Brain Matters

UNDERGRADUATE NEUROSCIENCE | JOURNAL

VOLUME V
ISSUE ii

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Outline on Exercise and Brain Function

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Abstract

Exercise is seen to physically improve the health and function of the brain. This involves a variety of molecular and cellular mechanisms, including significant increases of beneficial neurotrophic factors like BDNF. In addition, neurogenesis in the hippocampus is also increased after exercise. Hippocampal vascular structures, like blood flow, are improved. Plasticity is also improved. Additional molecular mechanisms can contribute to alleviate symptoms of aging and more serious neuropathic diseases. Negative factors like inflammation and reactive oxygen species are mitigated.

For quite a while, people considered the mind and body separate. René Descartes himself proposed the idea of what is called the Cartesian dualism, that whatever happens to our body leaves our minds untouched. It was believed only the mind can truly affect itself, and thus was born “I think, therefore I am.” More recent scientific advances proved quite the opposite. Our minds come from intricate neural connections in our brains. Both our bodies and outside influences affect the flow of messenger molecules in our brains analogously to the way our livers or muscles can be affected, to name a few. If anything, our minds could just be an extension of our body, rather than its own separate entity. For example, one of the best ways to improve our brain function is through exercise. While research is still discovering the complete effects of exercise on the brain, many molecular and cellular mechanisms have already been elucidated. Exercise is known to improve neural plasticity, increase neurotransmitter efficiency, expand neuron counts, and even prevent cognitive diseases.

One of the most significant findings of exercise on brain health was elucidated through neurotrophic factors. These molecules act as growth factors for brain cells, increasing cell growth, signaling, and neural wiring. Despite the importance of these factors for our brain, their expression depends on physical exercise. One of the most important neurotrophins is brain-derived neurotrophic factor (BDNF). This molecule can interact with synaptic development of dendrites and axons, allowing them to form specialized connections for specific neuron communication. In turn, better neural communication can aid in learning (Cohen-Cory et al., 2011). Improved learning can occur immediately after exercise. Human subjects were able to improve cognitive performances in learning new material after running on a treadmill. The increase in memory is correlated with BDNF concentration in the bloodstream that also spikes during exercise (Winter et al., 2007). It is also shown that consistent exercise can increase BDNF levels compared to sedentary behavior in rats (Berchtold et al., 2005). Conversely, blocking BDNF contributes to decreased synaptic efficacy and decreased vesicle proteins, both directly harming communication between neurons (Vaynman et al., 2006).

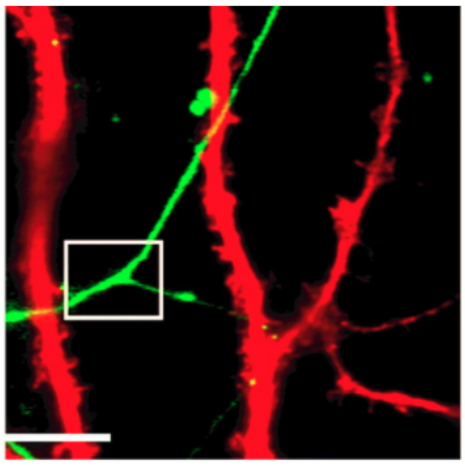

Figure 1A: Axon expressing BDNF-GFP (in green) superimposed with dendrites of second neuron, stained with MAP2 (in red) (Kohara, 2001).

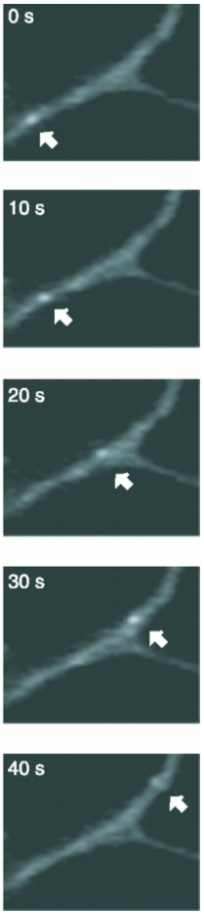

Figure 1B: Movement of BDNF-GFP in axon (Kohara, 2001).

(Other hormones, like the catecholamines dopamine, epinephrine, and norepinephrine were shown to increase through exercise. These hormones are thought to be associated with learning, as they increase signaling in the brain. It is also shown that increased levels of BDNF correlate with physical activity (Winter et al., 2007). There are also other neurotrophins with levels that increase with exercise. An example is IGF-1, which increases neuron counts in the hippocampus. (Trej et al., 2001). NMDA receptors, which are responsible for the health and function of neurons, also increase with exercise (Farmer et al., 2004). Other molecules include TNF-α and vascular endothelial growth factor (VEGF). Both these molecules improve vascular health, including blood vessel growth and differentiation throughout the body. TNF-α can also increase integrin protein production, which helps cells bind to extracellular structures. These activities can directly impact the vascular supply of nutrients in the brain (Ding et al., 2006). Because exercise can promote neurotrophic factors and hormones to signal in the brain, all of these effects can lead to a much healthier brain.

While the human brain's overall structure remains stable over adulthood, it can undergo slight changes for the better. Exercise can induce these modifications to physical structures. For example, exercise appears to promote neurogenesis, the creation of new neurons. While in most of the brain, the number of neurons stays the same throughout life, the number of neurons can increase in the hippocampus. Most of the newly generated neurons appear in the hippocampal dentate gyrus, a region highly responsible for learning and storing long-term memories (Cho et al., 2013). Higher rates of cell growth appeared in these regions for rats performing consistent treadmill exercise (Heo et al., 2014). Brain scans in animal studies have also shown improvement from exercise in vascular structures in the brain, like increased blood flow and permeability of the blood brain barrier (Yau et al., 2014). These are all correlated with supplying nutrients and cleansing factors to grow and protect neurons. Brain scans in mice have also confirmed greater growth in hippocampal areas after consistent exercise. Similarly, brain scans in humans have shown analogous changes in the hippocampus as well. The same human subjects were tested in cognitive trials like delayed recall, recognition, and source memory. Higher cognitive performance correlated significantly with more exercise (Peirera et al., 2007). Additionally, young neurons appear to contribute a greater learning potential. New neurons generate faster calcium and sodium concentration spikes, affecting action potentials and signal transduction to neighboring neurons. These neurons also change their behaviors more permanently to signals, compared to older neurons. (Schmidt-Hieber et al., 2004). These neurons are able to express greater responses to lower levels of signal as they mature, exhibiting long term potentiation. Older neurons are more resistant to these changes (Ge et al., 2007). Long term potentiation indicates increased plasticity, the ability to rewire neural circuits. Plasticity in the brain allows it to encode new information and boosts learning.

Therefore, as consistent exercise increases new neurons, it ultimately leads to more plasticity to the brain and thus increased learning.

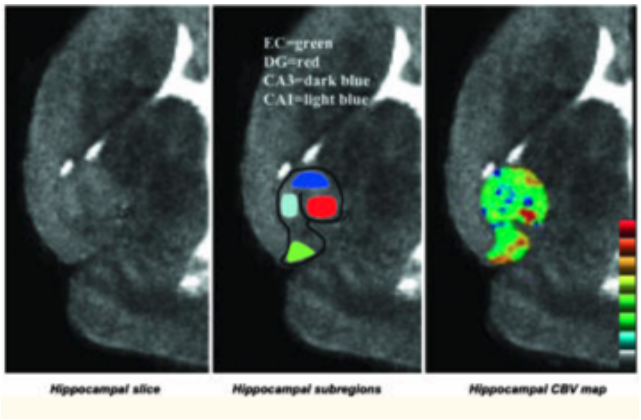

Figure 2A: Heat map showing neurogenesis activity in mice, based on cerebral blood volume (Peirera et al., 2007).

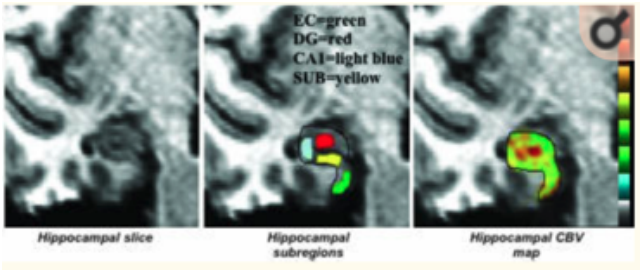

Figure 2B: Heat map showing neurogenesis activity in humans, based on cerebral blood volume (Peirera et al., 2007).

Exercise is associated with broader health effects as well. Even though neurological decline is correlated with aging, exercise has been shown to minimize and reverse these trends. For example, for older subjects, aerobic fitness has been associated with better performances on cognitive tasks, as well as retaining larger hippocampal sizes in the brain (Erickson et al., 2009). These trends also extend to symptoms of neurodegenerative diseases that tend to amplify in older age. For example, as exercise promotes neurogenesis in the hippocampus, it helps combat neuron loss in many diseases like Alzheimer's (Yau et al., 2014). Exercise is also seen to alleviate symptoms of diseases. In rats exhibiting symptoms of Parkinson's disease, consistent exercise appears to reduce short term memory damage (Cho et al., 2013). Similar findings are shown for rats exhibiting Alzheimer's symptoms, with exercise correlated with better performance in spatial learning (Heo et al., 2014). While exercise cannot cure neurodegenerative diseases, they can alleviate symptoms and improve quality of life for people with these diseases.

In addition to preventing neurodegenerative conditions, exercise also protects against physical damage to the brain. For example, exercise is shown to protect against stroke-like symptoms in the brain. In stroke, blood flow is deficient in the brain, which can cause swelling and cell death. In animal studies, these symptoms are reduced in animals who performed consistent exercise (Ding et al., 2006). Other physical damages to the brain come from reactive oxidative species (ROS), for example.

