by Sala et al. (2021) regarding cerebral hypometabolism described earlier.

The neural explanation of this effect is in its initial stages of study but is suggested to be that bilingualism mitigates atrophy not through memory systems but through executive function systems. Gold's hypothesis states that an increase in activity in the frontoparietal and frontostriatal networks, both of which are part of executive function systems, due to inhibiting and switching caused by bilingualism may protect against decline in executive control circuits. Neural mechanisms that arise from this include increased neuronal activity, enhanced glucose/oxygen delivery, myelination, myelin protection, and others (Gold, 2015). In other words, the usage of two languages may accumulate more reserve via adaptations in neural mechanisms within the executive functioning/control networks.

Bilingualism and Parkinson's Disease

Parkinson's disease (PD) is a disease that affects the nervous system, causing motor symptoms including tremors and/or stiffness (Mayo Clinic, 2023). In addition to motor symptoms, people with PD may also exhibit a range of cognitive impairment: healthy, mild cognitive impairment (PD-MCI), and dementia (PDD). PD has a range of etiology, including both genetic and environmental factors that make it a heterogenous disease (Voits et al., 2020). Pathology is largely characterized by loss of dopaminergic neurons in the nigrostriatal pathway of the brain, which can cause the motor symptoms that are often associated with Parkinson's (Poletti et al., 2011).

Neurologically, Parkinson's affects both gray and white matter structure and integrity. Notable regions of gray matter affected that may explain MCI are the basal ganglia, thalamus, caudate nucleus, putamen, hippocampus, amygdala, and nucleus accumbens. There have been findings that these regions are associated with deterioration in attention, executive functioning, and cognitive decline (Aarsland et al., 2017). There is widespread thinning of cortical gray matter that is associated with increased cognitive decline. Before gray matter deterioration, however, white matter is impaired first and has been found to predict the course of cognitive decline in PD patients towards PD-MCI (Voits et al., 2020).

In terms of the relationship between PD symptoms and CR, one of the most commonly studied proxies seems to be education. Like bilingualism, education can also impact the amount of CR an individual has because it can require more controlled processes and conceptualization abilities (Le Carret et al., 2010). In a systematic review of cognitive reserve and PD, Hindle et al. only found studies that used education as a proxy in their search that included education, occupation, and leisure activity (Hindle et al., 2014). Their review shows that while there was a significant association between higher education level and better performance on cognitive tests, there is insufficient evidence to make the conclusion that cognitive reserve has enough of an impact to delay the onset of PD-related cognitive decline or dementia. Another review that looked at PD-MCI and cognitive reserve also found education to exert a protective effect against cognitive decline (Poletti et al., 2011), and that having more education can decrease the risk of progressing from healthy cognition to PD-MCI (Gu & Xu, 2022). However, further research would be required to investigate the underpinnings of this relationship, along with investigation of how other proxies of cognitive reserve may affect MCI differently. Ciccarelli et al. tries to diverge from using solely education to measure reserve by including other factors like intelligence, occupation, and leisure activities (Ciccarelli et al., 2022). Through this new operationalization, they found that cognitive reserve is also associated with creative and cognitive leisure activities, such as playing music, along with education for both PD patients and healthy controls. This gives potential for bilingualism to have an impact on the progression of cognitive impairment in PD-diagnosed individuals.

In contrast to education and intelligence, bilingualism and its relation to PD is severely under-researched. There are only two studies to date (Hindle et al., 2015; Fishman et al., 2021) that investigate the two, specifically testing whether the cognitive reserve model holds in the face of cognitive impairment (Stern, 2002). Hindle et al. conducted a study that evaluated executive functioning performance in monolingual and bilingual PD patients with tasks that assess mental generativity and speed, working memory, inhibitions, response conflict monitoring, set shifting and switching, and attention. Results showed there was no significant difference between the two groups, suggesting that the cognitive reserve model does not apply. Similar findings were found by Fishman et al. where there were no significant differences found between bilingual and monolingual PD patient performance in executive functioning, memory, and

