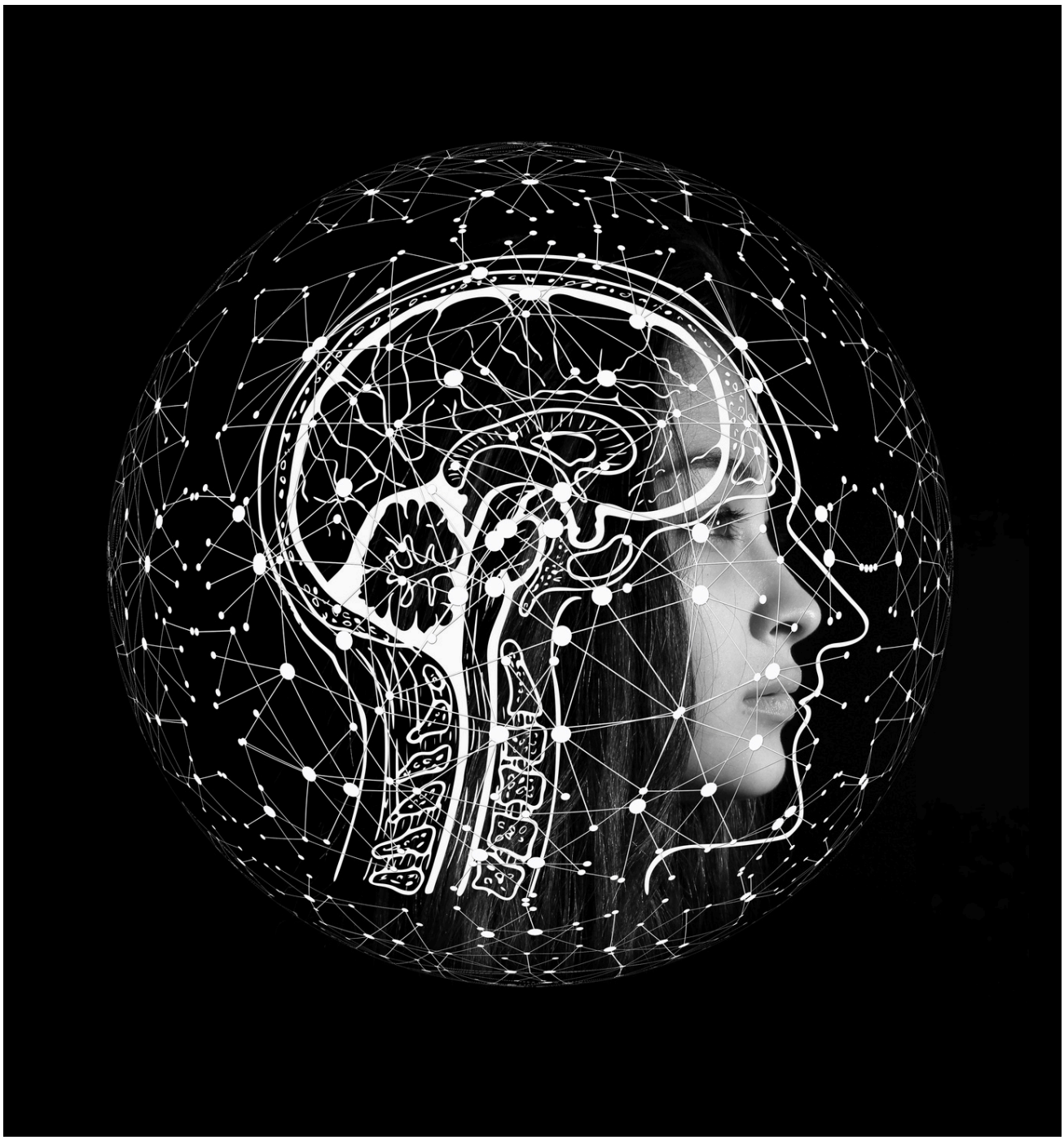
MCMASTER BRAIN RESEARCH SOCIETY

MBRS JOURNAL



4th Edition

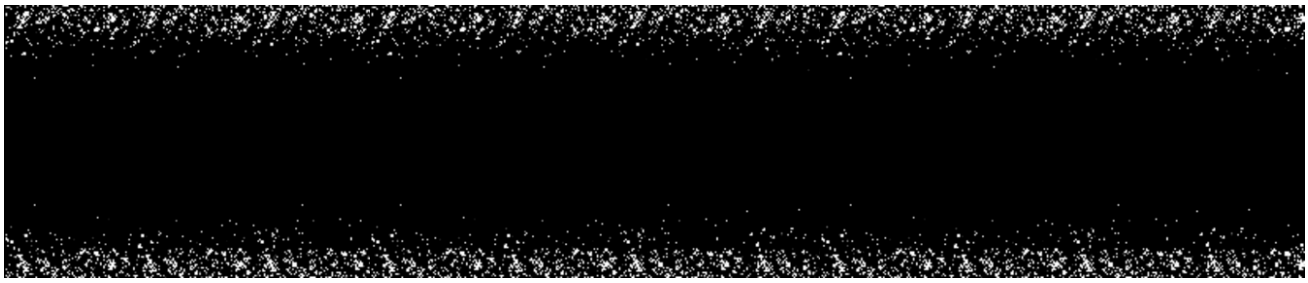
MCMASTER BRAIN RESEARCH SOCIETY

2023-2024 Executive Team

Co-Presidents	**Isha Masood & Ahad Daudi**
Director of Publications	**Anya Kylas**
Director of Events	**Raenita Puliyelil**
Director of Marketing	**Yumnah Jafri**
Director of Finance & Administration	**Shuani Wang**
Events Coordinators	**Tanishtha Arora & Cindy Vo**
Graphic Designer	**Varshaa Srivel**
Journal Editor	**Hiya Shah**

www.macbrs.org

McMaster University is located on the traditional territory shared between the Haudenosaunee confederacy and the Anishinabe nations, which was acknowledged in the Dish with One Spoon Wampum belt. That wampum uses the symbolism of a dish to represent the territory, and one spoon to represent that the people are to share the resources of the land and only take what they need.



McMaster Brain Research Society Journal: Volume 4

Table of Contents

Unraveling the Mysteries of Maternal Brain Changes: A Call for Further Research

Parneet Deo, Honours Biomedical Discovery and Commercialization *Class of 2024*

Abstract

This article delves into the intricacies of maternal brain changes during and after pregnancy, exploring existing research and identifying critical gaps that warrant further investigation and highlighting the need for a deeper understanding of brain changes in mothers who have conceived through in vitro fertilization . Critical examination of current research articles using structural magnetic resonance imaging (MRI) elucidated alterations in brain configuration during and after pregnancy. While existing studies point to both positive and negative changes during pregnancy and postpartum, methodological variations and limitations hinder conclusive insights. The article emphasizes the need for comprehensive and longitudinal investigations using standardized protocols and larger sample sizes to overcome inconsistencies and broaden our understanding of structural brain changes in mothers. Additionally, it sheds light on the challenges of enrolling participants in such studies, such as the reluctance of prospective mothers to undergo brain scanning and the historical regulations of MRI's during pregnancy. Enhanced research frameworks must be developed to unravel the complexities of maternal brain changes, contributing to advancements in neuroscience and fostering a more comprehensive understanding of the impact of pregnancy on the brain. Women are underrepresented in research, and this calls for a change.

Pregnancy is a transformative journey marked by physiological and psychological changes. While extensive research has explored the psychological distress associated with in vitro fertilization (IVF) outcomes, there remain gaps in understanding the effects of IVF hormones on the maternal brain. (1) This critical area of research provides insights that may influence decisions regarding this intricate journey. Pregnancy causes both physiological and psychological changes, which are sometimes detrimental. Despite the increasing prevalence of IVF, there is a scarcity of studies specifically examining the impact of IVF hormones on the configuration of the maternal brain. This gap in knowledge underscores the necessity for in-depth investigations that can shed light on the nuanced relationship between reproductive technologies and maternal brain structure.

Sex hormones, such as estrogens and progesterone, play major roles during pregnancy. (2) Estrogens and progesterone help the uterus grow, maintain the uterine lining, and orchestrate the feedback of other hormones. Past studies, primarily conducted through structural magnetic resonance imaging (MRI), have demonstrated changes in grey matter during pregnancy. (2) Notably, imaging during the postpartum period has been explored in detail, revealing improvements in brain structure after giving birth. Studies uniformly reported decreases in brain age, ventricle size, and increases in global brain size and regional volumes. (2) These findings suggest widespread tissue growth during the initial weeks and months postpartum, indicating a restorative phase for the maternal brain. (2)

Despite the potential insights offered by such research, enrolling participants in these studies poses significant challenges. Prospective studies often face difficulties in recruiting women planning to become pregnant, while reluctance among new or prospective mothers to undergo voluntary brain scanning further impedes progress. Historically, strict regulations on neuroimaging during pregnancy have also contributed to the sparsity of research in this domain.

Recently, restrictions on brain scanning during pregnancy have become more lenient with an increased understanding of how these scans affect patients. For example, studies suggest that MRI, when excluding Gadolinium-based contrast agents, poses minimal risk to the fetus. (3) Nonetheless, due to the extensive work put in by families through IVF, any potential risk to the fetus is likely avoided, as IVF is a long and difficult process for conceiving. These brain scans still have potential risks and side-effects, which makes mothers hesitant to accept them causing a barrier in research data collection.

The current understanding of structural brain changes during pregnancy remains limited, with conflicting outcomes from existing studies. The need for larger sample sizes, standardized protocols, and replication studies is evident. While some studies suggest tissue decreases during pregnancy, the majority indicate substantial tissue increases postpartum. (2) Future research should examine region-specific trajectories and the implications of these structural changes on maternal mood, cognition, and behaviour during and after pregnancy.