These are molecules that can originate as byproducts of metabolic reactions. However, ROS react inappropriately with other molecules in cells, stopping proper pathways for normal function. This can even affect signaling and cell survival. Exercise increases the amount of antioxidant enzymes in cells, protecting cellular function (Radak et al., 2016). In animal studies, the rat brain showed an increase in protease activity in cells in response to exercise. These proteases are responsible for breaking down proteins, including misfolded and damaged proteins that act as ROS (Ogonovsky et al., 2005). Exercise provides increased antioxidant protection, which protects the overall health and function of the brain.

Overall, exercise appears to play an overwhelmingly positive influence on the brain. Neurotrophins increase their function after exercise, promoting brain health and learning. Structures of the brain responsible for learning also change. Neurons increase their potential for efficient communication. Exercise also alleviates aging and neurodegenerative symptoms. Despite the knowledge already known about exercise, there is still much more to learn about its effects on the brain. Exercise also improves the rest of the body, in addition to the brain. Based on current knowledge of physical activity, consistent exercise would be a wise choice for improving quality of life.

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Ependymoma Tumor Diagnosis: Pathophysiology and Prognosis of Pediatric and Adult Patients

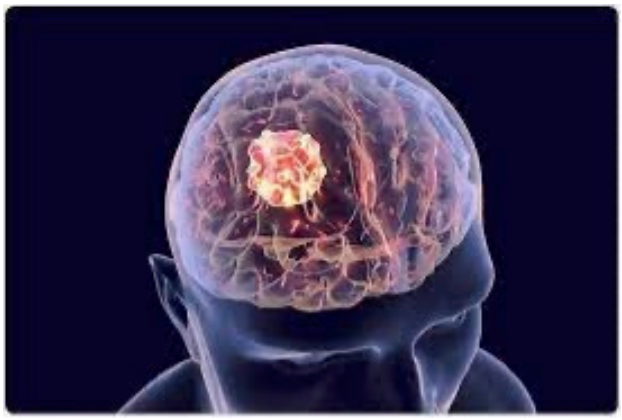
Christopher Jones

Abstract

Ependymomas are a rare type of tumor that affects the Central Nervous System (CNS) of adolescents and adults. The tumor derives from the Ependymal cells which are responsible for lining the ventricles containing cerebrospinal fluid within the brain and spinal cord. While pediatric patients are more likely to develop the tumor in the brain, adult patients mainly develop the tumor in the spinal cord region. (Gerstner, 2018). Ependymomas range from being slow growing Grade I tumors to malignant and fast growing Grade III tumors which are known as anaplastic. Current medical treatments for this tumor provide more positive outcomes for adult patients versus pediatric patients. This paper will explore the pathophysiology of the disease in both patient types in order to provide insight into possible differences that better explain the clinical outcome

Introduction

One of the negative consequences of cancer is the continuous and unregulated proliferation of cancer cells. Unlike regular cells which grow to appropriately regulated signals, cancer cells grow and divide “uncontrollably”, spreading to normal tissues and organs throughout the body by a process called metastasis. (Cooper, 2000) The unregulated growth of cancer cells is the result of an accumulation of abnormalities within multiple cell regulatory systems and is reflected in a manner that distinguishes cancer cells from their counterparts. These abnormalities can range from various types of mutations in the DNA sequence that can either cause issues with tumor suppressor genes or activating cancer promoting genes. With respect to cancer pathology, the most important issue is the distinction between malignant and benign tumors. (Cooper, 2000) A tumor is any abnormal proliferation of cells. A benign tumor such as a skin wart remains stagnant in a specific location and does not spread to other tissues and parts of the body. A malignant tumor can spread to nearby tissues as well as throughout the body via the circulatory and lymphatic systems through Metastasis. (Cooper, 2000). Brain tumors are a collection of neoplasms that arise either from within the brain itself, or from systemic tumors that have metastasized to the brain. Symptoms of Brain tumors include seizures, headaches, fatigue and cognitive dysfunction. (Butowski, 2015) There are currently over 120 types of cancers and tumors that effect the brain, however some of the more common ones are pilocytic astrocytoma’s, ependymomas, and medulloblastomas in children, and the diffuse astrocytic tumours (including astrocytoma, anaplastic astrocytoma’s, and glioblastomas), oligodendroglia’s, and meningioma’s in adults. (Collins, 2004) . Ependymomas are glial cell tumors that typically arise from the lining cells of the blood vessels of the brain and are less known to be found outside of the central nervous system. These tumors are genetically distinct from each other and affect children more than adults. (Zamora, 2020)



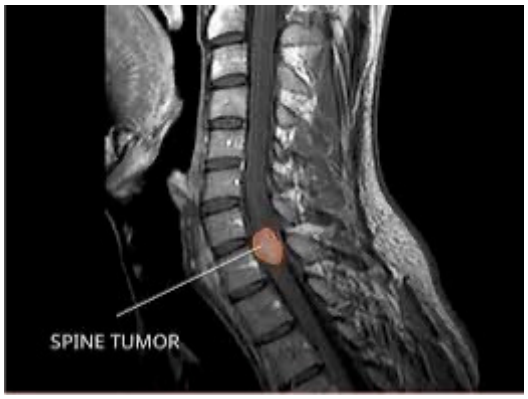
Imaging of a Pediatric Brain Tumor (2020).

Ependymomas Explained

Since ependymomas rarely spread outside the central nervous system, they do not follow the typical classification system. The classification starts with grade I tumors which are slow growing and are often considered benign, including subependymomas and myxopapillary ependymomas. This means they are less likely to be fatal. Subependymomas arise in the ventricular walls and are common in the fourth or lateral ventricles. They are histologically characterized by a hypocellular tissue presenting clusters of cells with a bland nucleus surrounded by glial matrix. Myxopapillary ependymomas arise in the cauda equina, filum terminale or conus medullaris, and present histologically as pseudopapillary structures with mucin-rich microcysts, the cells are cuboidal and radially arranged surrounding a myxoid stroma. These regions are in the tailbone or the base of the spinal cord. These tumors would occur in mostly the adult patient subtype. Grade II ependymomas are present in papillary structures. Cells are arranged regularly and present a clear cytoplasm. Grade III, are anaplastic ependymomas, presenting with abundant mitotic cells with pseudopalisading necrosis. This type is more deadly (Zamora, 2020). Ependymomas develop in all age groups but occur mostly in children and rarely in adults. According to the 2014 report published by the Central Brain Tumor Registry of the United States, ependymomas account for 5.2% of all brain and CNS

tumors in children and adolescents aged 0–19 years. With regards to ethnicity, the incidence rate per 100,000 is 0.40 in Caucasians versus 0.27 in African American (Wu 2016). The survival rate is the highest for those aged 20–44 years and gets lower with increasing age at the time of the diagnosis. The 10-year survival rate is only 28.1% in those aged older than 75 years. In children and adolescents aged 0–19 years, the 10-year survival rate is 66%. (Wu 2016) The prognosis of this tumor type is mainly based on the location of the tumor as well as the age of the patient. A study conducted by Rodriguez analyzed 2408 ependymoma cases- 2132 belonging to the grade 2 category and 276 belonging to the grade 3 category from the Surveillance, Epidemiology and End Results database 1997–2005. Some of the factors that contributed to poor clinical outcomes were younger age, male sex, higher tumor grade, intracranial location, and failure to undergo surgical resection. Even with these findings, the use of the central registry does suggest possible issues with diagnosis. Analysis of ependymoma cases in a single institution found that nearly 20% of cases had been misdiagnosed as another histological type of neoplasm prior to expert review. (Wu, 2016) In order to understand how the prognostic factors for pediatric patients are different from those of adults, (Amirian et al, 2016) the ependymoma cases from the SEER database are analyzed separately for pediatric and adult patients. Anaplastic and infratentorial location of tumors were associated with increased mortality rate in pediatric cases, while a supratentorial location was associated with higher mortality rate in adult patients. Surgical resection proved to be beneficial for both pediatric and adult patients. (Wu, 2016) The unfavorable prognostic impact of a supratentorial location was shown by analysis from a study involving seventy patients aged older than 17 years. However, only older age, and not supratentorial location, was found to be an unfavorable prognostic factor by multivariate analysis from the study. (Wu, 2016) A single institution study of 123 adult ependymoma patients was conducted at the University of Texas MD Anderson Cancer Center. Forty patients had tumors in the brain, 80 in the spinal cord, and 3 at both locations. Although most of the tumors were grade I or II, the study showed that brain location (versus spinal cord) and tumor anaplasia were associated with a worse outcome in adults measured by both overall survival (OS) and progression-free survival (PFS) (Wu 2016). Ependymal tumors have a rare occurrence, comprising 1.7% of all brain tumors, as reported in the CBTRUS statistical report. It has been difficult to find an effective treatment for the disease due to the low percentage of occurrence of these tumors (Zamora, 2020). Studies have shown an improved survival for patients who undergo resection with adjuvant radiation therapy. There is minimal and limited evidence supporting chemotherapy for adult ependymomas (Zamora, 2020). Currently none of the established guidelines use the molecular subgroups to guide treatment of ependymoma. The current consensus recommends that patients with PF-EPN-A positive ependymoma, who are older than 12 months undergo maximal safe micro-neurosurgical removal in addition to local radiotherapy. (Zamora, 2020).