and visuospatial domain assessing neuropsychological tests. Bilinguals also performed worse than their monolingual counterparts in both language-related tasks (Boston Naming Task, Test of Adult/Adolescent Word Finding: Verb Naming, Boston Diagnostic Aphasia Examination: Semantic Probe, Vocabulary) and attention/working-memory-related tasks (forward and backward Digit Span test). However, a major limitation of this study in particular is the ratio of bilingual to monolingual patients in the sample, with only 15% being bilingual. One plausible explanation for these results may be that the bilinguals have accumulated more severe atrophy than the monolinguals and are performing with similar cognitive ability, which cannot be known without establishing the amount of pathology each group experienced (Voits et al., 2020). Another explanation Voits et al. raises is the age of onset of PD, which is usually during old adulthood. Because of this, it may take much longer for clear differences to rise. In other words, cognitive impairment was too minimal for a difference to be observed.

Bilingualism and Multiple Sclerosis

Multiple sclerosis (MS) is a disease where the immune system attacks myelin in the central nervous system ("Multiple Sclerosis," 2023). It affects both gray and white matter, with common pathology including demyelination, axonal destruction, and loss of oligodendrocytes (Lassmann, 2018). MS differs from other neurodegenerative diseases in that the age of onset is much earlier (early adulthood between 20 to 40 years), and it presents itself differently person-to-person depending on the damage done (Voits et al., 2020; NIH). There are four subtypes of MS: relapsing remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive-relapsing MS (PRMS). The progressive subtypes are continuous, consequently having more severe cognitive outcomes. Because MS presentation consists of a variety of symptom presentations with different etiology, it is considered a heterogeneous disease (Voits et al., 2020). This variability results from the widespread development of lesions that can lead to independent cognitive, neuropsychiatric, and motor symptoms (Chiaravalloti & DeLuca, 2008).

While the trend between MS and reserve has not been thoroughly studied as much as that between AD and reserve, there is some evidence supporting the theory that increased cognitive reserve can delay the onset of cognitive decline that comes with the disease. In an investigation to see how cognitive reserve could affect cognitive functioning in MS patients, it was found that MS patients who had higher cognitive reserve performed as well as the healthy controls in tasks that tested processing speed (Symbol Digit Modalities Test – Oral version), working memory (Paced Auditory Serial Addition Test), and verbal learning and verbal memory (Logical Memory Subtests I and II). Healthy controls also outperformed MS patients with lower cognitive reserve (Sumowski et al., 2009). This supports Stern's cognitive reserve model (Stern, 2002) that having higher amounts of reserve can enable an individual to maintain their cognitive functioning in the face of increasing difficulty (task difficulty or difficulty due to damage) because they have learned to use networks more efficiently or recruit more networks.

There has also been literature by overlapping authors that delve further into cognitive reserve and MS specifically. Sumowski and Leavitt authored a review of literature that investigated the types of contributors to cognitive reserve and how they could reduce or delay cognitive decline (Sumowski & Leavitt, 2013). They described two major categories: larger maximal lifetime brain growth (MLBG), which is heritable, and lifetime intellectual enrichment, which is obtained from environmental factors. Essentially, MS patients with larger MLBG are able to withstand more severe brain atrophy while still being able to maintain cognitive functioning. In terms of intellectual enrichment, MS patients who had more intellectual enrichment (i.e. level of education, vocabulary knowledge) could perform better cognitively and, like those with higher MLBG, withstand greater atrophy while maintaining cognitive functioning. This establishes a trend in bilingualism and a delay in cognitive decline in MS patients. Sumowski and others follow up on the ideas of MLBG and intellectual enrichment by conducting a longitudinal investigation, which is a study design that collects data from the same people over a period of time. Results indicated that increased MLBG and increased lifetime intellectual enrichment have led to a delay in the decline of cognitive functioning by 4.5 years, further supporting the cognitive reserve model (Sumowski et al., 2014).