In conclusion, the journey to understand the intricate relationship between pregnancy, IVF outcomes, and the maternal brain is ongoing. There remains a lack of sufficient research on women and pregnancy. Women continue to be underrepresented in research, and there is a need to change this for better study results and to advance society. While there is research on the embryonic brain structure during pregnancy relative to IVF pregnancy, there is no work comparing maternal brain size. (4) While strides have been made, challenges persist, emphasizing the imperative for continued research in this vital field. A more comprehensive understanding of maternal brain changes holds the potential to guide clinical decisions and enhance the well-being of mothers navigating the complexities of reproduction.

1. Aimagambetova, G., et al. (2020). The effect of psychological distress on IVF outcomes: Reality or speculations? *PLoS One, 15*(12), e0242024. https://doi.org/10.1371/journal.pone.0242024
2. Luders, E., et al. (2022). The neuroanatomy of pregnancy and postpartum. *NeuroImage, 263*, 119646. https://doi.org/10.1016/j.neuroimage.2022.119646
3. Bouyssi-Kobar, M., du Plessis, A. J., Robertson, R. L., et al. (2015). Fetal magnetic resonance imaging: exposure times and functional outcomes at preschool age. *Pediatr Radiol, 45*, 1823-1830. https://doi.org/10.1007/s00247-015-3408-7
4. Chan, Y. L., Leung, K. Y., Lee, C. P., et al. (2003). Fetal MR imaging of normal brain development. *Eur J Radiol, 48*(2), 133-144. https://doi.org/10.1016/s0720-048x(03)00149-8

Understanding the Western View of Mental Health and a Reflection of the Impacts on South Asian Women

Harmandip Kaur Dhami, Honours Life Sciences *Class of 2027*

Abstract

Mental health disorder treatment has advanced exponentially in the past decades, with vast varieties of treatments available based on one's personal needs. However, current conventional treatments for illnesses including depression are often centered around Western-centric biopsychiatric models of mental illness that may not resonate with foreign cultures. In terms of how depression is categorized, the biopsychiatric model consists of attributing depression to dispositional issues, framing it as an individual problem rather than a community one. This predominantly Western method of defining depression can deter individuals of other cultures from identifying themselves as having depression due to associated stigma or misunderstandings. Additionally, the Western framework of mental health assumes that mental health is largely endogenous, requiring medical treatment and medications. This perspective views mental disorders as medical conditions, contrasting with the view held in non-Western societies, where depression is seen as a common emotion to cope with the troubles of life. Focusing on mental health as a medical issue is not commonly present in cultural groups outside of Western societies, resulting in low rates of clinical depression treatment in individuals from immigrated communities. In Ontario alone, social disparities within the access mental health services for children and youth have been identified for racialized and ethnic families, leaving these communities at an observable disadvantage. Research has indicated that these families in Ontario are about 40-50% less likely to contact a mental health professional for a child or youth member compared to self-identified white families. (4) To increase diversity and an intersectional approach in the mental health field, a focus on recognizing the harms of Western monoculture and an emphasis on consideration of other cultures needs to be implemented. Being aware of the lack of resonance with the Global North framework ensures all individuals receive culturally equitable treatment.

South Asian immigrant women in Western countries have been statistically found to have a high prevalence of common mental disorders and emotional distress, especially after marriage due to intimate partner violence. Prevalence of domestic abuse within South Asian immigrants have been predicted by researchers to be at a range of 30% - 50%, with women often remaining in abusive relationships enduring continuous emotional and physical abuse. (2) The accumulation of social stressors due to gender-based discrimination post-marriage including seclusion, domestic abuse, and immigration places South Asian women at an increased risk for self-harm and suicide. (6) Despite these alarming rates, South Asian immigrant women have consistently refrained from seeking psychiatric medical treatments for mental health. According to CAMH, South Asian communities generally have been found to be 85 percent less likely to seek out mental health care than those identifying as white. (1) This reluctance can be attributed to the perception of depression symptoms as normal responses to stress rather than diagnosable medical problems. Based on these cultural contexts, symptoms including persistent sadness, fatigue and worry have been associated with the word "Tension" and normalized to be an inherent aspect of life. (6)

Current mental health providers often overlook the role of families and communities in perpetuating abuse, resulting in inadequate support for South Asian women. (2) Within South Asian families, women are frequently placed in vulnerable positions with minimal community support due to the deep-rooted paternalism, where men are socialized to think of themselves as superior and authoritative over their spouse, promoting domestic physical abuse as a means of discipline. (2) Women end up taking the role as subservient wives, blaming themselves for angering their partner and rationalizing abuse as being a deserved punishment. These mindsets deter women from seeking care from a general practitioner for emotional distress, to appease their families and community. (2) This reluctance was demonstrated within a comparative study on mental illness perceptions between North Indian and White British Women. In this study, the two groups were presented with a case study of a woman undergoing symptoms of anxiety and depression. Only 20% of the Indian Women indicated they would visit a health professional if they were in a situation presented, considerably lower than the 46% of white women. (10) These social perceptions only add an additional barrier to receive required mental health care for disadvantaged immigrant communities. (2) Without any intervention and necessary adjustments in current mental health services to recognize these social dynamics that are misogynistic, South Asian women will continue to silently endure the abuse due to lack of culturally sensitive resources, perpetuating these power imbalances for the future generations of women.

The current effective gap for mental health treatment can be attributed to the absence of conceptual synergy. This overlooks the need to adjust treatment to align with the cultural variations and diverse perceptions of mental health. (6) In order to encourage the seeking of mental health treatment in cultural communities, Community-Based Participatory Research (CBPR) has been utilized to foster collaborative initiatives aimed at developing effective strategies to assist minority populations. (8) These community based projects have been successful in pinpointing the social, contextual, language and cultural factors influencing one's decision to seek out treatment. Consequently, this information can be utilized to develop strategies to alter current westernized treatments and increase inclusivity. (9)

These collective findings served as the basis for the development of a Community-Based Participatory Research (CBPR) initiative that focused on Bangladeshi women in New York. The objectives focused on conceptualizing mental health issues in the community and constructing culturally sensitive interventions. (5) The CBPR project, "Bondu" (meaning 'Friend' in Bangla) began with establishing trust between mental health professionals, researchers and participants. Through participant-led discussions, researchers decided to concentrate on the concept of "Tension," and the associated symptoms experienced by Bengali women during this phase of life. (6) Through these discussions, a notable discovery emerged, revealing that the presence of somatic symptoms frequently signaled the need to seek out medical intervention. Recognition of somatic manifestations of stress including headaches, muscle pains and weakness was deemed essential to identify depression risk in this study. This can be attributed to the tendency for South Asians to communicate their mental health concerns through physical symptoms. (6,8) Interestingly, this pattern has been consistently observed in other minority groups including African, and Chinese, contrasting the way patients in Western societies focus on psychological symptoms. Identifying these cultural variations aids mental health professionals in effectively identifying mental illness within minority communities. (5) For instance, integrating psychological emotions and somatic symptoms into an assessment tool can enhance the detection within diverse communities and successfully targeting a larger outreach. (5) In short, the participant-led discussions led researchers to be able to develop a survey that focuses on the ideologies of mental health established within Bengali women to assess risk. (6)

The promotion of mental health treatment within non-Western cultural groups requires identifying the cultural ideologies associated with mental health. (5) Understanding how perceptions of mental health are unique to cultures can create inclusive treatments that attract vulnerable communities and promote seeking help.[3] Consequences of colonization and racism have left ethnic groups with a form of mistrust within the medical field, and inefficiency to provide adequate care preventing individuals from seeking care. Change requires acknowledgement of intersecting factors of culture identity, illness perception, vulnerability and social stressors present within groups to strengthen the quality of life of ethnic groups. (3) Complex issues found within non-Western societies require a deeper delve and awareness in present stigmas, racism and effects of colonization which prevent individuals from attaining care. Marginalized groups including African Americans, First Nations and Latino communities have all demonstrated mistrust within healthcare structures due to constant racial persecution. (3)

This bias is evident within adults when understanding diagnosis-based need for mental health or substance abuse care, where 37.6% of Whites, but only 22.4% of Latinos and 25.0% of African Americans, receive quality treatment and care.[7] Preventing equitable care only increases cultural division, lowering the quality of life of immigrant communities. Mental health research involving community-based participatory research is a small but necessary first step to begin dismantling monocultural viewpoints surrounding treatment of mental health. (8) The findings from CBPR studies not only propose possible interventions that focus on different cultural beliefs, but add to the discussion of respecting cultural perspectives that clash with Western ideas during mental health treatment. Fostering diversity within mental health care will ensure that modern medicine steers away from ideas that only focus on the well-being of populations in the Global North.[2] Mental health professionals can incorporate culturally aware treatments that will result in the ability to provide equitable assistance by acknowledging the vast cultural norms and beliefs. (8) Understanding these differences will enhance treatment outcomes and cultivate an inclusive approach in mental health care that recognizes the intersectional factors that influence the unique needs of non-Western cultural groups.