For intracranial ependymomas, surgery is the main treatment. Complete resection without residual disease has presented better clinical outcomes and better overall survival rate than partial resection. (Zamora, 2020) As discussed previously, there is insufficient evidence to support the use of chemotherapy. Patients who are long term survivors from central nervous system tumors present a diverse array of complications, including neurological deficits, cognitive limitations, hearing loss, endocrine and growth abnormalities, and secondary malignancies. Adult patients may present long term complications, most commonly fatigue, numbness and tingling, pain, and disturbed sleep. (Zamora, 2020)Childhood intracranial ependymoma has a poor prognosis, especially in young children when a gross total resection cannot be performed. Even without radiologically proven residuum, around two-thirds of these young children will have a relapse. (Grill, 2003). Adjuvant therapy is necessary for most, if not all, patients. Craniospinal irradiation combined with posterior fossa boost has deleterious effects on cognition. Pediatric oncology teams have tried to use chemotherapy to avoid irradiation and reduce irradiation fields to the tumor bed without altering the prognosis. Cisplatin, at a dose of 120 mg is the only single agent that has reproducibly shown some efficacy in ependymoma. (Grill, 2003) Despite some combinations showing efficacy in the adjuvant setting, childhood intracranial ependymomas can be considered chemo resistant. The overexpression of the multidrug resistance-1 gene and the 06-methylguanine-DNA methyltransferase have been implicated as possible mechanisms for this phenomenon. As the use of chemotherapy with current agents is questionable, phase II studies with new agents and combinations become necessary. (Grill, 2003) Since the main problem of this disease is local relapse, it may not be necessary to irradiate the whole posterior fossa region. However, local control of the disease by irradiation must be improved. In this respect, hyper- fractionation or radio sensitizers may be valuable therapeutic options. The treatment of children with ependymoma is a challenge for all caregivers. There is no doubt that any possible improvement in the management of this rare tumor will only be the result of well-designed cooperative trials (Grill 2003).



A MRI image of an Ependymoma Tumor in the Spinal Cord (N.C.I, 2021).

Conclusion

Ependymomas are a very aggressive type of brain tumor that occur in both pediatric and adult patient types.

While most cases of this tumor type effect pediatric patients in the brain with very little metastasis from other regions of the body, it still has a worse prognosis compared to adult patients. The common treatment for these tumors include surgery as well as chemotherapy, however the tumor has shown to be chemo resistant. Typically when a Tumor is chemo resistant it will end up growing back not too long after the chemotherapy and continue to spread. There has been research conducted that shows chemotherapy may not be the best treatment due to its lasting complications it may cause. Therefore, upon initial surgery, it is recommended that the surgeons remove most of the tumor in order to try and eliminate as much as possible. More research needs to be done to understand ependymomas on a molecular level in order to offer a more effective treatment for pediatric “patients”.

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The Academic Advantages of a Bilingual Brain

Emma Ibanez

Bilingualism in young children has several cognitive benefits that lead to increased academic performance. Between monolingual and bilingual children, behavioral differences can be observed as early as infancy. Studies show that bilingualism influences the development of executive control, which includes cognitive abilities such as problem-solving, memory, and inhibition control. This early cognitive advantage carries into the classroom where skills such as problem solving and adapting to new information are critical for educational success. Learning a second language trains the mind to better recognize linguistic patterns that can be applied to increased reading skill.

Infancy is a stage for critical lingual development in children. Although their behavior may seem relatively simple, infants are constantly making observations that will guide their cognitive development. For example, newborn babies can sense a difference between their mother's voice and a stranger's voice (Winkler et al., 2003). Babies must learn to recognize the unique phonemes in the languages surrounding them before they can learn how to speak. In her book Train Your Mind, Change Your Brain, author Sharon Begley discusses how the neuroplasticity of infant brains is the basis for forming lifelong neural circuits in parts of the brain that are responsible for language (2008). In babies, hearing a language exercises the neural circuits in the brain that will encode the unique phonemes required for fluency. Thus, sounds heard in the earliest years of life structure language-related brain tissue.

Neuroplasticity involves the relationship between an individual's brain and external environment. For bilinguals, the additional language-learning practice changes the physical composition of white and grey matter in their brains. White matter refers to the myelinated nerve axons in the brain while grey matter represents the unmyelinated nerve cell bodies (Mercadante & Tadi, 2020). Through VBM brain imaging, Mechelli et al. found that bilinguals have a higher amount of grey matter in the left inferior parietal cortex, a region responsible for language processing, than monolinguals (2004). Furthermore, they compared grey matter composition between "early bilinguals" who learned their second language before age five and "late bilinguals" who learned their second language during adolescence. The researchers showed that early bilinguals have a stronger increase in grey matter than late bilinguals. Additionally, bilinguals completed tests to measure skill level in their second language, and imaging analysis concluded that subjects with higher test scores had increased grey matter than those with lower scores. Overall, the evidence of increased grey matter in bilinguals could explain the observed differences in executive function between bilinguals and monolinguals.

Researchers, Agnes Melinda Kovács and Jacques Mehler (2009), designed an experiment to assess the effect of bilingualism on the executive function in babies. The researchers placed 7-month-old monolingual and bilingual babies in front of a screen divided into right and left sections. To begin each trial, a predetermined word was said to the baby. Right after the baby heard the word, a picture of a puppet appeared on the left or right side of the screen. The puppet appeared on the same side of the screen for the first part of the experiment, and trials were repeated so that the baby learned to expect the puppet after hearing the word. For the 2nd phase of the experiment, the researchers changed the location of the puppet to the opposite side of the screen and measured how many rounds were necessary for the baby to adapt to the change. The experimental data showed that bilingual babies relearned the puppet location faster than monolingual babies (Kovács & Mehler, 2009). This ability to adjust to a new stimulus is a measurable indication of executive control, proving that bilingual babies have better executive control than monolingual babies. Cognitive gains from bilingualism represented by similar studies signal language development in infancy as the foundation for enhanced academic performance observed in older age.

As children learn how to speak, executive control is measured using a wide variety of tests because they can respond to verbal or written instructions. One commonly explored cognitive advantage in bilinguals is the idea of "conceptual inhibition," which measures the ability of the participant to redirect their focus to a new stimulus after having learned to associate a predetermined sensory cue with an old stimulus (Carlson & Meltzoff, 2008). This method of measuring inhibition was also the premise for the infant study that assessed the babies' ability to relearn which side to expect the puppet picture. Researchers, Stephanie M. Carlson and Andrew N. Meltzoff, measured executive control in groups of bilingual and monolingual children to better understand the relationship between bilingualism and conceptual inhibition. One experiment--the Advanced Dimensional Change Card Sort (DCCS) test--required the children to separate a stack of cards. Various shapes and colors were pictured on all the cards, but a portion of the cards also had a star next to the shape. Then, the children were told to organize the cards by shape unless the card had a star. Instead, cards with stars were categorized based off the card's color. The children had to inhibit the instruction to separate by shape each time they pulled out a card with a star. Inhibition tests like the Advanced DCCS from the Carlson and Meltzoff study found that bilingual children were better than monolingual children in evaluating conflicting information through suppression of a previously learned

concept to adapt to the new requirements of a task. Thus, organizing one's own brain around two languages induces early problem-solving practice that can be applied in academic environments.

Bilinguals also have an advantage in developing metalinguistic awareness, which is a skill involved in learning how to read. Metalinguistic awareness is "the metacognitive ability that consciously reflects on the structure of linguistic knowledge and the cognitive processes engaged in literacy learning" (Sun 1, 2016). Therefore, an individual with high metalinguistic awareness can effectively analyze their language's rules for grammar, syntax, etc. In a study conducted by Lichao Sun, monolingual and bilingual children were given the same exercises that measured metalinguistic awareness. One exercise, called the "Zoo Game," involves a similar premise of conceptual inhibition used in the other studies. Children had to choose whether to press a button depending on what animal appeared on screen i.e., clicking the button when an orangutan appeared was considered an incorrect response. In the collected data, bilingual children made fewer mistakes than monolingual children in choosing the right response, meaning that they were better able to inhibit a conflicting response by remembering the game rules and applying them to the provided stimulus. Additionally, the bilingual children gave their responses quicker than the monolingual children.

Although bilingualism lends its cognitive advantages to the classroom environment, secondary factors like socioeconomic status influence greatly to the extent of an individual's academic performance. For example, the Carlson and Meltzoff study included participants from various socioeconomic backgrounds, which is an extra variable during data analysis. Bilinguals of different socioeconomic backgrounds might display different characteristics of executive control due to individual access to books, libraries, teachers, and other resources involved in language development. Ultimately, Carlson and Meltzoff were able to adjust for variability in socioeconomic status in order to isolate differences in executive function that were directly related to monolingualism and bilingualism. In addition, the Sun study was able to compare monolingual and bilingual children of similar socioeconomic backgrounds and conclude that bilinguals had a metalinguistic advantage over monolinguals.

In the United States, a 2010 survey found that 22% of school-going children speak another language within their household (National Center for Education Statistics, 2012). Thus, bilingual children make up a significant portion of classrooms where their enhanced executive control and metalinguistic awareness can be essential assets for problem solving and literacy development. Socioeconomic conditions can help or hinder the overall academic performance of both bilingual and monolingual students, so specialized attention from educators may vary across individual needs within the classroom. Beyond childhood, bilingualism provides an increased communication capacity that is helpful for pursuing job opportunities. Therefore, individuals can benefit from their bilingualism at each stage of life.

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The Duality of Languages: Bilingualism and Its Effects on the Brain

Estefania Baez

Abstract

Research over the past two decades has shown the vital role of brain plasticity in language acquisition, specifically in children. When compared with older adolescents, kids in early childhood are more efficient at learning a second language. Researchers still seek to know the physiological differences in brain structure and function between bilinguals and monolinguals. Promising studies show disparities between white and grey matter structures. In addition, bilingual individuals experience a specific pattern of brain activity when switching from one language to another- dubbed ‘codeswitching’. Such a pattern is found in two regions: the anterior cingulate cortex, which helps us pay attention, and the prefrontal cortex, which is the 'thinking' part of the brain (Mcrae, 2018). The culmination of elevated neurocognitive processes experienced by bilingual individuals leads to their variations in protection against neurodegenerative diseases and heightened performances in cognitive tasks.