Bilingualism as a cognitive reserve proxy against MS has not been yet thoroughly studied, but there may be some preliminary conclusions that can be made about this relationship. In a study comprising of patients diagnosed with RRMS, Aveledo et al. examined for differences between the performances of bilingual and monolingual patients on the flanker task, assessing monitoring load and cost (monitoring mechanism) and conflict effect, or the time it takes to resolve a conflict like those presented in the Flanker task (inhibitory control) (Aveledo et al., 2021). A flanker task is a test displaying a series of five arrows from which the participant has to determine if the arrows are congruent or not based on the target arrow (middle arrow), and which direction the target arrow is facing as fast as possible. In this study in particular, the arrows are replaced by five fish, and monitoring load and costs were measured by performance accuracy, and the difference in performance between the high-monitoring (equal number of incongruent and congruent trials) and low-monitoring (greater number of congruent trials) conditions, respectively. The bilingual group did as well or better than healthy controls in monitoring, but performed no differently than monolinguals in inhibitory control. On the other hand, in a study of patients diagnosed with RRMS that compared the executive functioning tasks of bilinguals and monolinguals showed the bilingual group only outperformed the monolingual group with significance in non-verbal tasks involving both attention and inhibitory control (Soltani et al., 2018). As of now, there are not any conclusive theories that can be made about how the bilingual experience could

impact MS symptoms with regards to inhibition and attention. It is especially difficult to identify differences that occur potentially because of bilingualism because the advantages that are seen with bilingualism are more prominent in older populations (Aveledo et al., 2021; Gold et al., 2013). There is also the need to address the heterogeneity of MS presentation which could also be a confounding source to some of these results. Because participants were diagnosed with RRMS, the subtype of MS least subject to cognitive decline, they may not have experienced sufficient impairment to demonstrate a significant difference between monolinguals and bilinguals in executive functioning performance (Aveledo et al., 2021; Voits et al., 2020). While there is still more research that would need to be done, there is potential for bilingualism to have a positive impact on people diagnosed with MS in maintaining some of their executive functioning.

Conclusion

Bilingualism and AD has been much more thoroughly studied than with PD, MS, or other neurodegenerative diseases. However, given the findings of previous research, it is becoming important to investigate these other probable links especially with bilingualism becoming a recurring cognitive reserve proxy in reserve studies.

Bilingualism, specifically for those who have been bilingual since a young age, is classified as having the potential to increase both brain and cognitive reserve because the control of languages in use lead to anatomical structural adaptations and functional activity. In the case of Alzheimer's disease, there have been repeated findings of delay in onset of AD symptoms and diagnosis in bilinguals. While PD and MS have not been studied as much, there is potential to find more direct reserve effects because of bilingualism based on the reserve effects by levels of intelligence and education.

While not a cure for these diseases, being able to ground a relationship between neurodegenerative cognitive impairment could provide methods for improving the quality of life for more years in the older adult population.

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Brain Matters Board

President

Katy is a graduating Senior in MCB with a certificate in Neuroscience. Her favorite thing about being the President of Brain Matters has been meeting new people each semester and sharing her passion for neuroscience. Her research interests center around the interactions between the peripheral immune system and the brain, with a particular focus on the modulation of microglia by peripheral infection. After graduation, she plans to attend Ohio State University to pursue a PhD in neuroscience.

Co-Chief Editor

Andrew is a sophomore with a major in Neuroscience and minors in Spanish and Chemistry. One favorite thing about being Editor in Chief for BrainMatters is that he gets to read so many interesting articles about Neuroscience-related discoveries everyday! Outside of the club, he pursues research regarding optimization with on-tissue chemical derivatization and proteomics projects.

Co-Chief Editor

Manan is a Senior majoring in Brain and Cognitive Sciences and is pursuing a minor in Chemistry. Apart from being a pre-dental student, Manan has previously been an Orientation Leader at UIUC. Last summer, Manan worked with people of determination and designed thinking modules for underprivileged students in India. Outside of class, Manan is deeply interested in reading books that pertain to cognitive psychology and productivity, engaging in insightful scientific dialogue and community service. He looks forward to making Brain Matters an inclusive and engaging scientific committee on campus

Vice President

Shireen Aydogan is a senior majoring in Molecular and Cellular Biology on a pre-med track and exploring the possibility of an Arabic and Communications minor. She devotes time to teach English to refugees and volunteer at the free health clinic in the community throughout the school year as well. In her free time she enjoys playing the guitar, and spending time with her family. She also likes to stay active by playing basketball and snowboarding. She hopes to increase awareness in neuroscience through her writing and as Social/Advertising Chair for brain matters.