1. CAMH to create new mental health supports for South Asian communities; 2019 Aug [Internet]. CAMH. Available from: https://www.camh.ca/en/camh-news-and-stories/camh-to-create-new-mental-health-supports-for-south-asian-communities
2. Finfgeld-Connett D, Johnson ED. Abused South Asian Women in Westernized Countries and Their Experiences Seeking Help. Issues in mental health nursing. 2013;34(12):863-73. doi: 10.3109/01612840.2013.833318
3. Gopalkrishnan N. Cultural Diversity and Mental Health: Considerations for Policy and Practice. Frontiers in public health. 2018;6:179-179. doi:10.3389/fpubh.2018.00179
4. Kamali M, Edwards J, Anderson LN, Duku E, Georgiades K. Social Disparities in Mental Health Service Use Among Children and Youth in Ontario: Evidence From a General, Population-Based Survey. Canadian journal of psychiatry. 2023;68(8):596-604. doi:10.1177/07067437221144630
5. Karasz A, Garcia N, Ferri L. Conceptual Models of Depression in Primary Care Patients: A Comparative Study. Journal of cross-cultural psychology. 2009;40(6):1041-59. doi: 10.1177/0022022109348782.
6. Karasz A, Patel V, Kabita M, Shimu P. "Tension" in South Asian Women: Developing a Measure of Common Mental Disorder Using Participatory Methods. Progress in community health partnerships. 2013;7(4):429-41. doi: 10.1353/cpr.2013.0046.
7. McGuire TG, Miranda J. Racial and Ethnic Disparities in Mental Health Care: Evidence and Policy Implications. Health affairs (Project Hope). 2008;27(2):393-403. doi: 10.1377/hlthaff.27.2.393
8. Mumford D, Bavington J, Bhatnagar K, Hussain Y, Mirza S, Naraghi M. The Bradford Somatic Inventory. A multi-ethnic inventory of somatic symptoms reported by anxious and depressed patients in Britain and the Indo-Pakistan subcontinent. British journal of psychiatry. 1991;158(3):379-86. doi: 10.1192/bjp.158.3.379.
9. Stacciarini JR, Shattell MM, Coady M, Wiens B. Review: Community-Based Participatory Research Approach to Address Mental Health in Minority Populations. Community Ment Health J 2011 10;47(5):489-97. doi: 10.1007/s10597-010-9319-z
10. Taylor R, Brown JSL, Weinman J. A comparison of the illness perceptions of North Indian and white British women. Journal of mental health (Abingdon, England). 2013;22(1):22-32. doi:10.3109/09638237.2012.734664

Unraveling Alzheimer's Disease: Chaperone Protein 4-Phenylbutyrate's Promising Role in Restoring Cognitive Health

Natasha Lacku, Honours Life Sciences *Class of 2024*

Abstract

Alzheimer's disease, a progressive neurodegenerative disorder leading to dementia, presents a significant treatment challenge that persists into the twenty-first century, with no cure currently available. Alzheimer's has been most frequently attributed to incorrect protein folding of tau proteins from hyperphosphorylation, and the accumulation of aggregated Aβ peptides causing proteostasis. While several theories attempt to explain its etiology, factors such as genetics, environment, and aging are believed to play significant roles in the onset of the disease. Despite being incurable with current interventions, several drug classes have been approved to alleviate the symptoms of the disease, while researchers strive to comprehend its complete pathology. Varying causing factors necessitate different pharmacologic interventions based on the symptoms targeted. For example, cholinesterase inhibitors are used to alleviate confusion and memory loss in order to improve overall cognitive function. Researchers have recently identified 4-phenylbutyrate (PBA) as a promising chaperone molecule for Alzheimer's treatment, offering potential breakthroughs by targeting prevention of protein misfolding, exploring novel treatment strategies, and possibly leading to a cure.

Alzheimer's disease (AD) is classified as a progressive neurodegenerative brain disorder, recognized as the primary leading cause of dementia in older adults, and categorized by a gradual decline in cognitive functions and awareness. (1,2) There are various pathogenic pathways for AD, encompassing both amyloid and cholinergic mechanisms, further complicated by several other factors that must be considered. The cholinergic hypothesis, developed in 1982 for the pathogenesis of AD, posits that cognitive decline arises from the loss of cholinergic function within the central nervous system. (6) Subsequently, in 1991 and 1992, the amyloid hypothesis was formulated, contradicting previous research by suggesting that Aβ is the initiator and cause of neuronal degeneration and dementia seen in AD. (5) This includes, but is not limited to, head injuries, vascular infections and diseases, environmental and genetic factors, as well as the progressively increasing age of an individual. (2) However, varying causing factors for the disease necessitate different pharmacologic interventions based on the symptoms observed. For example, cholinesterase inhibitors are used to alleviate confusion and memory loss in order to improve overall cognitive function. (1)

Only two drug classes are approved for the treatment of symptoms and improvement of quality of life for AD patients: cholinesterase enzyme inhibitors, and N-methyl D-aspartate antagonists. Symptoms include progressive memory loss, agnosia, apraxia, and/or impairment in daily life activities, all of which serve as diagnostic criteria. While encountering numerous challenges in the development of pharmacologic treatments for AD, researchers persist in their primary focus on comprehensively understanding the pathology to devise interventions that improve the course of the disease. With dedication and ongoing research efforts, the quest for effective treatments continues.

AD has been most frequently attributed to the misfolding of tau proteins due to hyperphosphorylation, and the accumulation of aggregated amyloid-beta peptides, forming plaques that lead to neurodegeneration. (5) Proteostasis, akin to the concept of homeostasis, pertains specifically to the regulation of cellular proteins, encompassing tasks such as maintaining post-translational modifications, degradation and protein synthesis. However, in AD, proteostasis becomes dysfunctional, hindering the ability to refold or degrade flawed proteins. Consequently, this dysfunction leads to impaired memory formation and synaptic plasticity, resulting in neuronal stress, synapse loss as well as memory deficits observed in AD. (3) Furthermore, an overproduction of Aβ proteins is evident in AD. These proteins are harmful as they can form aggregated neurotoxic plaques, leading to mitochondrial damage, brain oxidative stress, synapse failure, memory deficits, and deregulation of intracellular signaling pathways.

With over six million individuals in the Americas living with AD, researchers strive to determine whether the disease's etiology, specifically dysfunctional proteostasis, can be targeted to find a cure. A 2023 study conducted by researchers at the University of Pennsylvania Perelman School of Medicine aimed to investigate the role of chaperone molecules in genetically predisposed mice to AD. They found that increasing the dosage of the chaperone molecule 4-phenylbutyrate (PBA) enhanced focus on the rodent hippocampus, a brain region involved in learning and memory, thereby improving memory performance and reversing consolidation deficits. Additionally, in its role as a cellular chaperone, PBA also aids in protein functionality by repairing proteostasis processes, which was hypothesized to potentially benefit those with AD. (3)

In this 2023 study conducted by Hafycz et al., the mice groups were separated to administer treatment at various phases of Alzheimer's progression. While one group initiated chaperone treatment early upon symptom onset, others commenced treatment later as the disease progressed further. The divergence in administration aimed to assess both the efficacy of the chaperone molecule across various stages of AD in mice and to mirror the observed progression stages in humans affected by AD. (3) The study's findings demonstrated effectiveness as both mice receiving early and late administration of PBA exemplified enhanced cognitive functions, as assessed through various cognitive behavioral testing procedures following the completion of PBA treatments. One such evaluation involved the Y-Maze test, where a mouse was positioned at the center of a Y-shaped apparatus and permitted to explore freely for five minutes. The assessment involved recording the mouse's entries into the arms of the Y-maze and their sequential order, providing insight into its spatial working memory.

Early treatment administration was provided to mice aged between 4 to 6 weeks, whereas late administration was administered to mice aged 10 to 12 months, lasting for 10 to 12 weeks. Throughout the treatment period, mice received PBA twice weekly through intraperitoneal injections at a dosage of 40 mg/kg, along with PBA supplementation in their drinking water at a concentration of 0.008% PBA in 1% sucrose. (5) In addition to improved cognitive function, the mice exhibited a more uniform and consistent distribution of proteins within their hippocampal brain cells, indicating an improvement in proteostasis functioning. This was assessed through immunohistochemical (IHC) assays, which included slicing brain sections at a 40-micron thickness using a cryostat, followed by cryopreservation at -20 degrees Celsius for staining, allowing for visualization of specific brain and protein structures. Moreover, stress markers in hippocampal brain cells exhibited reduction. Additionally, alongside the observed decrease in harmful Aβ proteins, there was an increase in beneficial proteins, illustrating PBA's ability to address both cellular dysfunctions as well as symptom alleviation. (3) These beneficial proteins included ADAM10, facilitating the production of non-toxic cleavage fragments instead of Aβ peptides, BDNF, essential for synaptic plasticity and memory formation, BiP, aiding in proteostasis and protein folding as a chaperone molecule, and XBP1, enhancing protein folding capacity and chaperone synthesis. (5)

PBA has been demonstrated to facilitate proper protein folding and inhibit the formation of toxic protein aggregates in brain cells. This aids in the prevention of Aβ protein accumulation and maintains cellular homeostasis, targeting both the disease's pathological processes and symptom alleviation. As stated by the study's senior author, Dr. Nirinjini Naidoo, enhancement to both cellular and neuronal health could potentially delay the progression of AD. (5) Additionally, regaining lost brain functions may involve mitigating proteotoxicity, thereby highlighting the importance of understanding its role in AD pathogenesis for developing novel therapeutic strategies.

While the results of this study may be promising and give researchers hope for prospective AD therapies, many necessary steps must take place before administration to the affected public. Currently, PBA is generally administered to those with urea cycle disorders and has been determined safe but is required to be reassessed in the treatment of AD patient profiles. (4) Thus, clinical trials in humans are necessary to confirm potential health benefits, as studies with rodent subjects cannot be deemed generalizable. All in all, PBA treatment offers an optimistic future in AD and dementia research through a deep focus on its cellular mechanisms and pathological processes, by treatment administration throughout AD progression.

1. Birks, J. S. (2006). Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database of Systematic Reviews, 2016(3). https://doi.org/10.1002/14651858.cd005593.
2. Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on Alzheimer's disease: Causes and treatment. Comprehensive Review on Alzheimer's Disease: Causes and Treatment, 25(24), 5789. https://doi.org/10.3390/molecules25245789.
3. Cozachenco, D., Ribeiro, F. C., & Ferreira, S. T. (2023). Defective Proteostasis in Alzheimer's disease. Ageing Research Reviews, 85, 101862. https://doi.org/10.1016/j.arr.2023.101862.
4. Cuadrado-Tejedor, M., Garcia-Osta, A., Ricobaraza, A., Oyarzabal, J., & Franco, R. (2011). Defining the mechanism of action of 4-phenylbutyrate to develop a small-molecule-based therapy for Alzheimer's disease. Current Medicinal Chemistry, 18(36), 5545-5553. https://doi.org/10.2174/092986711798347315.
5. Naidoo, N., Hafycz, J. M., Strus, E., & Sengupta, K. (2023). Early and late chaperone intervention therapy boosts XBP1s and ADAM10, restores proteostasis, and rescues learning in Alzheimer's disease mice. Aging Biology, 1(1), 20230017. https://doi.org/10.59368/agingbio.20230017.
6. Pákáski, M., & Kálmán, J. (2008). Interactions between the amyloid and cholinergic mechanisms in Alzheimer's disease. Neurochemistry International, 53(5), 103-111. https://doi.org/10.1016/j.neuint.2008.06.005.