Introduction

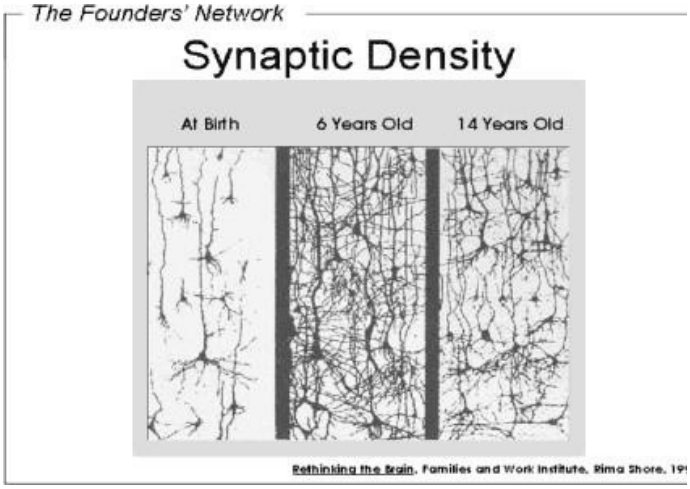
It is estimated that over half of the worlds’ population is fluent in more than one language. When you think about children in North America who speak English at school and another language at home, there was not necessarily a choice of becoming bilingual- it was a matter of housing, family, place of birth, immigration history, etc. (Bialystok, 2012) that cultivated an environment for it. It was commonly thought that learning two languages at once would be confusing and detrimental to children- but researchers argue that it actually provides cognitive and neurological benefits. Ever growing inquiries about the plasticity of the brain creates a pathway for us to discover why younger people are more likely than older adults to acquire fluency in more than one language. The physiological differences between bilingual and monolingual brains continue to intrigue researchers, and discussions about cognitive benefits of speaking more than one language should be continued and further held.

Plasticity and Brain Differences

From the ages of 0-3, an infant's brain reaches peak lifetime plasticity. Neuroplasticity can be referred to as the brain’s ability to adapt, modify, or alter in response to lifelong growth, learning, or changes. For children that grow up in households where more than one language is spoken, it comes easy for them to learn both at the same time. Learning a new language uses
plasticity because it includes repeated auditory exposure, semantic processing, retrieval, and speaking. The repetition of these processes over time results in gaining fluency of a language. There is a critical period that every human experiences, which is a timeframe that an individual has for optimal language acquisition. After the critical period, which is around the first 5 years of a person’s life, it becomes increasingly difficult for primary language acquisition to occur.

In a study hosted by Paul Thompson, it was discovered through continuous brain scans of children aged 3-15 that peak growth rates were attenuated after puberty.

The discovery arose through studying the fibers that innervate association and language cortices, for example the temporal lobe or visual cortex. These contrasted sharply with a severe, spatially localized loss of subcortical grey matter (Thompson et. al, 2000). During these critical periods, children are perceiving language for the first time, which leaves a large impression and allows for the greatest amount of growth in the brain and plasticity. While they are learning words and forming associations every day, the process of synaptic pruning contributes to the loss of subcortical grey matter. Grey matter is made up of dendrites and cell bodies of neurons, while white matter is made up of myelinated axons. Dendrites are branches in neurons that extend to synapses and receive information from other cells, and axons are the lengthy tubes of the neurons that transmit information to the synapse, where another nearby neuron can receive it.



This pruning is a process that is important for learning and memory because it removes unused synapses so that the brain can work as coherently as it can. These processes occur faster at younger ages and allow adults with more developed brains to transmit information more efficiently.

In a general view, bilinguals of all ages demonstrate better executive control than monolinguals who are matched in age and other background factors. Bilingual children have outperformed monolingual children in non-verbal conflict tasks, and bilingual adults performed better than their monolingual counterparts in tests like the Stroop effect and Simon tasks (Bialystok et. al, 2012). These neurocognitive tasks are commonly used to test monitoring of interference, focus, and ability to focus on stimuli. Successful performance on cognitive tasks can translate into real-world problem-solving skills, like recalling details, inhibitory control, and quick decision making; these are universal abilities that aid in workplaces, education, and everyday incompetencies.

Studies show evidential parallels of bilingual individuals experiencing neural processes where increased activity is detected. Highly proficient bilinguals show increased subcortical representation of linguistic sounds, as revealed by a larger electrical brain response in the range of the sounds' fundamental frequencies. This suggests that bilinguals have more efficient and flexible auditory processing than monolinguals (Costa et. al, 2014). When neurons are consistently firing at higher rates and increasing action potentials, Long-Term Potentiation (LTP) occurs. LTP is the process of strengthening synaptic connections between neurons that has long lasting effects. The increasing processing demands that come with bilingualism can be associated with higher performances on cognitive tasks, as well as the refined synaptic connections that allow for speedy neural transmission.

In bilingual individuals, previous studies have shown our anterior cingulate and prefrontal cortices activate when we jump from one language to another (Mcrae, 2018). It was shown that it isn't starting to speak one language that is costly in brain effort, but the stopping of one language to start speaking in a second one that activates the most brain activity. Individuals who are fluent in both English and American Sign Language (ASL) have been studied for this phenomenon and have provided evidence to support the idea. While repeating prompted words in both languages, 'switching off' the ASL and continuing to produce words in English proved to be more effortful than 'switching on' the ASL (Blanco-Elorrieta et. al, 2018). Turning a language off required increased engagement of the prefrontal cortex and anterior cingulate cortex, both part of the frontal lobe, which is the area of the brain largely responsible for decision making and impulse control. These series of specific neural activations are processes that monolinguals don't especially use, and could be explanations as to why they underperform in cognitive tasks and show less neural activity compared to their bilingual counterparts.

As for long-term structural changes, a study of older, highly proficient, successive bilingual adults (70-year-olds) reported greater white matter integrity in the corpus callosum in comparison to monolinguals (Costa et. al, 2014).

White matter in the brain consists of axons wrapped in myelin sheaths, which aid in the acceleration of action potentials and insulation of the axon. The more protected and the more that a neuron fires, the more the likelihood that the onset of neuro-degenerative disease would be delayed. Findings indicate that lifelong bilingualism acts as a powerful Cognitive Reserve proxy in dementia and exerts neuroprotective effects against neurodegeneration. For example, bilingual elders have displayed an average of a 4.5-year delay in the onset of Alzheimer's' Dementia compared with monolinguals of similar age (Perani et.al, 2017). Predicted causes for this delay include neural reserve and neural compensation for hypometabolism, which is the decreased metabolic rate of neurotransmitters. Hypometabolism is also often associated with neurodegenerative diseases such as Alzheimer's. Along with symptom delay, bilingual individuals with Alzheimer's Dementia also showed increased activity in frontal brain regions when the posterior regions had lower metabolic activity. The likely cause for this effect would be the consistent neural transmission over time that comes with the executive function of controlling two languages. This results in a neural reserve that eventually renders the bilingual brain more resistant against brain aging effects (Perani et. al, 2017).

Conclusion

Study after study, we find increasing evidence that the benefits of acquiring a second language at an early childhood age would translate to increased cognitive processes. In comparison with monolinguals, people who are fluent in more than one language have shown better performance on cognitive tasks, as well as physiological differences in white and grey matter density. The implications of being bilingual from an early age are consistent with having increased attention, focusing ability, and interference control. There is especially evidence of frontal lobe neural reserve that is hypothesized to be behind protection against early onset dementia. There are still many unknown neurological mechanisms that we seek to understand, such as the compartmentalization of various languages, as well as the precise neuro-preventative effects of bilingualism. Even so, educators and leaders around the world should emphasize the benefits of becoming fluent in another language and perhaps encourage further exploration into the world of multilingualism.

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The Thalamic Bridge to Cognition and Consciousness

Lina Issa

Abstract

From an evolutionary perspective, deeper brain structures are postulated as being more primitive than those that were developed later on. As such, the thalamus, being a deep brain structure, is generally believed to occupy one such primitive role: that of a 'sensory relay station'. Recent evidence, however, suggests that the thalamus is in fact responsible for more complex and higher order functions involving cognition and consciousness, processes previously attributed solely to the cerebral cortex. This review examines several of these emerging theories through the lens neural pathways, with particular focus placed on how the complex circuitry of the thalamus allows for the intricate connectivity between itself, the cerebral cortex, and other subcortical structures.

Introduction

The thalamus remains a mysterious structure in neurobiology: arising from the diencephalon and playing numerous essential roles in human physiology. The diencephalon can be divided into four parts: the epithalamus, the dorsal thalamus, the ventral thalamus, and the hypothalamus. This review will focus primarily on the dorsal division, as this is the portion that innervates the cerebral cortex, which is most relevant to this discussion. The thalamus is a paired gray matter structure composed of an array of different nuclei each serving a specific purpose. It is conveniently located between subcortical structures and the cerebral cortex, which facilitates its relay function, filtering information about sensory inputs (i.e. taste, touch, sound, etc.) between the brain and the body. The thalamus' advantageous location and specialized nuclei has given rise to speculation of whether the structure serves a more intricate function, one involved in cognition and consciousness.

First Order and Higher Order Nuclei

The anatomy of the thalamus is one of great complexity. Brain nuclei, such as that which the thalamus is composed of, are collections of neuronal cell bodies and thus are classified as gray matter. Thalamic-specific nuclei can be further classified as either 'first-order' (FO) or 'higher-order' (HO). 'First-order' thalamic nuclei correspond with earlier proposed functions of the thalamus, that is, with relaying sensory information from subcortical structures. Alternatively, 'higher-order' thalamic nuclei receive inputs from cortical layer 5 instead of the periphery and are thus being implicated as potentially carrying out higher order function, as their name implies. This theory is also supported by the role of HO nuclei in cortico-thalamo-cortical pathways, as they allow communication between cortical areas. This information has given rise to speculation that HO nuclei play a more integrative role while FO nuclei solely facilitate sensory relay function. However, these theories are being challenged by new evidence suggesting that both system's purposes are more complex and are both involved in higher order functions.