Treasurer

Kamile Aleksaite is a senior in Bioengineering with a minor in Health Administration. She is the Treasurer, co-Social chair, and editor for the Brain Matters journal. Her hobbies include playing volleyball and tennis, and she works as a lab technician at the Evolutionary Immunology and Genomics Laboratory. She plans to continue her studies at UIUC through the Master's program in Bioengineering.

Social Events Chair

Hello! My name is Celeste and I'm a December '23 MCB and Psychology Alum. My last semester as a student I had the privilege to serve on the Brain Matters Exec Board as Social Chair. I currently work as a Mental Health Technician Trainee at an in-patient hospital in Chicago. I plan to continue working as I prepare myself to apply to medical school next year! My current hobbies include reading, spending time with my family and friends, and playing Animal Crossing New Horizons.

Social Media Chair

Vani Sharma is majoring in MCB Honors on the pre-med track, with a minor in public health & neuroscience certificate. She is a writer for Brain Matters, which allows her the opportunity to learn about the brain & its neuroanatomy in depth along with her interest in brain disorders. On campus, she is heavily involved with medical clubs & the Illini Strings Orchestra, serves as an undergraduate research ambassador, is a part of the Madak Erdogan Women's Health & Metabolism Lab, and works as a teaching assistant for chemistry. After graduating from UIUC, she hopes to attend medical school.

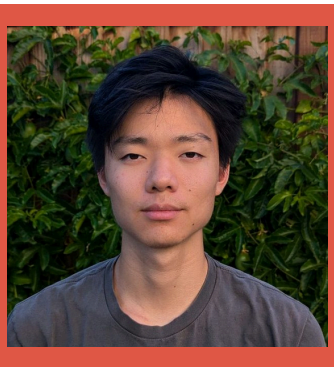
Design Head

Michelle Bishka is a junior majoring in Specialized Chemistry and minoring in Computer Science. Outside of Brain Matters, she is an undergraduate researcher in the Silverman Lab and a member of American Chemical Society. She later hopes to pursue graduate studies in chemistry.

Design Board

Madelyn Feliciano is sophomore majoring in neuroscience and psychology. She is passionate about biopsychological research, with a particular focus on neurodevelopmental disorders and supporting individuals with intellectual disabilities.

Hi! My name is Jessica George and I'm a junior majoring in Molecular and Cellular Biology and Brain and Cognitive Science. Outside of school, I volunteer at a nursing home in the activities department, where I work closely with residents who have dementia. In my free time I love dancing, listening to music, and trying new restaurants!



Edward Lin is a freshman majoring in Neural Engineering. He spends much of his time exploring the intricate connections between artificial intelligence and neural networks, with a focus on developing advanced neural interfaces. In his free time, Edward enjoys playing volleyball, starting up business ventures, and editing videos.

Sarah Masud is a sophomore studying Psychology and Information Sciences with a minor in Art & Design. Some of her academic interests include cognition, human-computer interaction, and treating psychiatric disorders. She enjoys drawing, finding new music, and crocheting as well! Outside of Brain Matters, Sarah is also involved in Design Innovation Illinois, the Undergraduate Psychology Association, and Psi Eta Mu, a professional information sciences fraternity. She hopes to continue furthering her understanding of neuroscience and exploring topics she's passionate about through writing for the journal.

Editors

Kamile Aleksaite is a senior in Bioengineering with a minor in Health Administration. She is the Treasurer, co-Social chair, and editor for the Brain Matters journal. Her hobbies include playing volleyball and tennis, and she works as a lab technician at the Evolutionary Immunology and Genomics Laboratory. She plans to continue her studies at UIUC through the Master's program in Bioengineering.

Meghan Blomberg is a Sophomore majoring in Bioengineering and pursuing a minor in Electrical Engineering. She hopes to integrate her interests in electronic sensing into the neural space. Apart from being an editor for the journal, she is involved in Illinois MicroTech, where she learns about microfabrication of electronic devices. She is also a part of the Illinois Scholars for Undergraduate Research (ISUR) program. In her free time, she enjoys figure skating and competes on behalf of the University of Illinois Intercollegiate Figure Skating Team.

Holly Foskett is one of the editors for the Brain Matters Journal and is currently a freshman at UIUC majoring in Neuroscience. Outside of the journal, Holly loves to read, workout, and play tennis. She is also looking to conduct research of her own in the field of Neuroscience in the future.