The Power of Prevention

Aytal Everstov, Honours Health Sciences *Class of 2027*

We all know that to improve cardiovascular health and reduce the risk of heart disease, it is important to avoid smoking, exercise regularly, eat a diet rich in fruits, vegetables, and whole grains, and to avoid foods that are high in sodium, as well as saturated and trans fats.

As a society, we have had great success in understanding the correlation between these lifestyle choices and cardiovascular health, and effectively communicating this information to the public. Most people reading this have likely already been taught the methods I've listed to improve the health of their circulatory system. However, I challenge you to reflect on if you can you name a way to improve the health of your brain and reduce your risk of dementia or Parkinson's disease (PD)? I would wager that many of us can't. This is because we have had significantly less success in understanding and communicating the risk factors for neurological disorders.

In some cases, the primary issue in effective knowledge dissemination is gaps in current research. The etiology of PD, for example, is very poorly understood. We understand some of the mechanisms underlying PD; the disease is spurred by the death of dopaminergic neurons in the substantia nigra region of the brain. (1) Dopamine produced and released in the substantia nigra is critical for the activity of the basal ganglia, which is responsible for the regulation of voluntary motion by coordinating desired movements and suppressing undesired movements. However, we cannot conclusively determine who may end up developing PD. While there are theories regarding prognostic factors, scientists have not yet found any conclusive proof for risk factors. There are very interesting findings regarding a chemical known as trichloroethylene (TCE). An epidemiological study on PD patients with unaffected identical twins found that exposure to TCE may potentially increase the risk of developing PD sixfold. (2) Another trial found that mice repeatedly exposed to TCE develop degeneration of dopaminergic neurons in the substantia nigra as seen in PD patients. (3) This is a widely used chemical, commonly found in commercial solvent and imported to Canada in massive quantities, being hundreds of tons in 2020. (4) Research that conclusively establishes this chemical as a risk factor for Parkinson's could lead to wider bans on this compound, preventing countless people from being exposed. This could be one of many potential preventable risk factors. Still, valuable research is being conducted and scientific progress is always in motion. I'm certain that within my lifetime this article will become obsolete as we understand the underlying causes of PD. However, scientific progress does not move on its own. We will never discover more about these potential risk factors if we don't fund research into the topic.

There are organizations that are doing commendable work to raise money for Parkinson's research, such as the Parkinson Canada National Research Program, which has raised $31 million since 1981 to fund novel Canadian research. (5) But when compared to the success of the Heart & Stroke Foundation, which invested $10.4 million in 2021 alone to fund research to improve diagnostics, treatment, and quality of life for heart disease and stroke patients, it seems like a much lesser amount. (6) We have only been able to gain such an understanding of cardiovascular disease because we have extensively funded the research that has opened our eyes to relevant risk factors and the mechanisms of action allowing us to pursue new treatments. Making research into neurodegenerative disorders a funding priority for governments and universities, and promoting donations to non-governmental organizations supporting brain research like Parkinson Canada can help spur research that will, in the long run, improve our understanding of diseases affecting the brain, and allow us to create strategies to significantly reduce the number of patients that will develop PD in the future.

On the other hand, there are instances where we have done a good job of understanding the causes and risk factors of a disease, but have not done enough to spread awareness of these risks to the general public. For example, research at the University of Exeter in England has demonstrated that a diet with plenty of fruits, vegetables, whole grains and unsaturated fat can reduce the risk of dementia by up to 25%. (7) We also have evidence that suggests that physical activity is linked to a reduction in brain tissue loss and neurotoxic factors in aging adults (8) and that maintaining at least 2-3 close relationships with other individuals reduces the risk of dementia by approximately a whopping 60%. (9) With 10 million new cases of dementia every year, informing the general public of these statistics could improve quality of life for millions of seniors in the future, allowing individuals to make informed lifestyle adjustments such as including more fruits and vegetables in their diets, or making more of an effort to spend quality time with elderly relatives. Unfortunately, we have had limited success communicating this information to the public, according to a survey of UK adults in November 2023 that found that only 36% of participants believed that it was possible to reduce one's risk of developing dementia. (10) If all of the promising research conducted isn't made readily accessible and actively communicated to the general public, preventative strategies will never be able to achieve their full potential.

Ultimately, preventing the onset of brain-related illnesses could be a game-changer for neurological healthcare in the future. With more people armed with the knowledge of the risk factors of neurological disorders that would allow them to take more agency of their brain health, we could be able to prevent millions of future cases of PD and dementia. If people know who is at risk of developing neurological ailments and know how risk can be minimized, we can effectively fight neurodegenerative disease before initial symptoms even begin to show themselves. Think of how many cases of heart disease may have been prevented by educating the public about healthy dieting, exercise, the dangers of smoking and so on. How many people have been able to enjoy greater longevity and a higher quality of life? How many never required difficult and costly treatment because they were adequately informed of risks and steps they can take to reduce these risks?

Preventative care strategies are absolutely critical for neurological disorders given the impact they have on quality of life and health and the fact that their incidence is poised to significantly grow in the foreseeable future. These are health issues that can be debilitating for memory, mobility and cognition. They can leave patients unable to take a walk outside, cook themselves food or connect with their loved ones. Canada's aging population and high life expectancy means these diseases that primarily impact seniors are becoming increasingly prevalent. In fact, the number of patients afflicted with PD in the early 2030s is already suspected to be double the number afflicted in the early 2010s. (11) From an economic standpoint, the costs of providing supportive care for patients that are affected by neurological disorders are much higher than for the general senior population, these costs being 5.5 times higher in the case of dementia. (12) This paints an alarming picture for the ability of the overburdened healthcare system to provide adequate care for patients in the future. These projections for the future are likely to be accurate unless we equip individuals with knowledge about neurodegenerative illnesses by making preventative strategies a priority in the field.

1. Liu Y, Deng J, Liu Y, Li W, Nie X. FGF, Mechanism of Action, Role in Parkinson's disease, and Therapeutics [Internet]. Frontiers; 2021 [cited 2024 Mar 14]. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2021.675725/full
2. Goldman SM, Quinlan PJ, Ross GW, Marras C, Meng C, Bhudhikanok GS, et al. Solvent exposures and parkinson disease risk in twins [Internet]. U.S. National Library of Medicine; 2012 [cited 2024 Mar 14]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3366287/
3. Adamson A, Ilieva N, Stone WJ, De Miranda BR. Low-dose inhalation exposure to trichloroethylene induces dopaminergic neurodegeneration in rodents [Internet]. Oxford University Press; 2023 [cited 2024 Mar 14]. Available from: https://academic.oup.com/toxsci/advance-article/doi/10.1093/toxsci/kfad090/7260540
4. Trichloroethylene [Internet]. CAREX Canada; 2023 [cited 2024 Mar 14]. Available from: https://www.carexcanada.ca/profile/trichloroethylene/
5. Parkinson canada research program [Internet]. Parkinson Canada; 2021 [cited 2024 Mar 14]. Available from: https://www.parkinson.ca/research/parkinson-canada-research-program/
6. Impact [Internet]. Heart and Stroke Foundation of Canada; 2023 [cited 2024 Mar 14]. Available from: https://www.heartandstroke.ca/what-we-do/research/impact
7. Shannon OM, Ranson JM, Gregory S, Macpherson H, Milte C, Lentjes M, et al. Mediterranean diet adherence is associated with lower dementia risk, independent of genetic predisposition: Findings from the UK biobank prospective cohort study - BMC medicine [Internet]. BioMed Central; 2023 [cited 2024 Mar 14]. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-023-02772-3
8. Cheng S-T. Cognitive Reserve and the prevention of dementia: The role of physical and cognitive activities [Internet]. U.S. National Library of Medicine; 2016 [cited 2024 Mar 14]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4969323/
9. Rafnsson SB, Orrell M, d'Orsi E, Hogervorst E, Steptoe A. Loneliness, social integration, and incident dementia over 6 years: Prospective findings from the English Longitudinal Study of Ageing [Internet]. Oxford University Press; 2017 [cited 2024 Mar 14]. Available from: https://academic.oup.com/psychsocgerontology/article/75/1/114/3896175
10. Public attitudes towards dementia [Internet]. Alzheimer's Research UK; 2023 [cited 2024 Mar 14]. Available from: https://www.dementiastatistics.org/attitudes/
11. Government of Canada [Internet]. Public Health Agency of Canada; 2019 [cited 2024 Mar 14]. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/parkinsonism.html
12. How dementia impacts Canadians [Internet]. Canadian Institute for Health Information; [cited 2024 Mar 14]. Available from: https://www.cihi.ca/en/dementia-in-canada/how-dementia-impacts-canadians

Modern Day 'Inception' Experiment in Sleeping Mice

Sehaj Kang, Honours Biochemistry *Class of 2026*

Inception, a well-known movie released back in 2010, profoundly captivated viewers worldwide. This blockbuster, starring Leonardo DiCaprio, Ken Watanabe, Joseph Gordon-Levitt, Marion Cotillard among many other skilled actors, is an action Sci-Fi that shines light on the possibility of entering one's dreams and stealing secrets from their subconsciousness. (1) As a result, many viewers were left fascinated by the captivating plot, pondering about the thin line between reality and the subconscious world. (1) The question remaining is if any of this dream-sharing is possible in real life?