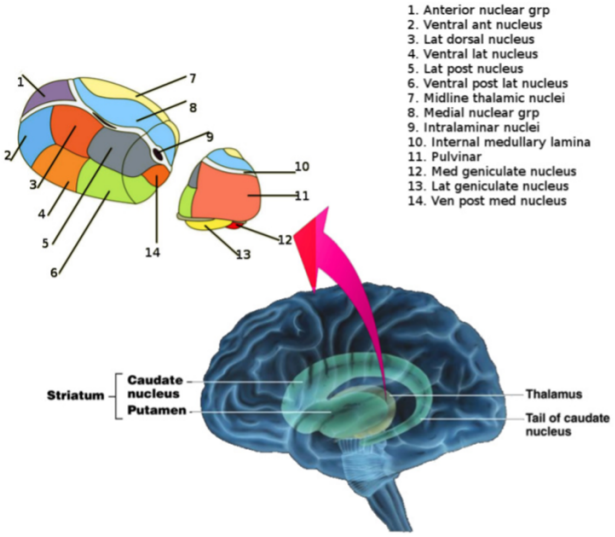

Figure 1: Thalamic nuclei. Image courtesy S Bhimji MD.

Both HO and FO nuclei may in fact represent a 'thalamic bridge', in which the thalamus occupies an integrative role between sensory perception and cognition.

Modulatory vs. Driver Input

The differential properties of synapses also contribute a great deal to thalamic activity. It is postulated that two distinct forms of synaptic inputs exist: 'driver input' and 'modulatory input'. Drivers carry the message whereas modulators modify how driver inputs are processed through processes such as attenuation or amplification. This further promotes categorization of thalamic nuclei as either 'first-order' (FO) or 'higher-order' (HO) based on where they receive their driving input from. FO nuclei receive driver input from subcortical structures while HO nuclei are mainly innervated by descending corticothalamic inputs from layer 5. Layer 6 cells provide modulatory feedback input to all thalamic nuclei, projecting to thalamic regions and providing thalamocortical input to the same cortical region from which they originate. Modulatory inputs from the cortex thus reach both HO and FO thalamic nuclei and affect the functionality of thalamocortical neurons.

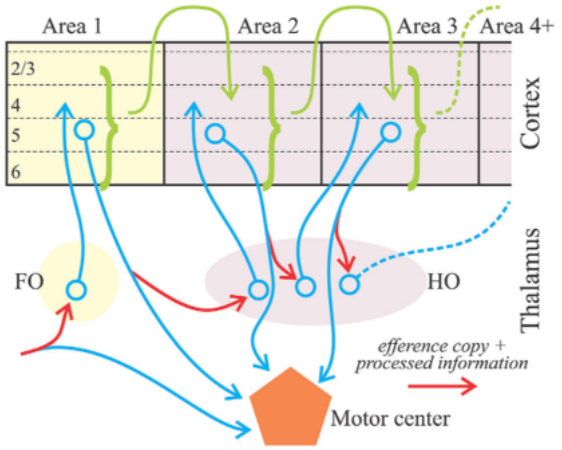

Figure 2: Thalamocortical circuitry (Usrey & Sherman, 2017.

The implications of this set-up are that sensory signals relayed via FO nuclei are processed in the cortex and then transmitted via HO to different cortical areas. This phenomena promotes a functional aspect of HO nuclei in trans-thalamic communication, one that allows cortical areas to communicate with each other outside of the direct connections between different cortical areas. It is also important to recognize that the inputs to both 'first-order' and 'higher-order' nuclei arrive via branching axons with extra thalamic branches innervating a motor center carrying a message that can be interpreted as an efference copy (an internal copy of an efferent). Efference copies are neural representations of motor outputs that predict reafferent sensory feedback. This phenomena is observed in tickling, where efference copies are created when you attempt to tickle yourself, which allows for the prediction of the sensory consequences of the movement. Yet, when other people tickle you, it is not predicted, and the sensation is much more intense.

The Cognitive Thalamus

The circuitry between the thalamus and cortex gives rise to a cognitive function of the thalamus, particularly in memory and learning. The link between the thalamus and memory has long been speculated in accordance with evidence indicating that damage to the thalamus invariably occurs in Korsakoff syndrome, a chronic memory disorder. One prominent thalamic nucleus assumed to be linked to memory is the anterior nuclei of the thalamus (ANT) which is located at the rostral end of the dorsal thalamus. The ANT is a key component of the hippocampal system for episodic memory, connecting the anterior cingulate (which is implicated in complex cognitive function) and orbitomedial prefrontal cortex (which is involved in decision-making). Early evidence shows a specific role of the anterior thalamus in Pavlovian conditioning, a learning procedure that involves the pairing of a potent stimulus with a neutral one to ultimately elicit a potent response in the subject to the neutral stimulus. Data indicate that the ATN is specifically involved in the acquisition phase of Pavlovian learning. One study on rats demonstrates that acquisition of contextual fear memory is delayed after ATN lesions. Another prominent thalamic nuclei involved in memory and learning is the mediodorsal nucleus of the thalamus (MD).

The MD has been implicated in executive functions (involving planning, working memory, and decision-making) because of its significant interconnectivity with the prefrontal cortex (PFC) which is ultimately responsible for cognitive control functions. As discussed previously, the involvement of 'higher-order' thalamic nuclei in distributing efference copies of the cerebral cortex signals to other cortical areas through a mode termed transthalamic communication gives insight into the significance of thalamic connections.

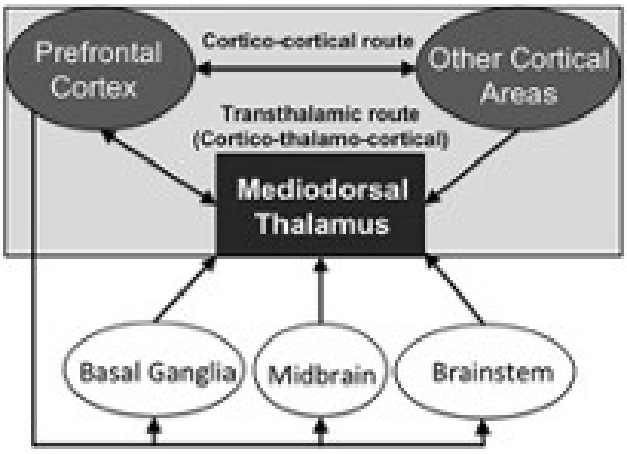

Figure 3: Corticocortical and transthalamic routes of transmission via the mediodorsal thalamus (Ouhaz et al., 2018)

Thus, using the example of the mediodorsal thalamic nucleus previously discussed, lesions to this structure would disrupt connections between the thalamus and cortex. As a result, the direct connections via different cortical areas and the transthalamic connections of different cortical areas would no longer be aligned, ultimately altering our internal perception of sensory stimuli. Our senses of sound, taste smell, etc. would no longer properly feed into subsequent processes which rely on accurate information, consequently impacting mental processes such as thinking and learning. An evident manifestation of this pathology would be people demonstrating unexplained behaviors or verbalizing nonsensical thoughts. Thus, it is evident that the mediodorsal nucleus of the thalamus is essential in this higher order cognitive scheme.

The Thalamus and Consciousness

In addition to the role of the thalamus in cognition, studies have shown that this structure may also be heavily affiliated with consciousness, which is also dependent on thalamocortical and corticocortical interactions. The higher-order thalamic nuclei which facilitate cortical communication may play a role in modulating corticocortical interaction across different conscious states. One specific region of the thalamus that has been highlighted in relation to consciousness is the central lateral thalamus (CL). Consciousness is thought to involve feedforward and feedback interactions between cortical layers and areas and the CL is connected to both deep and superficial cortical layers. A study done on macaques shows promising evidence for CL function in consciousness. Electrical stimulation of the CL in two anesthetized macaques produced behavioral indications of arousal.

It was also shown that sleep and anesthesia were associated with less activity in the CL, whereas CL stimulation reversed these changes. This finding can be explained by thalamic circuitry, one of these circuits carries sensory information from the thalamus to the cerebral cortex and another carries feedback about predictions, attention, etc., all of which are needed to facilitate consciousness in organisms.

Conclusion

From this brief overview we can see that the thalamus is not a simple, crude structure but is instead involved in many dynamic processes that significantly alter the nature of the information relayed to the cortex. The distinct cell groups/nuclei in the thalamus provide insight into how such a structure is able to perform these broad range of functions. Specifically, it is the 'higher-order' nuclei that allow for the cross talk between different cortical areas. As for the 'first-order' nuclei, they provide a path for the outside world and the various subcortical structures to communicate with the cerebral cortex. This review also highlighted some key thalamic nuclei that have been specifically implicated in cognition and arousal. Altogether, although a myriad of recent research is emerging looking at the thalamus and its sophisticated circuitry, we still have a long way to go to truly understand all the roles this alluring structure takes on.

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The Future of Neuroregeneration

Hanifa Mohammed

Abstract

As the average lifespan for humans is growing, neurodegenerative diseases are becoming more common. The two most common neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD). Both of these diseases cause the progressive degeneration of the central nervous system (CNS). To combat the effects of these disorders it's crucial to be able to regenerate the lost neurons. The issue is that cells in the brain reduce their plasticity as age increases, leading to little to no regeneration of the lost cells. Induced pluripotent stem cell (iPSC) is a new avenue of research regarding neuroregeneration as the ability to specialize them into neurons provides a method to combat the progressive degenerative nature of neurodegenerative diseases. Research in AD has shown successful experiments in specializing iPSCs into glial cells and cholinergic neurons to improve memory loss in AD mice. Research in PD has shown a method to specialize iPSC to neurons and thereby obtaining patient-specific transplants. The transplants and their effects have been successful in many animal models, leading to the potential of clinical trials in the near future.

Neurodegenerative diseases are disorders in which the structure and function of the central nervous system (CNS) and/or the peripheral nervous system (PNS) are degraded. Neurodegenerative diseases arise in mid to late life, and with the increasingly aging population in the world it's predicted that more than 12 million Americans will have neurodegenerative diseases by 2030 (The Challenge of Neurodegenerative Diseases, n.d.). In mammals the neurons in the CNS do not spontaneously regenerate which leads to multiple complications related to diseases that affect brain or spinal cord repair. These complications lead to disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Huebner, E. A., & Strittmatter, S. M. (2009)). Currently there are multiple conceptual solutions to battle these disorders, all of which focus on replacement of lost neuronal cell bodies, or in other words neuroregeneration.