Macy is a freshman at UIUC majoring in Brain and Cognitive Science with minors in Integrative Biology and Music. She's from Evanston, Illinois, and when she isn't studying for yet another exam, she plays violin with the UIUC Philharmonia and enjoys reading. She currently works for Dr. Husain at the Auditory Cognitive Neuroscience (ACN) Lab. She loves editing for Brain Matters and is also a member of the Undergraduate Neuroscience Society (UNS).

Praise Kim is a freshman majoring in Brain and Cognitive Science and Spanish. Her intellectual passions include the development of linguistic ability, mapping how the brain represents psychological phenomena, and environmental factors on intelligence. She joined Brain Matters as an editor to expand her knowledge on a variety of psychological and neurological processes. Other organizations she is involved in include various language practice groups and NAMI. In her free time, she is with her church, working out, or reading. She plans on becoming an academic or psychologist in the future.

Amy Li is a freshman studying psychology at the University of Illinois at Urbana Champaign. She got involved as a writer for this journal because she is interested in developmental and clinical psychology, and wanted to learn about the neuroscience behind those disciplines. In addition to writing for Brain Matters, Amy is involved in Women in Psychology, Women's Glee Club, Planned Parenthood Gen Action, and Girl Gains on campus.

Megan Lu is a Sophomore majoring in Brain & Cognitive Science with a minor in Health Administration and Business. She is involved in various RSOs on campus, including FHCE (Future Healthcare Executives) and Alpha Epsilon Delta (a pre-health fraternity). She is also currently involved in research with the Illinois Alternative Protein Project. In her free time, Megan spends most of her time at the gym working out, cooking new recipes, or listening to true crime podcasts. She hopes to deepen her understanding and appreciation of the brain through writing with Brain Matters.

Brain Matters Writers

Hello! My name is Celeste and I'm a December '23 MCB and Psychology Alum. My last semester as a student I had the privilege to serve on the Brain Matters Exec Board as Social Chair. I currently work as a Mental Health Technician Trainee at an in-patient hospital in Chicago. I plan to continue working as I prepare myself to apply to medical school next year! My current hobbies include reading, spending time with my family and friends, and playing Animal Crossing New Horizons.

Isabelle is a Freshman at the University of Illinois majoring in Neuroscience. Isabelle became involved in Brain Matters to learn more about writing scientific articles and innovations in neuroscience. In addition to writing for Brain Matters, Isabelle is involved in McKinley Health Stress Management Peers, LAS Leaders, and Women's Glee Club. In the future, Isabelle hopes to attend medical school and continue reading and writing about new scientific innovations!

Krisha Agarwal is a sophomore in MCB Honors. She is currently working in Prasanth Lab, which explores long non-coding RNAs in terms of hypoxia in cancer. Some of her interests include film, photography, and fashion. Brain Matters fuels her interest in writing and acts as a stepping stone for acquiring the necessary skills to publish her own research in the future, as she builds on her scientific knowledge. After her undergraduate years, she hopes to continue research in graduate school.

Joy Akindulureni is a Junior studying Psychology with a concentration in Cognitive Neuroscience and minors in informatics and integrative biology. Her research interests are in neuroimaging, neurodegenerative diseases and aging.

Erin Ford is a sophomore majoring in Chemical Engineering with a concentration in Biomolecular Engineering. In her free time, she enjoys playing tennis and painting. She hopes to help others increase their knowledge about neuroscience through her writing in Brain Matters.

Harrison Kennedy is a freshman studying neuroscience and Spanish with a minor in legal studies on a pre-law track. He spends most of his time in the Auerbach Lab as an undergraduate research assistant where he investigates auditory perception in rats and the interactions between fragile x syndrome and cerebral processing of auditory stimuli. Outside of lab work, he is an active member in the Spikeball/Roundnet club, Pre-law Honors Society, Phi Alpha Delta professional pre-law fraternity, and he's in the process of registering a new RSO for next semester. In his free time, he loves to hike, write, and have fun with friends.