Although there is not much research done on this concept using human participants, scientists have studied the concept of memory implanting on sleeping mice, leading them to find some interesting results. Scientists at the Industrial Physics and Chemistry Higher Educational Institution in Paris conducted an experiment to show that they can influence dreams in mice. In the experiment, researchers placed electric signals in the form of electrodes into 'place cells' in the hippocampus of a mouse's brain. (2) They used these electrodes to send reward signals to the mice's brains, allowing the rodents to create a positive association with the mice's geographic location. (2) As such, later, when the mice woke up, they seemed to go toward the place that had been associated with the reward signal in their dreams. "The mouse develops a goal-directed behavior to go towards the place," said Karim Benchenane, who led the research, in an interview with New Scientist. (2)

Conclusively, this experiment provided rather interesting results about the truth of the movie's dream-sharing capacity, and its effects on one's mind. In fact, the ability to almost insert a memory into the brain of a mouse, whereby they are driven to associate an award with a specific place, has many fascinating implications on future research in dream-sharing and invasion of intellectual property. (2) Looking into the future however, it does not seem like this experiment will be conducted with humans since it is quite an invasive procedure to be able to insert an electrode into one's brain. Nonetheless, there is still faith that somehow the results and method of this experiment can be applied to treat traumatic memories in victims to help patients. As such, until then, it is safe to say that it is best to keep all things 'mind-control' anchored to the Hollywood realm.

1. Foley, K. E. (n.d.). Studies show that "inception" is possible-at least in sleeping mice. Quartz. Retrieved December 4, 2021, from https://qz.com/440029/studies-show-that-inception-is-possible-at-least-in-sleeping-mice/.
2. Tayag, Y. (2015, June 30). Scientists are incepting mouse dreams. Inverse. Retrieved December 4, 2021, from https://www.inverse.com/article/4194-scientists-are-incepting-mouse-dreams.

Treatment of Alzheimer's Disease using Axitinib

Lana Zgonjanin, Honours Science *Class of 2026*

Scientific breakthroughs in medicine provide hope for patients and families who are affected by disease, particularly incurable ones. A new neurodegenerative disease discovery involves the repurposing of a chemotherapy drug as a treatment for Alzheimer's disease, or AD. (1) The chemotherapy drug, Axitinib, is used to treat renal cancer by inhibiting the growth of blood vessels in tumours, further preventing tumour growth and metastasis, and overall resulting in necrosis of the malignant cells. (2) In a study conducted at the University of British Columbia, findings showed that Axitinib improved the cognitive function of mice with AD by inhibiting blood vessel growth, which is crucial to restoring the blood-brain barrier that is disrupted by the disease. (3)

AD is caused by the abnormal accumulation of the amyloid-beta protein, a protein normally required for the maintenance of neurons. (4) This accumulation drives angiogenesis, the process by which the formation of new blood vessels occurs, resulting in hypervascularity and tight junction disruptions. (3) Tight junctions reduce the permeability of the blood-brain barrier, which prevents the diffusion of unwanted particles from the bloodstream into the brain. Thus, disruptions in the tight junctions result in leaks of the blood-brain barrier, harming its normal protective function. (5) By performing experiments on mice with AD, researchers discovered that the blood vessel growth inhibition role of Axitinib is useful for treating AD in a way similar to how it targets malignant tumours. The drug restored damaged blood-brain barriers of mice by drastically reducing angiogenesis. As a result, mice that were given the drug for one month showed improved memory and cognitive function by excelling on various tests they had initially performed poorly on prior to treatment. (3)

The novel use of Axitinib as treatment for AD is inspired by previous research which demonstrated that certain drugs, such as Aspirin, may have multiple uses. Aspirin was originally developed and sold in 1899 as an analgesic, but was repurposed in the early 1980s to treat various cardiovascular problems. (6) Dr. Lawrence Craven, MD, General Practitioner, observed the antithrombotic properties of the drug, which led to the use of Aspirin and its blood thinning abilities to act as a preventative agent against heart attacks. (7)

The results of this study prove to be extremely promising in finding a treatment for AD, providing hope for affected patients and families. Over 99 percent of previous drug development attempts targeting amyloid-beta proteins and their contribution to AD have failed during clinical trials. The use of Axitinib takes a different approach and targets angiogenesis instead, offering new possibilities for treatment of AD. (1)

1. Fernandes, T., 2021. Cancer Drug Helps Alzheimer's Mice Remember. Labroots, [online]Available at: https://www.labroots.com/trending/immunology/21457/cancer-drug-helps-alzheimer-s-mice-remember [Accessed 18 October 2021].
2. Nishida, N., Yano, H., Nishida, T., Kamura, T. and Kojiro, M., 2006. Angiogenesis in Cancer. Vascular Health and Risk Management. [e-journal] 2(3), pp.213-219. 10.2147/vhrm.2006.2.3.213.
3. Singh, C.S.B., Choi, K.B., Munro, L., Wang, H.Y., Pfeifer, C.G. and Jefferies, W.A., 2021. Reversing pathology in a preclinical model of Alzheimer's disease by hacking cerebrovascular neoangiogenesis with advanced cancer therapeutics. EBioMedicine - The Lancet. [e-journal] 71(103503). https://doi.org/10.1016/j.ebiom.2021.103503.
4. Goodsell, D., 2006. Molecule of the month: Amyloid-beta precursor protein. [online] Available at: http://doi.org/10.2210/rcsb_pdb/mom_2006_7 [Accessed 16 March 2024].
5. Liu, W., Wang, Z., Zhang, L., Wei, X. and Li, L., 2012. Tight Junction in Blood-Brain Barrier: An Overview of Structure, Regulation, and Regulator Substance. CNS Neuroscience & Therapeutics. [e-journal] 18(8), pp.609-615. https://doi.org/10.1111/j.1755-5949.2012.00340.x.
6. Jourdan, J., Bureau, R., Rochais, C. and Dallemagne, P., 2020. Drug repositioning: a brief overview. Journal of Pharmacy and Pharmacology. [e-journal] 72(9), pp.1145-1151. https://doi.org/10.1111/jphp.13273.
7. Miner, J., & Hoffhines, A., 2007. The discovery of Aspirin's antithrombotic effects. Tex Heart Inst J. [e-journal] 34(2), pp.179-186. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1894700/

Traumatic Brain Injury: The Role of Neuroinflammation in Long-Term Central Nervous System Damage

Viktoryia Shtop, Honours Biochemistry *Class of 2025*

Abstract

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality worldwide. In the United States alone, an average of 1.4 million people seek medical services for traumatic brain injuries annually. While initial symptoms from physical trauma to the head may be resolved after a short period of time, individuals who survive TBI can experience long-term, sustained damage to their central nervous systems (CNS). Neuroinflammation in the acute phase of TBI can be beneficial and stimulate cells to carry out repair responses. However, excessive neuroinflammation shifts TBI into the chronic stage, resulting in edema, inefficient repair of damaged brain tissue, and an increased likelihood of developing neurodegenerative disorders. This review seeks to discuss the pathophysiology of acute and chronic neuroinflammation post-TBI and the factors that can influence the outcomes of TBI patients.

A traumatic brain injury (TBI) is an injury caused by an external force to the head that damages brain tissue and affects brain function. (1) Inflammation is a protective defense mechanism against injury and infection within the body; consequently, neuroinflammation refers to the inflammatory response within the central nervous system (CNS). (1) All bodily injuries are accompanied by a certain level of acute inflammation that can restore tissues to their pre-injury state due to a release of mediators aiding in tissue repair. (2) However, this inflammation can sometimes become chronic and persist in tissues for months or years, posing a danger to bodily health. (2) This is the case for TBI, where a physical injury to the head can result in long-term consequences in the CNS. (1)

TBI is typically classified into one of three categories: closed head, penetrating, or explosive-blast TBI. (3) Closed head TBI is caused by a strong blunt force that may result from sports activities or driving accidents. (3) In comparison, penetrating TBI occurs when a foreign body, such as a bullet, penetrates the skull and lacerates the brain tissue. (3) Explosive-blast TBI results from rapid pressure shock waves produced by explosions. (3)

In TBI, both primary and secondary injuries contribute to brain dysfunction and neuronal tissue damage. (3) Primary injury is the trauma that ensues from the mechanical injury, and usually results in direct damage to neurons, axons, and blood vessels within the brain. (1) Secondary injury presents itself in a cascade of events triggered by primary injury, including biochemical, cellular, and physiological events. (1,3) These events include mitochondrial dysfunction, increased generation of free radicals, apoptosis, and neuroinflammation. Out of these processes, neuroinflammation is considered the biggest contributor to secondary cell death and a hallmark of both acute and chronic TBI. (3)

Within the acute post-TBI period of 24 hours, neuronal death from physical injury causes the release of damage-associated molecular patterns (DAMPs) which activate microglia, the resident macrophages of the CNS. (1) These microglial cells produce pro-inflammatory cytokines that can induce astrocytes, another CNS resident cell, to become active and form glial scars. (1) These scars are chemical and physical barriers that surround healthy portions of the brain to prevent further damage to the CNS. (1) While for some individuals the resolution of the acute phase marks the end of the TBI condition, for others, the acute stage of TBI can quickly transition to the chronic stage. In the transition to chronic inflammation, microglia activation, and consequently, astrocyte activation, becomes excessive. At this point, the barrier offered by the glial scars acts as a hindrance to the repair of damaged tissue, suggesting that disproportionate activation of astrocytes impairs brain repair. (1) In addition, prolonged microglial activation increases the level of pro-inflammatory cytokines, which can weaken the blood brain barrier (BBB). (1) BBB damage can persist for many years after TBI, and can allow peripheral immune cells to enter the brain and exacerbate the neuroinflammatory response. (4) Mast cells are one such peripheral immune cell, and secrete cytokines and other vasodilatory factors that perpetuate the chemoattraction of peripheral immune cells and contribute to edema. 5,6 Furthermore, prolonged neuroinflammation in TBI patients can result in neuron degeneration and a decline in cognitive, social, and physical abilities. (4) Neuronal damage from persistent inflammation can increase the risk of developing neurodegenerative disorders such as Alzheimer-like dementia. (7)