Studies have shown that the "lack of intrinsic regenerative ability of CNS axons" is due to the expression of adult neuronal genes (Nagappan, P. G., Chen, H., & Wang, D. Y. (2020)). Neuroregenration of CNS neurons requires tenascin-binding integrin to assist in the organization of the extracellular matrix glycoprotein, tenascin, which modulates cell adhesion (Tucker & Chiquet-Ehrismann, 2015). The tenascin-binding integrin is not made in a fully differentiated adult neuron cell and thus adult neurons cannot undergo mitosis and produce more neurons (Nagappan, P. G., Chen, H., & Wang, D. Y. (2020)). Embryonic axons can make tenascin-binding integrin as they remain undifferentiated, meaning they have better chances to grow new neurons in the CNS than adult axons (Nagappan, P. G., Chen, H., & Wang, D. Y. (2020)).

The use of pluripotent embryonic stem cells (ESC) could be the answer to treat many conditions that often have only palliative care as a treatment. ESCs though come with ethical limitations since they are derived from human embryos. Induced pluripotent stem cells (iPSC), are a novel system that can overcome this limitation by generating a pluripotent stem cell from a somatic cell, a cell that is not a gamete or an undifferentiated stem cell. They also have the added benefit of being created per-patient so that immune system rejection is minimized. In the laboratory, iPSCs have shown great promise in regenerative medicine as they can give rise to any cell type in the body, including neurons (Fig 1).

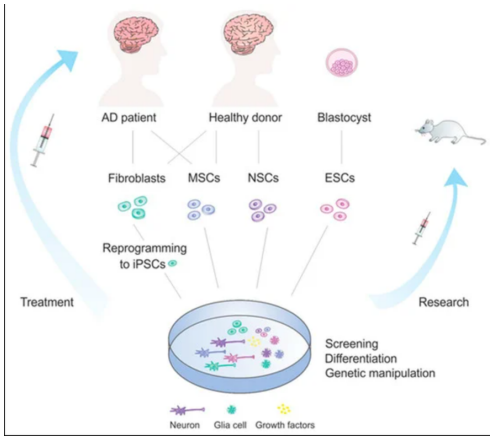

Figure 1: Cells can be gathered from the patient in concern. They can then be reprogrammed to iPSCs and used to differentiate into the desired cell for treatment. This creates iPSCs specifically tailored to the patient, thus reducing chances of immune rejection. Image from Vasic et al., 2019.

With the growing interest in the possibilities iPSCs provide to many neurodegenerative diseases, many researchers have begun to investigate how iPSCs can mitigate the two most common neurodegenerative diseases Alzhemier's Disease (AD) and Parkinson's Disease (PD).

AD is the most common neurodegenerative disease, with a predicted 6.2 million people in the US alone suffering from the disease (Alzheimer's Disease Questions and Answers, n.d.). AD is sporadic and age-related and results in the gradual deterioration of cognitive functions . The brain of an AD patient has a noticeably reduced volume (Fig 2).

This reduction in brain volume was particularly centered at the hippocampus, which is responsible for learning and memory, the loss in volume was attributed to death of neurons and degeneration of synapses. Moreover, research suggests the unique occurrence of amyloid plaques, aggregated misfolded protein that cannot be broken down by the body, in the extracellular space of the AD brain is a causative factor in the development of this disease (Vasic et al., 2019;Cha M. Y. et al. (2017)).

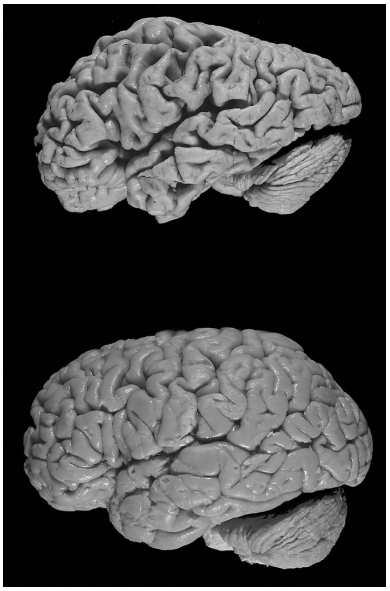

Figure 2: The brain volume of an AD patient (top) as compared to the brain volume of a normal patient (bottom). Image from: Hersenbank. (2008).

In order to study how iPSCs could reverse the effects of amyloid plaques, a study by Fujiwara et al., treated transgenic mice with amyloid plaque build up with an iPSC therapy.

Firstly, amyloid plaques have been duplicated in PDGF promoter driven amyloid precursor protein (PDAPP) transgenic mouse models. PDAPP is a mutant of the human amyloid precursor protein (APP) which results in the formation of amyloid plaques, and the buildup of amyloid plaques when mutated.

Now that the transgenic mice had a build up of amyloid plaques Fujiwara et al. implanted human iPSC into these mice and attempted to regenerate cholinergic neurons, common nerve cells that serve as acetylcholine neurotransmitters, to ascertain the role iPSC cells may have in reversing the buildup phenotype.

The iPSC cells that were injected had been specialized into neuronal precursors that would display a cholinergic neuron phenotype and were injected into the bilateral hippocampus of mice that had high levels of amyloid plaques (Fig 3A-C) (Fujiwara et al., 2013). As a control, some PDAPP mice were injected with PBS (Fujiwara et al., 2013).

In order to measure neuroregeneration, the spatial memory function, a skill that utilizes the hippocampus, of the PDAPP mice was measured prior to and after the injection at various intervals (Fujiwara et al., 2013) (Fig 3D-G).

If the spatial memory function of the PDAPP mice, with the transplanted iPSC cell, improves after the injection, it's indicative of neuroregeneration in the hippocampal region which could point to reversal of AD phenotype (Fujiwara et al., 2013).

Upon grafting the neuronal precursors into the mice, it was noticed that they dispersed throughout the hippocampus and became cholinergic and

GABAergic neurons (Fujiwara et al., 2013). GABAergic neurons are hypothesized to have similar growth conditions as cholinergic neurons and as a result have also regenerated (Fujiwara et al., 2013). Regardless, the spatial memory function of the mice with the iPSC transplantation was seen to improve after the grafting (Fujiwara et al., 2013) (Fig 3D-G).

The exact mechanisms involved in the improvement of spatial memory function in these mice are unknown. Although, it is thought that the "neuronal precursors reconstruct neural networks essential for spatial memory function" (Fujiwara et al., 2013). This implies that iPSCs can be used to alleviate and delay the symptoms of AD.

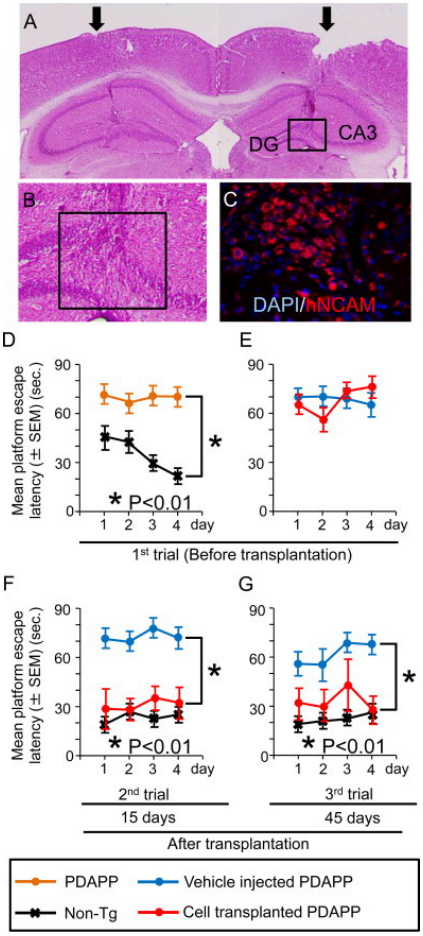

Figure 3: iPSCs were transplanted in the hippocampus as indicated by the black square on panel A and B. The neurons were fluorescently labelled by DAPI to check for cell viability as seen n panel C. Mean platform escape measures the time it takes for the mice to escape a maze, effectively measuring spatial memory. Before the transplantation both the PDAPP with the iPSC cell transplantation and the control with the PBS have similar, comparable spatial memory (D-E). Within the second and third trial the PDAPP with the cell transplantation shows an improved spatial memory (F-G). Image from Fujiwara et al., 2013.

Another study, Cha et al., has shown that iPSCs can be used to prevent neurodegeneration without regenerating neurons. Research on neuron-astrocyte interactions has suggested that glial cells take part in regulating nerve activity and intracellular signalling by releasing neuromodulatory factors. (Cha M. Y. et al. (2017)). Glial cells can be a causative factor to AD as their hyperactivation leads to formation of excess amyloid plaques (Types of glia. (2016)).

5XFAD is a transgenic mouse model that has five mutations that result in formation of amyloid plaques (Shin et al., 2021). Protein-iPSCs are adult cells that were injected with the proteins of an ESC, resulting in the adult cell gene expression being that of an ESC. Protein-iPSCs is another method of obtaining iPSCs. Cha et al., injected protein-iPSCs into 5XFAD mice for the purpose of improving AD pathogenesis, and specifically focusing on their effect on amyloid plaques. To test the effects of protein-iPSCs on the 5XAD mice, spatial memory functions were tested. Mice with the injected protein-iPSCs displayed better spatial memory then those mice with no injected protein-iPSCs (Cha M. Y. et al. (2017)). Furthermore, these protein-iPSCs were found to have become glial cells, mostly oligodendrocytes, implying that healthy oligodendrocytes, which create support for axons in the CNS by producing myelin, may “improve memory function by maintaining axonal integrity” hence reducing the neurodegenerative effects of the AD (Cha M. Y. et al. (2017)).