Sarah Masud is a sophomore studying Psychology and Information Sciences with a minor in Art & Design. Some of her academic interests include cognition, human-computer interaction, and treating psychiatric disorders. She enjoys drawing, finding new music, and crocheting as well! Outside of Brain Matters, Sarah is also involved in Design Innovation Illinois, the Undergraduate Psychology Association, and Psi Eta Mu, a professional information sciences fraternity. She hopes to continue furthering her understanding of neuroscience and exploring topics she's passionate about through writing for the journal.

Casey is a sophomore majoring in chemical and biomolecular engineering. She works in the Sirk Lab, conducting research on the gut microbiome. In her free time, she enjoys reading and taking her dog for hikes. After graduation, she hopes to attend medical school.

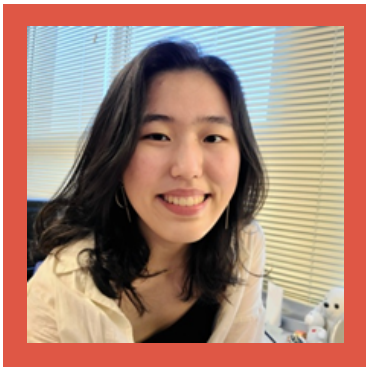
Vraj is a Freshman at the University of Illinois majoring in Neuroscience. Vraj joined Brain Matters to learn about more niche topics in neuroscience and research in the field. In addition to writing for Brain Matters, Vraj is a Course Assistant for STAT 100 and a volunteer at Avicenna Community Health Center. Vraj hopes to explore more in the field of neuroscience from a medical perspective in the future!

Ananya Sampathkumar is a freshman majoring in Neuroscience with an interest in minoring in journalism. Outside of Brain Matters, Ananya is a part of TFN, Mannmukti, a volunteer at Carle Hospital, and works at the Office of Undergraduate Admissions as a tour guide and student ambassador. In her free time, Ananya likes to read books, make jewelry, watch movies, and hangout with her friends!

Vani Sharma is majoring in MCB Honors on the pre-med track, with a minor in public health & neuroscience certificate. She is a writer for Brain Matters, which allows her the opportunity to learn about the brain & its neuroanatomy in depth along with her interest in brain disorders. On campus, she is heavily involved with medical clubs & the Illini Strings Orchestra, serves as an undergraduate research ambassador, is a part of the Madak Erdogan Women's Health & Metabolism Lab, and works as a teaching assistant for chemistry. After graduating from UIUC, she hopes to attend medical school.

Pravika Srivastava is a rising sophomore at the University of Illinois Urbana-Champaign, majoring in Neuroscience on the pre-medical track. She is an aspiring physician hoping to specialize in psychiatry. She is a writer for Brain Matters which gives her the opportunity to fully immerse herself in her interests regarding the nervous system and brain. In addition to writing, she pursues several other activities on campus. These include volunteering in the Pediatric ICU at Carle Foundation Hospital, serving as a chair member for the American Medical Students Association as well as being a member of the pre-health professional fraternity Alpha Epsilon Delta. Pravika is thrilled to share her first article and latest research with Brain Matters. Through this organization and the several others, she is a part of, Pravika is determined to increase awareness and understanding about the brain and field of neuroscience.

Kaitlyn is a sophomore in bioengineering on the therapeutics track with a minor in statistics. She is involved in various RSOs such as the Society of Women Engineers (SWE), Women in Engineering (WIE), and the Biomedical Engineering Society (BMES). She is currently in two research labs the I^2 Lab and Gritton Lab. In her free time, Kaitlyn loves to bake puff pastries, go to the gym, learn new pieces on the piano, and hang out with her friends. She hopes to spark readers' interest in neurological issues and deepen her knowledge through Brain Matters.



Esther Nam is a sophomore on the pre-med track majoring in Psychology with a minor in Public Health. She is currently interested in exploring the cognitive and neurological aspects of bilingualism but is still open to other areas of research. While having started her experience in the Educational Psychology Psycholinguistics Lab with a focus on cognitive psychology, she hopes to branch out to other areas as well, including neuroscience. Outside of academics, she enjoys digital drawing, watching shows, and playing video games with friends. After undergrad, she hopes to attend medical school and pursue a career in medicine.

Want To Get Involved?

Brain Matters is a Registered Student Organization (RSO) on campus that welcomes all years and majors. Please email brainmattersuiuc@gmail.com with inquiries about getting involved with the journal or RSO.