However, not all individuals who suffer from TBI experience such severe consequences following their injury. Indeed, part of the reason as to why TBI is a complex condition to treat is that the outcomes of neuroinflammation vary strongly on a case-by-case basis. Several factors have been observed to influence the progression of neuroinflammation within the body, including injury severity, age, and sex. (4) As previously mentioned, there are a wide range of injuries that can be classified as TBI. (1) When measuring the severity of an injury, factors such as the number of diagnoses, days on a ventilator, systolic blood pressure, as well as the Glasgow Coma Scale (GCS) score, are all taken into account. (8) Individuals who suffer from a mild TBI experience less severe damage to the brain and less lasting neuroinflammation than those suffering from more severe TBIs. In addition, age is another determinant of TBI survival, with advanced age being associated with longer recovery time and worse outcomes. (4) This is thought to be due to the reduced plasticity of older individuals and their high susceptibility to functional deficits. (4) Sex differences can also influence outcomes post-TBI. 4 It is thought that in females, sex hormones offer neuroprotection, which results in slower and less pronounced microglia activation as compared to males. (4) As such, males may experience a more aggressive neuroinflammation profile. (4)

Overall, chronic neuroinflammation post-TBI poses significant health risks to affected individuals, including impairment of brain tissue repair, edema, and enhanced susceptibility to neurodegenerative diseases. Increasing awareness of the long-term risks of TBI can promote early detection of symptoms and the quick implementation of treatment plans. When developing effective, personalized pharmacological interventions, researchers should consider differences in sex, age, and the severity of the injury—all factors that influence the outcomes of TBI patients.

1. Schimmel SJ, Acosta S, Lozano D. Neuroinflammation in traumatic brain injury: A chronic response to an acute injury. Brain Circ. 2017;3(3):135-142. doi: 10.4103/bc.bc_18_17.
2. Pahwa R, Goyal A, Jialal I. Chronic Inflammation. Florida: StatsPearls Publishing; 2024.
3. Ng SY, Lee AYW. Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. Front. Cell. Neurosci. 2019;13. doi: 10.3389/fncel.2019.00528
4. Xiong Y, Mahmood A, Chopp M. Current understanding of neuroinflammation after traumatic brain injury and cell-based therapeutic opportunities. Chin J Traumatol. 2018;21(3):137-151. doi: 10.1016/j.cjtee.2018.02.003.
5. Ward PA, Lentsch AB. The Acute Inflammatory Response and Its Regulation. Arch Surg. 1999;134(6):666-669. doi: 10.1001/archsurg.134.6.666
6. Passaro AP, Lebos AL, Yao Y, Stice SL. Immune Response in Neurological Pathology: Emerging Role of Central and Peripheral Immune Crosstalk. Front Immunol. 2021;12:676621. doi: 10.3389/fimmu.2021.676621.
7. Simon D, McGeachy M, Bayır H et al. The far-reaching scope of neuroinflammation after traumatic brain injury. Nat Rev Neurol. 2017;13:171-191. doi: 10.1038/nrneurol.2017.13
8. Piatt J. Racial disparities in mortality after severe traumatic brain injury in childhood: mediators identified by Oaxaca-Blinder decomposition of trauma registry data. Inj Epidemiol. 2021;8(1):1. doi: 10.1186/s40621-020-00295-

Does Time Actually Heal all Wounds?

Rupinder Pamma, Honours Sciences *Class of 2025*

For over 84 years, the placebo effect has been used extensively to explain the influence of one's mind on the effectiveness of certain treatments. (1,2) But could our mind also affect the rate at which healing occurs? A recent study conducted by Aungle and Langer in 2023 investigated the influence of one's perception of time on their body's rate of healing. (3) The experiment involved producing cupping marks on subjects to wound them, then using a manipulated timer to alter the participant's perceived time. Measured rates of healing were recorded for each respective condition. Three test conditions were utilized, including slow time, which is half as fast as the clock time, normal time, and lastly, fast time, which is twice as fast as the clock time. Researchers of this experiment hypothesized that the wounds would heal proportionally to how time was perceived, such that the wounds of participants in the fast time condition would heal the quickest. This prediction was based on the theory of mind, which suggests that the mind influences how healthy the body is.

Indeed, in the fast time condition, participants believed that a larger amount of time had passed, which led to the induced wounds healing more quickly than the wounds of participants that perceived a shorter length of time to have elapsed. Furthermore, although the actual time elapsed in all three conditions was 28 minutes, more healing was observed in the normal condition compared to the slow time condition. Additionally, an increased amount of healing was recorded in the fast time condition compared to the normal time one. These findings support the proposed hypothesis and demonstrate how an individual's perception of time affects physical healing, independent of the true elapsed time.

Currently, this study is one of the few that indicates an evident psychological impact on physical healing, however, it overlooks the nuances of the perception of clock time in relation to one's internalized concept of time. For instance, people living in non-Western communities may interpret clock time differently, in that they view time as cyclical and endless, contrasting the Western perspective of time as linear and limited. (4) This major difference in perspective would alter the influence that perceived time has on an individual's physical healing. While this is powerful evidence of the profound impact that psychology has on the physical health of humans, future research should explore the influences of the human mind on healing, in diverse populations. The connection between the mind and body is a phenomenon that is not yet fully understood, but continued research on mind-body unity may ultimately be used to improve overall human health.

1. Munnangi S, Sundjaja JH, Singh K, Dua A, Angus LD. Placebo Effect. In: StatPearls [Internet]. Treasure Island, Florida: StatPearls Publishing; 2023 [cited 2024 Mar 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513296/
2. E; AP. Physical healing as a function of perceived time [Internet]. U.S. National Library of Medicine; 2023 [cited 2024 Jan 24]. Available from: https://pubmed.ncbi.nlm.nih.gov/38104155/
3. Harvard Health Publisher. The power of the placebo effect [Internet]. 2021 [cited 2024 Jan 24]. Available from: https://www.health.harvard.edu/mental-health/the-power-of-the-placebo-effect
4. Mraovic J. The perception of time in different cultures [Internet]. 2024 [cited 2024 Mar 4]. Available from: https://clockify.me/blog/managing-time/time-perception/#:~:text=Timekeeping%20in%20different%20cultures&text=Western%20cultures%20(including%20some%20parts,is%20event%20or%20personality%2Drelated.

Overlooking a key risk? Careful considerations concerning non-invasive brain stimulation protocols for post-stroke rehabilitative recovery

Mustaali Hussain, Honours Kinesiology *Class of 2024*

Abstract

Stroke is currently the second leading cause of disability and death worldwide, necessitating exploration into rehabilitative treatments to improve stroke-induced impairments. Non-invasive brain stimulation (NIBS) has emerged as a potential therapeutic for improving patients' movement impairments. Specifically, stimulation protocols that suppress activity in the unaffected hemisphere have been among the most prevalent interventions explored in recent clinical trials. However, the widespread administration of this protocol may not be suitable for all stroke patients. In this article, it is discussed how patient-specific characteristics must be accounted for prior to the administration of NIBS protocols, to prevent detrimental clinical outcomes.

Stroke is characterized by a sudden disruption of blood flow to a given hemisphere in the brain, caused by either a blockage or rupture of the brain's blood vessels, ultimately resulting in the death of neurons within this affected hemisphere. (1) Currently, stroke is the second leading cause of both disability and death worldwide, and with the continuous rise in the aging population globally, the incidence of stroke is expected to rise by over 9% by 2030. (2) Therefore, exploring rehabilitative treatments to improve stroke-induced impairments is crucial for minimizing the potential large scale increase in disability among the population, along with improving the overall quality of life for these patients.

Neural Mechanisms Underlying Movement Impairments

Despite its potential to cause a range of neurological deficits, stroke most commonly leads to chronic movement impairments, such as such as reduced strength, coordination, and overall voluntary control. (1) Upon closer examination, a key mechanism theorized to play a role in the persistence of these motor impairments is the dysregulation of interhemispheric inhibitory signaling processes due to the stroke-induced neural injury. (3) In healthy individuals, both hemispheres exert reciprocal inhibitory signals onto each other. During movement specifically, neural signals initiating limb movement from one hemisphere are accompanied by an inhibitory signal that acts on the opposite hemisphere. (3,4) These inhibitory signals help to both suppress unwanted movements, while also allowing for controlled and coordinated movement. (3) However, due to stroke, the affected hemisphere is unable to transmit such inhibitory signals, resulting in hyper-excitability of the unaffected hemisphere. (3) Consequently, this heightened activity of the unaffected hemisphere leads to an overabundance of inhibitory signals onto the affected hemisphere, suppressing its function (see Figure 1 for visual depiction). (3) This imbalance ultimately disrupts motor signalling, resulting in persistent movement impairments.