Parkinson’s Disease (PD) is another neurodegenerative disorder that affects more than 10 million people worldwide (Statistics, n.d.). PD involves the degradation of the dopaminergic neurons of the substantia nigra pars compacta (SNc) (Elkouzi et al., 2019). This degradation of dopaminergic neurons cuts off the connection between the SNc and the striatum, effectively reducing dopamine source. This results in the distinct tremors, rigidity, bradykinesia and postural instability that is noticeable in PD patients (Elkouzi et al., 2019). The challenge with PD is the heterogeneity of the disease due to common genetic variants (Greenland et al., 2019). This results in difficulty in finding one treatment that works for all PD patients, so to effectively treat PD a method to establish individualized treatments is necessary (Elkouzi et al., 2019). While it’s possible to take ESC and specialize them to dopaminergic neurons to replace lost dopaminergic neurons, it’s difficult to reach the desired level of specification that is required for an adept PD treatment (Elkouzi et al., 2019).

iPSCs were used to establish a method to treat PD subtypes that arose from the common genetic variants. Because iPSCs can be generated from the patient, individualization of the treatment is possible.

The blood of PD patients has been collected for research into the disease for a long period of time, resulting in a large data bank of different types of PD haplotypes (Deleidi et al., 2011). This large data bank can be used to create iPSC lines specific to variants of PD.

Deleidi et al., used Mauritian cynomolgus macaques (CM) to generate iPSCs. CM has seven holtypes, so if iPSCs can be generated by all seven haplotypes and still be able to regenerate neurons, then this process would indicate that individualized treatment for PD is plausible (Deleidi et al., 2011).

CM iPSCs went through in vitro differentiation into dopaminergic neurons (Deleidi et al., 2011). 400,000 differentiated iPSCs were then transplanted into the striatum of 6-OHDA rats (Deleidi et al., 2011). 6-OHDA rats is an animal model that has neurotoxin-induced neurodegeneration, behavioral deficits and motor dysfunction to model PD in a rat (Simola et al., 2007). These models were used to examine how the PD phenotype would change after iPSC transplant.

Upon examining the dopaminergic neural graft after 4-16 weeks post-transplantation, it was found, through amphetamine and apomorphine responses, that the dopaminergic neurons were able to rebuild the connection between the striatum and SNc that 6-OHDA rats did not have (Deleidi et al., 2011) (Fig 4). The disconnection between the striatum and SNc is a common cause of PD in humans So this finding implies the possibility that iPSCs could be used to create dopaminergic neural grafts and combat the pathogenesis of PD (Deleidi et al.). Having successfully repeated this experiment on monkeys, human clinical trials are the next step in creating an adept treatment for PD (Deleidi et al., 2011). Kyoto, Japan has begun clinical trials, which have shown both long-term survival and good integration into brain networks (Elkouzi et al., 2019).

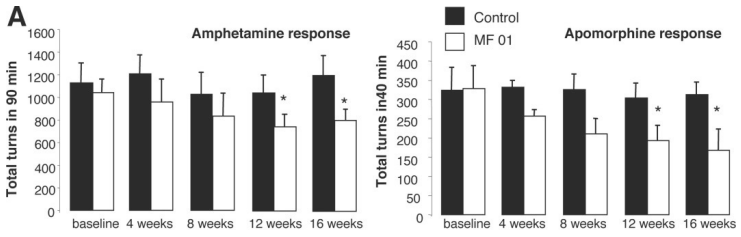

Figure 4: The amphetamine and apomorphine levels were recorded between before transplantation of the iPSCs and after the said translation at weeks 4, 8, 12, 16. It is clear that both amphetamine and apomorphine decrease after transplantation. Image from Deleidi et al., 2011.

To conclude, iPSCs show great promise in neuro-regeneration due to their autologous translatability and pluripotency. When it comes to treating neurodegenerative diseases, iPSCs can be used to regenerate or restore lost and damaged brain networks. Alzehimer’s Disease, the most common neurodegenerative disease, is marked with amyloid plaques, which aid in progression of the disease.

The effect of these amyloid plaques can be removed by regenerating cholinergic neurons at the hippocampus, helping restore lost neurons and allowing the individual to retain their memory and learning skills. Furthermore, the effect of amyloid plaques can also be mitigated by protein-iPSCs turned glial cells. Glial cells, like oligodendrocytes, play a major role in regenerating axons in the CNS. Parkinson's Disease, another common neurodegenerative disease, is heterogenous and so no one treatment exists to help all those who are suffering from it. To develop a method for individualized and personalized treatment, iPSCs were used to create custom dopaminergic neural grafts. These grafts could then be transplanted into the striatum where they rebuild the connection between the striatum and SNc that many PD patients lack. This experiment yields high success rates in animals, and so it moves onto clinical trials. Many researchers have been using iPSCs to both regenerate neurons as well as other cells that slow down the degeneration of neurons.

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Olfactory Responses by Memory

Laura Kilikevicius

The sense of smell is powerful for its ability to evoke a response to a past experience, whether it was experienced years ago or an hour ago. This could be associated with a cooked dinner, a hike in a forest after rain, or the stench of garbage in a city alleyway. Yet the association between a smell and the memory surrounding it leaves many unanswered questions about the process and the ways it is used in people. For example, one may wonder whether infants experience the same sort of memory retrieval due to olfactory stimulus that adults do, or what changes occur in the brain as a result of loss of the ability to smell. It is important to note that the reason our senses are such powerful tools lies in their connections to the brain; since our brain is perhaps the least understood organ, we already have a sense of its vast complexity and capability for what may be the unthinkable. While it may seem simple in nature that we have memories associated with smell, this trait can leave a large impact on us as we grow older. It is also this property that is exploited commercially by fragrance companies to make scents more appealing to consumers. Because the brain has certain effects and capabilities in response to various stimuli, we are also able to compare these responses to other signals and how they differentiate from smell - in other words what makes smell special to us.

In order to better understand the process of connecting a scent with the brain, we can begin by asking: how does the brain take apart scents to process them? To answer we must look first in the nose and olfactory bulbs. The olfactory bulb is a part of the forebrain and is equipped with a set of nerves that extend past the Cribriform plate – a part of the Ethmoid bone that is located between the eyes – into the nasal cavity. When receptors in the nose pick up molecules from a specific scent, it is transmitted as an electrical signal to the olfactory bulb (Manzini et al., 2014). In order to perceive something as a smell, the molecule must be an odorant, meaning it must meet some criteria, typically having some hydrophobicity and volatility (Mayhew et al., 2022). The human nose is said to have approximately 350 different receptor types which can react to various smells through their molecular components (Rinberg, 2020). Olfactory receptors operate such that any combination of odor molecules can activate different sets of receptors (Malnic et al., 1999). The molecules' recognition and interaction with the receptors operates in a combinatorial way (Malnic et al., 1999). This results in a system of activation allowing one to recognize what is now estimated to be up to 1 trillion different odors (Bushdid et al., 2014).

Since the glomeruli, nerve ending bulbs found in the olfactory bulb, are unique to interactions with different smells, our perception of smell is highly dependent on how well they are activated and in what order. As a result, if we switch up the sequence in which they are activated or inactivate some of the receptors, we are likely to have a loss in ability to sense odors. One experiment testing this phenomenon of sequential activation impact on recognition was completed using a mouse model, which found that a delay or an interruption of a specific receptor receiving an orderant would decrease the system of cooperation between the receptors (NYU Langone Health, 2020). It was found that through the changing of the first glomeruli activated, as much as 30% of a drop could be recognized in the ability of a mouse to correctly sense the odor signal (NYU Langone Health, 2020). By contrast, if the last of the glomeruli was changed, only about 5% would be potentially dropped in the ability of the mouse to sense the correct odor. (NYU Langone Health, 2020). In order to identify what odors stand out within a mixture as well, the right sensors must be activated in the right order and time. Any deviation in either of these abilities would result in the decreased ability to recognize and categorize the smell accurately. Following this transmission of electrical signals to the glomeruli they will proceed to the brain's cortex (NYU Langone Health, 2020).

Once the signal reaches the neurons of the cortex the brain takes further action. The piriform complex, a set of neurons right behind the olfactory bulb, will work in attempts to recognize the smell itself. This complex is the only known structure other than the hippocampus to have a three-layered allocortical structure, and is activated when the pyramidal cell, a type of neuron, receives information from the glomeruli and transmits it to other regions of the brain (Vaughan, 2014). This also helps with responses to specific odor mixtures by aiding in the formation of a neural network that is capable of reliably transmitting these messages. The anterior piriform complex is thought to hold information of the molecular features of the odorant, whereas the posterior piriform for the quality of the odor (Gottfried, 2006). The piriform complex additionally is used to help differentiate odors (Howard et al., 2009) and is involved with the working memory where the odor information can be temporarily stored (Zelano et al., 2009). In other words, it is of crucial importance that this complex is responsive and active in order to retain a highly functioning smell identification and memory connection system. It is from this complex that the information can then be further passed over to other areas of the brain.

Having left off in our pathway at the piriform complex, various cells within this structure will signal and move the information to the thalamus, a complex key for translating the neural impulses that come from the receptors to the cerebral cortex. It is also important for various sensorimotor association functions, including motor activity, emotion, and memory, among others (Blumenfeld, 2018). From the thalamus, the information can be passed to multiple locations, including the hippocampus. This area is a key part of the brain that stores information involved with learning and memory, and is a crucial component of the olfactory system for this connection to memory. When the neurons signal to the amygdala, the portion of the brain involved with emotion, they are able to activate it in ways that depend highly on the pleasantness of smell to the individual (Zald & Pardo, 1997). The location of the amygdala is what helps make the association between memory and smell so strong (Walsh, 2020). The amygdala portion of this process contains a series of steps that refine the process, and since the olfactory bulb also signals directly to the limbic system, it is easy to register the emotions that are in close coordination with the smells encountered. Analyzing how the sense of smell is associated with memory therefore very closely is related to the location of the centers in the brain that will respond. Since the amygdala is so involved in the olfactory response, an expected response of emotional connection and memory creation/retrieval is bound to occur. Just as how some people associate a certain smell with a bad memory, the brain links various memories with the senses experienced resulting in these unfortunate retrievals. In a similar manner, we can experience positive emotions with a particular smell, and both of these examples would include many different interactions of the brain to create the overall sensations that we experience. The combination of memory and smell is one that is unique in many ways for its strong connections with multiple key areas of the brain and the ability to recognize an abundance of smells.

To smell an odor does much more than evoke a particular memory, despite being an important emotional contribution to the human experience. It has the capability to create connections and respond in ways in the brain that are stronger than previously thought while being a crucial contributor to our brain function.

The sense of smell is powerful for its ability to evoke a response to an experience, whether it was experienced years ago or an hour ago. This could be associated with a cooked dinner, a hike in a forest after rain, or the stench of garbage in a city alleyway. However, the association between a smell and the memory surrounding it leaves many unanswered questions about the process and how it is used in people. For example, one may wonder whether infants experience the same sort of memory retrieval due to olfactory stimulus that adults do or what changes occur in the brain due to losing the ability to smell.

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To smell an odor does much more than evoke a particular memory, despite being an essential emotional contribution to the human experience. It can create connections and respond more substantially in the brain than previously thought while contributing to brain function.

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Brain Matters Board

Chief Editor

Laura is a Junior majoring in Molecular and Cellular Biology and is pursuing a minor in Food Science. She is very excited to showcase the new volume and hopes to expand the journal to new horizons. Aside from working on the journal, she is an assistant researcher in the Robinson Lab, is an MCB leader, an Orientation Leader, a member of Bioscience Journal club, and an executive board member of the Undergraduate Neuroscience Society.

Assistant Chief Editor

Fiza is a Junior majoring in Molecular and Cellular Biology on the pre-med track. In addition to her involvement in the Neuroscience Journal Committee, she has communicated her Illinois experience by being a former UIUC admissions blogger and enjoys science through volunteering at a local free clinic and doing research at Vet Med. She is thrilled to promote a neuroscience dialogue on campus!

Public Relations Chair

Julia Gainski is a junior majoring in Integrative Biology with a minor in German. She is the Public Relations Chair and a writer for Brain Matters. She is a research assistant at the Control & Network Connectivity Team (CONNECTlab) at the Beckman Institute of Advanced Science and Technology, where she assists with an EEG procedure in a concurrent EEG-fMRI study. Additionally, she is a personal assistant for students with physical disabilities at Beckwith Residential Support Services at Nugent Hall on campus, the secretary and a mentor of the Pre-Physician Assistant Club, and a member of the Illini Club Tennis team.

Editors

Carolyn is a junior majoring in Molecular and Cellular Biology and is currently conducting research in neurochemistry in Dr. Jonathan V. Sweedler's lab. Outside of academics, she is passionate about IlliniThon, the University of Illinois' Dance Mara- thon program that fundraises for St. John's Children's Hospital in Springfield, IL. She is excited to collaborate with the other students behind "Brain Matters" and promote brain awareness on campus.

Samantha is a junior majoring in Journalism with a minor in Astronomy. Outside of academics, Samantha photographs and models for The Fashion Network. She is excited about mixing her skills of writing and photography to promote brain awareness and neuroscience knowledge on campus.

Eva is a junior majoring in Molecular and Cellular Biology and minoring in Creative Writing. Aside from her passion for mental health and neuroscience awareness, she enjoys writing and dancing, and is a proud member of UIUC's Legend Dance Company. She is so excited to work with her fellow students to expand our campus's appreciation for neuroscience through Brain Matters!

Rajvi Javeri is a Sophomore pursuing a major in Psychology with a Concentration in Behavioral Neuroscience and a minor in Music. Apart from being a part of the Undergraduate Neuroscience Society, she helps out as a research assistant at the Cognitive Neuroimaging Laboratory at the Beckman Institute. In her free time. she likes to practice guitar and sing. She also loves drinking infused teas and reading books whenever she can. She loves going on treks and any outdoor activities in general and is also a part of the UIUC archery club!

Sarah is a Junior majoring in Biochemistry and Intradisciplinary Psychology. In addition to editing for Brain Matters, Sarah works in Dr. Auinash Kalsotra's biochemistry lab as a research assistant and in Dr. Kara Federmeier's cognitive neuroscience lab. In the future, Sarah hopes to pursue an MD-PhD in Biochemistry to study the mechanisms of neurodegenerative disorders. In her free time, Sarah loves to play soccer, go hiking, watch television, and spend time with friends.

Design Board*

Manan is a Junior 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

Katy Simmons is an MCB major pursuing a certificate in neuroscience! Her interests include cellular neuroscience and neuroimmunology. She is involved in Brain Matters as a design team member, editor, and former writer. Her favorite thing about being a part of the journal is meeting and engaging with others that are passionate about neuroscience. Apart from her role in Brain Matters, she is a research assistant in the Physical Activity and Neurocognitive Health Lab, as well as the Evolutionary Immunology and Genomics Laboratory. After undergrad, she plans to attend grad school to conduct her own research in cellular neuroscience!

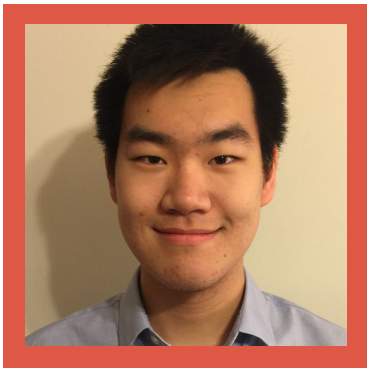
Zainab Hashmi is a sophomore pursuing a dual degree in Psychology and Information Science with a minor in computer science. Previously a writer for Brain Matters, she joined the Design board in 2022. She's involved in research at the Adaptive Cognition and Interaction Design Lab at UIUC, is a UX designer for Design Innovation, Design Chair of Muslim Student Association, and also works as a graphic designer at Spurlock Museum on campus. She is excited to be a part of the journal and to make the vast topics of neuroscience more accessible to everyone.

Apil is a sophomore majoring in Molecular and Cellular biology with interests in Neuroscience Research. Outside of studying biology, he volunteers at both Riverside hospital and Riverside Senior Life Center where he works with Alzheimer patients. His other hobbies include playing basketball and soccer.

Jade is a third year undergraduate in Cognitive Science with a concentration in Linguistics. She is passionate about voice technology and its effects on human behavior. In her free time she sings, plays guitar and piano, and loves trying new foods. She also enjoys traveling and immersing herself in other cultures. Her love of writing and editing is shown through her work for the Illinimedia Company and article written for SoundHound Inc's Speech-to-Meaning blog. She is happy to be editing and designing for the "Brain Matters" journal.

*Due to publishing delays, Volume V issue ii was designed by the Design Board from the 2022-2023 academic year

Brain Matters Writers



Andrew Zhang is a sophomore majoring in Molecular and Cellular Biology. Currently, he is a research assistant in Dr. Huimin Zhao's lab and also part of UIUC's American Chemistry Society and REACT. He believes that neuroscience is a great field to learn about. There are so many things to learn about the brain - especially ideas that can improve our lives. He is excited to be a part of Brain Matters in sharing neuro- science!

My name is Christopher Jones. I am a Community Health-Pre Med major. As an Undergraduate student I have been involved in several activities including Minorities in Medicine (MAPS), Intramural Basketball, as well as various volunteering opportunities throughout the Champaign-Urbana community. I am also a member of The Omega Psi Phi Fraternity inc. One of my most memorable moments thus far was belong selected to participate in the NIAMS Summer Research Fellowship at the National Institutes of Health in Washington D.C. My goal is to attend Medical School and become a Neurosurgeon.

Emma Ibanez is a senior majoring in MCB with a minor in chemistry. As an undergraduate research assistant in the Rhodes lab, she genetically modifies clownfish for studying socially influenced sex change. Emma also enjoys caring for her plant collection and learning how to play the piano. After graduation, she plans to attend graduate school for further research in neuroendocrinology.

Lina graduated from the University of Illinois at Urbana-Champaign in 2021 and is now a first-year medical student at the University of Illinois at Chicago. She was previously doing research in an auditory neuroscience lab at the Beckman Institute on campus and was awarded the 2021 Berkowitz Summer Fellowship for her work there. Lina was also published in Cells for her contributions in looking at age-related hearing loss and the distribution of serum lipidomic biomarkers as a means of predicting the development of Alzheimer's Disease. Outside of academics, she is involved in social justice work and volunteers through various organizations to serve in underserved communities. She is very excited to share her passion for neuroscience through Brain Matters!

Hanifa is a Senior at the University of Illinois majoring in Molecular and Cellular Biology with Honors Concentration and minoring in Philosophy. She has been interested in neuroscience after reading Paul Kalanithi's autobiography When Breath Becomes Air. In addition to writing for Brain Matters, Hanifa is currently researching the effect of AVP on the brain's glymphatic system in Dr. Martha Gillette's lab. She volunteers at Carle, Avicenna, Salt and Light, and the Illini Medical Screening Society.

Laura is a Junior majoring in Molecular and Cellular Biology and is pursuing a minor in Food Science. She is very excited to showcase the new volume and hopes to expand the journal to new horizons. Aside from working on the journal, she is an assistant researcher in the Robinson Lab, is an MCB leader, an Orientation Leader, a member of Bioscience Journal club, and an executive board member of the Undergraduate Neuroscience Society.

About Brain Matters

Brain Matters discusses all things neuroscience, psychology, and biology written by UIUC's very own. Authors come from diverse backgrounds, such as computer science and engineering majors. Not to mention, the journal welcomes all authors no matter their area of study or year. This diversity allows volumes to have a wide range of articles. The journal is mainly written for the college community yet is accessible to anyone as Brain Matters is uploaded as an Open Access Journal format by the University Library.

Sponsors

The Undergraduate Neuroscience Society (UNS) sponsors the Brain Matters journal. UNS is a UIUC registered student organization that is dedicated to establishing and growing the Neuroscience community on campus.