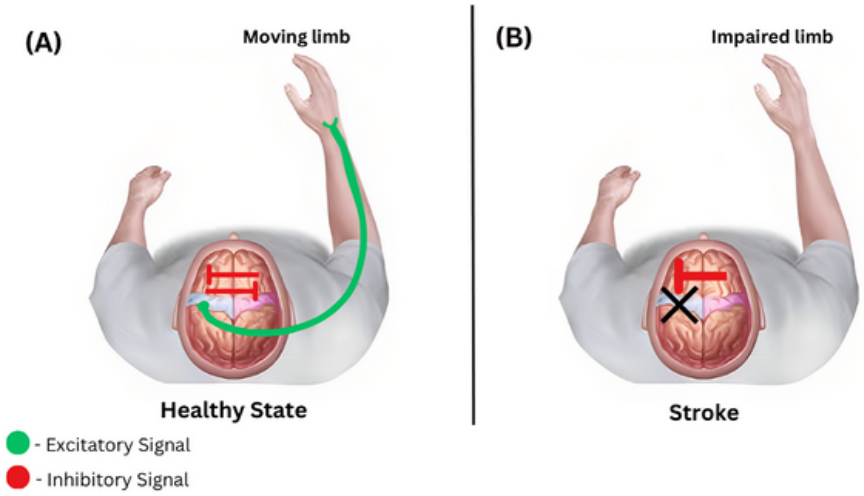


Figure 1: Interhemispheric inhibition processes during voluntary movement. (4) Line thickness indicates relative excitation of the neural pathway, with thicker lines representing greater activation.
A. In a healthy individual, neural signals initiating movement (green line) are accompanied by inhibitory signals from each hemisphere (red line), which act on the opposite hemisphere. (3,4)
These inhibitory mechanisms ensure controlled and coordinated movements of the limbs. (3)
B. Hemispheric damage resulting from stroke (denoted by the 'X') renders the damaged hemisphere unable to generate interhemispheric inhibitory signaling. (3) Consequently, increased activity in the unaffected hemisphere results in an overabundance of inhibitory signals from the unaffected onto the affected hemisphere (thick red line), disrupting motor signaling to the impaired limb. (3)

Therapeutic Approaches

Fortunately, recent advances in medical technology have allowed for the development of non-invasive brain stimulation (NIBS) therapies to address this neural signaling imbalance. NIBS modalities, such as transcranial direct-current stimulation (tDCS) and transcranial magnetic stimulation (TMS), transmit electrical stimulation across the scalp to induce either activation or inhibition of nearby cortical neurons. (5)

For stroke patients in particular, the stimulation protocols that have been widely prescribed in clinical studies consist of the application of cathodal-tDCS (c-tDCS), or low-frequency repetitive TMS (LF-rTMS) over the unaffected hemisphere. (3,5) Both protocols are inhibitory in nature, and act to suppress the hyper-excitability of the unaffected hemisphere, which in turn helps to decrease its inhibitory influence on the affected hemisphere. (3,5) In theory, this would ultimately allow for the restoration of some functionality in the affected hemisphere, potentially leading to improvements in motor function in the impaired limb. (3,5)

Indeed, this intervention has shown promising effects in restoring function of the affected hemisphere and subsequently improving motor function for stroke patients. Meta-analyses of clinical trials over the past two decades have revealed that suppression of the unaffected hemisphere via c-TDCS or LF-rTMS, in conjunction with traditional physical therapy significantly improved finger dexterity, hand strength, and overall range of motion of the impaired upper limb in stroke patients, compared to those undergoing physical therapy alone. (6,7)

Concerns Underlying Inhibitory NIBS Protocols

However, a key consideration that has been largely overlooked when administering this specific protocol has been the injury severity status of stroke patients. Stroke can cause a mild, moderate, or severe level of tissue damage to the affected hemisphere. (1,8) For mild to moderately injured patients, an adequate level of intact neural tissue in the affected hemisphere is still able to be retained. (8,9) Hence, maximizing the function of this remaining functional tissue in the affected hemisphere is an optimal rehabilitation strategy for these patients. (8) Accordingly, suppressing the hyper-activity of the unaffected hemisphere via c-tDCS or LF-rTMS, which allows for the restoration of function for the affected hemisphere, may indeed be an appropriate stimulation protocol for facilitating motor recovery for mild or moderately impaired patients. (8) However, on the other hand, severely injured stroke patients have minimal neural tissue intact within the damaged hemisphere post-stroke, meaning that this hemisphere can no longer be restored and contribute towards motor control. (8) To overcome this deficit, neuroplastic changes within these severely impaired patients' brain allows the unaffected hemisphere, which in the healthy state usually plays a minor role in controlling movements of the side of the body impaired by stroke, to markedly increase its contribution to motor control of this affected side (see Figure 2 for a visual depiction). (8,9) Therefore, NIBS aimed at reducing the activity of the unaffected hemisphere via c-tDCS or LF-rTMS may not be an effective protocol for these severely injured patients, and may even impede their motor recovery, as this would suppress the only source of descending motor control to the impaired limb. (8) As a result, the widespread administration of suppressive brain stimulation over the unaffected hemisphere to all stroke patients in future clinical studies may pose potential risks if patients' specific injury statuses are not considered.

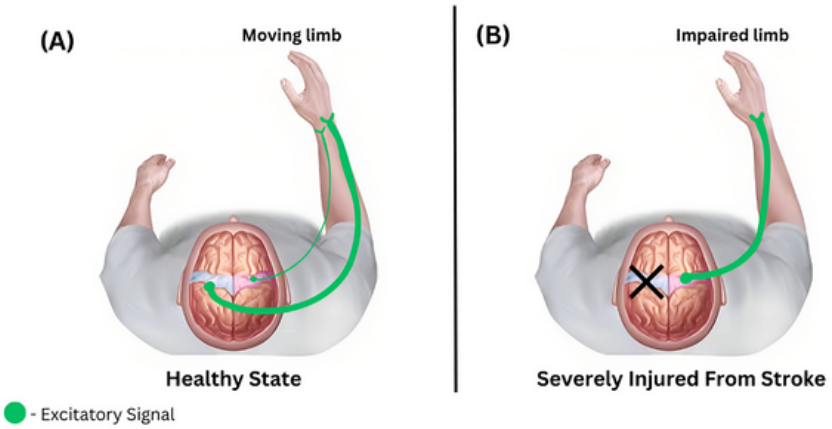


Figure 2: Neurophysiological mechanisms underlying motor control in both the healthy state and after a severe stroke injury. (4) Line thickness indicates relative excitation of the neural pathway, with thicker lines representing greater activation.
A. In a healthy individual, the brain hemisphere opposite to the moving limb is primarily responsible for generating motor signals that execute movement. (8,9) The hemisphere on the same side as the moving limb only plays a minor role in assisting movement signalling for this limb. (8,9)
B. Following a severe injury from stroke (denoted by the 'X'), the affected hemisphere is no longer able to generate neural signals for movement due to the loss of functional neuronal tissue. (8,9) As a compensatory mechanism, the hemisphere on the same side as the impaired limb increases its contribution towards controlling movement of this limb, providing some level of motor recovery. (8,9)

Ultimately, if advancements in research pave the way for integrating NIBS into clinical practice as a viable treatment option for post-stroke recovery, it is imperative that these brain stimulation protocols are not prescribed in a one-size-fits-all approach. Instead, disease severity statuses specific to each patient should be assessed prior to the prescription of suppressive NIBS protocols. Techniques such as Magnetic Resonance Imaging can be used to objectively categorize patients as either mild, moderate, or severely injured from stroke, and using this information, the appropriate NIBS protocol can be administered to maximize motor recovery. (8)

1. Shatri G, Senst B. Acute Stroke. StatPearls [Internet]. 2023 Aug 17 [cited 2024 Jan 29]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK535369/
2. Pu L, Wang L, Zhang R, Zhao T, Jiang Y, Han L. Projected Global Trends in Ischemic Stroke Incidence, Deaths and Disability-Adjusted Life Years From 2020 to 2030. Stroke [Internet]. 2023 May 1 [cited 2024 Jan 29];54(5):1330-9. Available from: https://www.ahajournals.org/doi/abs/10.1161/STROKEAHA.122.040073
3. Boddington LJ, Reynolds JNJ. Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. Brain Stimul. 2017 Mar 1;10(2):214-22.
4. Bundy DT, Leuthardt EC. The Cortical Physiology of Ipsilateral Limb Movements. Trends Neurosci [Internet]. 2019 Nov 1 [cited 2024 Jan 29];42(11):825. Available from: /pmc/articles/PMC6825896/
5. Li KP, Wu JJ, Zhou ZL, Xu DS, Zheng MX, Hua XY, et al. Noninvasive Brain Stimulation for Neurorehabilitation in Post-Stroke Patients. Brain Sci [Internet]. 2023 Mar 1 [cited 2024 Jan 29];13(3). Available from: /pmc/articles/PMC10046557/
6. Van Hoornweder S, Vanderzande L, Bloemers E, Verstraelen S, Depestele S, Cuypers K, et al. The effects of transcranial direct current stimulation on upper-limb function post-stroke: A meta-analysis of multiple-session studies. Clinical Neurophysiology. 2021 Aug 1;132(8):1897-918.
7. Zhang L, Xing G, Shuai S, Guo Z, Chen H, McClure MA, et al. Low-Frequency Repetitive Transcranial Magnetic Stimulation for Stroke-Induced Upper Limb Motor Deficit: A Meta-Analysis. Neural Plast [Internet]. 2017 [cited 2024 Jan 29];2017. Available from: /pmc/articles/PMC5756908/
8. Bradnam L V., Stinear CM, Byblow WD. Ipsilateral Motor Pathways after Stroke: Implications for Non-Invasive Brain Stimulation. Front Hum Neurosci [Internet]. 2013 Apr 23 [cited 2023 Dec 9];7(APR 2013). Available from: /pmc/articles/PMC3647244/
9. Buetefisch CM. Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. Front Neurol. 2015 Oct 16;6(OCT):152367.

Beyond Symptoms: Headpulse Biometrics Reveals Lingering Concussion Risks in Athletes and the Perils of Premature Return to Play

Farhaan Javed, Honours Life Sciences *Class of 2027*

Abstract

With an estimated 1.6 to 3.8 million sports-related concussions annually, concussions are a severe issue that pose prolonged neurological risks for athletes. (1) Recent concussion research conducted by Halabi et al. measured cranial acceleration following cardiac contraction, a method dubbed Headpulse. (2) Their study revealed distinctive headpulse patterns in concussed athletes, persisting even after the absence of symptoms. Furthermore, a systematic review conducted by Giza and Kutcher, shows that disruptions in metabolic pathways caused by concussions increase vulnerability to subsequent severe injuries. (2) Thus, premature return-to-play not only prolongs recovery but also increases the probability of second impact syndrome, a rapid swelling of the brain shortly after suffering a second concussion. Based on the latest research on concussions, this paper strongly advocates for a paradigm shift in concussion management, prioritizing the long-term well-being of athletes over competitive pressures.

Concussions are one of the most common injuries athletes suffer in contact sports, such as ice hockey, football, and rugby. (3) While there is no clearly established definition, most researchers agree that concussions can be classified as a form of traumatic brain injury sustained due to forceful head contact, leading to the rapid acceleration of the brain towards and subsequent impact with the skull. (4) After experiencing a concussion, athletes are cleared to resume play once concussion symptoms have resolved, generally within 12 days. (2)

However, a recent study conducted at the University of California shows that brain damage may persist in athletes, even after the apparent resolution of symptoms. (2) To identify concussions, researchers used headpulse biometrics, a method that utilizes a specialized headset to detect the subtle force exerted by the brain on the inside of the head with each pulse of the heart. (2) These cardiac forces are measured using non-invasive accelerometers attached to a headband, and the resulting waveform is dubbed the "headpulse". (2) This study, focusing on two cohorts of Australian Rules Football players, revealed that concussed players had an abnormal headpulse pattern absent in non-injured players. (2) Many displayed high Z scores, indicating that the frequency shift of their headpulse was more pronounced compared to non-injured players. Moreover, the headpulse pattern associated with concussions remained non-concussed athletes for up to 14 days after symptoms abated and was exacerbated by unsupervised physical activities and return-to-play. (2) These findings highlight that while the symptoms of a concussion may seemingly resolve within a few days, it takes considerably more time for athletes' brains to undergo a full recovery from the trauma associated with the collision against the skull.

Allowing athletes to return to play before achieving full recovery has been shown to have serious implications for their health. After a concussive injury, the cellular membranes are distorted, resulting in transient membrane defects. (1) The resulting imbalance of sodium, potassium, and calcium ions can depolarize the neurons, subsequently causing decreases in glucose metabolism (known as CMRglc depression). (1,5) The correlation between CMRglc depression and concussions was explored in a study conducted by Prins et al., in which rats experienced traumatic brain injury (TBI) at varying intervals. (5) It was found that CMRglc levels would experience sharp decreases after a single TBI but would stabilize after recovery, thus serving as a reliable biomarker for a window of increased vulnerability following a TBI. (5) The ensuing results show that when a second TBI is administered before re-stabilization, the consequent CMRglc depression is at a far greater level than if the second TBI is introduced after complete recovery. (5) This leads to a concussion with more severe symptoms and a longer recovery period. (1)

Furthermore, in rare instances, repeated trauma occurring before complete recovery may result in second impact syndrome (SIS), a condition in which rapid brain swelling results in the impairment of the brain's vascular autoregulation system, as well as increased intracranial pressure, SIS commonly manifests in the form of collapse, respiratory failure, pupil dilation, and a semi-comatose state. (4) With a mortality rate of approximately 50% and a disability rate of 100%, the dangers of SIS emphasize the importance of ensuring that athletes are fully recovered before returning to play. (4)

Ultimately, the issue of concussions in contact sports is a critical concern due to its adverse effects that extend beyond visible symptoms. The use of headpulse biometrics as a method of detecting subclinical concussions highlights the importance of implementing measures to ensure athletes fully recover before rejoining the game, thus decreasing the probability of a subsequent, more severe injury. As our understanding of concussions continues to improve, it is imperative to adapt our approach to protect the health and safety of athletes in contact sports and prioritize their long-term well-being over the team's short-term demands.

1. Giza CC, Kutcher JS. An introduction to sports concussions. Continuum (Minneapolis, Minn.). 2014. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4274166/#R26 (Accessed: 30 October 2023).
2. Halabi C, Norton L, Norton K, Smith W. Headpulse biometric measures following concussion in young adult athletes. JAMA network open. 2023. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10422194/ (Accessed: 30 October 2023).
3. Ianof JN, Friere FR, Calado VTG, Lacerda JR, Coelha F, Vietzman S, Schmidt M, Machado S, Velasques B, Ribeiro P, Basile LFH, Paiva WS, Amorim R, Anghinah R. Sport-related concussions. Dementia & Neuropsychologia. 2014. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5619443/ (Accessed: 30 October 2023).
4. Wolf C, Fast K. 'Put me back in, coach!' concussion and return to play. Missouri medicine. 2017. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6143567/#b23-ms114_p0036 (Accessed: 30 October 2023).
5. Prins ML, Alexander D, Giza CC, Hovda D. Repeated mild traumatic brain injury: Mechanisms of cerebral vulnerability. Journal of neurotrauma. 2013. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4047842/ (Accessed: 30 October 2023).

Searching for Colour

Audrey Harun, Honours Sciences *Class of 2027*

Artist Statement

This poem highlights the significance of depression from the perspective of someone with depression through an anatomical exploration of the disease. When learning about mental health, the most commonly discussed illness is depression. As McMaster's Brain Research Society's mission is to underscore the importance of brain research and mental illness, it is important to recall that the individuals involved are all undergraduate students. This poem was made as a connection between education and the reality of mental state for those suffering from depression. Mental health is often overlooked by students due to academic stress, however, it should be valued and discussed more to raise awareness and eliminate stigma. By creating this piece, I hope that students and readers appreciate the academic study of how depression works within the brain, while also understanding the illness from a more emotional and heartfelt perspective.

The world is gray, constantly searching for colour
It feels as though the clouds never move, staying in a constant shade of dark gray Cold overwhelming waves are consuming, fresh from the depths of Thunder Bay Depression is found in various spaces
Whether it be the amygdala, dorsomedial thalamus or the amygdala Structural and functional abnormalities have been found with depression, voila
Get some rest, shut the eyes
But sleep just is not a way to recharge the human system anymore, it is an escape Surrounded by darkness, and silence, shut the doors and close the drape
It is no wonder why the mind feels sedate Depression causes the hippocampus to raise cortisol levels
Slowing the development of neurons, bringing rise to the mind's devils
Feeling disconnected from the world
Not knowing what is going on or not having the energy to care
But suddenly it becomes too much, and the only feeling is despair
Changes go unnoticed but are not non-existent
Having days feel like years in a constant state of tiredness and feeling empty Feeling as though seeing the world through a window, eyes always heavy Though it is no mystery why energy levels are depleted
The monoamine-deficiency theory assumes depression is a depletion of neurotransmitters Serotonin, Norepinephrine, and Dopamine, all the most common chemical hitters
It may all be theory for depression, but one thing is for sure A body fighting for survival
But a mind that wants to die
A mind not wanting to look for a shade other than gray or black But a body treading for a chance to win the old mind back
For those with depression, the world is gray, and they are constantly searching for colour

-Audrey Harun

1. Amiel M. What happens to the brain during Depression - Transformations Center [Internet]. 2021 [cited 2023 Dec 27]. Available from: https://www.transformationstreatment.center/treatment/what-happens-to-the-brain-during-depression/#:~:text=Depression%20causes%20the%20hippocampus%20to,of%20cortisol%2C%20the%20amygdala%20enlarges
2. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry. 2010 Oct;9(3):155-61. doi: 10.1002/j.2051-5545.2010.tb00298.x. PMID: 20975857; PMCID: PMC2950973.
3. Pandya M, Altinay M, Malone DA Jr, Anand A. Where in the brain is depression? Curr Psychiatry Rep. 2012 Dec;14(6):634-42. doi: 10.1007/s11920-012-0322-7. PMID: 23055003; PMCID: PMC3619732.

Fading Away...

Gloria Olotu, Honours Life Sciences *Class of 2025*

Artist Statement

“Fading away” is a poem about the experience of living with dementia, particularly within the setting of a nursing home. Dementia is a syndrome characterized by a decline in cognitive abilities, including memory loss, communication difficulties, disorientation, and other symptoms. (1) Research suggests that individuals with dementia will experience more stability when they remain in familiar surroundings, such as their own home, rather than being transferred to a nursing home. (2) This is because relocation can lead to "transfer trauma," exacerbating confusion, loneliness, anxiety, and worsening symptoms. (3)

In "Fading Away," the protagonist, referred to as Rosie, represents the countless individuals struggling with dementia in nursing homes. The poem vividly portrays Rosie's confusion, disorientation, and longing to return home through its imagery and language. The repetition of phrases underscores the frustration and bewilderment of forgetting one's past. The constant need to go home reveals the inner pain at the memories she is struggling to grasp onto, she wants to go home and be surrounded by the things she is familiar with and possibly remember some things, like the faces of the people in the picture on her walls. Maybe going home will spark some memories, yet she is then grabbed back into her room. Through this exploration, the poem sheds light on the emotional and practical challenges faced by those living with dementia and offers insight into their inner world.

They call me Rosie.
Where am I?
The beige walls fill all corners of the room.
Pictures of people I do not know.
I want to go somewhere; I know this is not my home.
Wandering in the dark, finding my way around.
What was I looking for again?

Circles and circles I go.
Lost in my train of thought.
Lost in my way around.
If only I could find my way.
If only I could remember...

Fading away,
Smiling and laughter
Joys of yesterday
I cannot remember,
Wandering in the dark,
Looking for my way out,
A dark tunnel swallows my mind.
What was I looking for again?

Confusion fills my mind.
My head spins.
Footsteps approach closer.
People speaking echo in the halls.
Voices I do not recognize.
“Rosie, are you okay?”
Too stunned to speak.
Who is Rosie?
Thoughts flood my mind.
Someone grabs me.
Where am I?
If only I could remember...

What was I looking for again?
They call me Rosie.
And I want to go home.

-Gloria Olotu

1. 1016/j.amjmed.2018.01.022
2. Alnes, R. E., Malmdal, W., Nordtug, B., Steinsheim, G., & Blindheim, K. (2022). Improving everyday life of people with dementia living at home: Health care professionals' experiences. Journal of Nursing Management, 30(7). https://doi.org/10.1111/jonm.13819
3. Ryman, F. V. M., Erisman, J. C., Darvey, L. M., Osborne, J., Swartsenburg, E., & Syurina, E. V. (2018). Health Effects of the Relocation of Patients With Dementia: A Scoping Review to Inform Medical and Policy Decision-Making. The Gerontologist, 59(6), e674-e682. https://doi.org/10.1093/geront/gny031
4. What Are the Signs of Alzheimer's Disease? (2022, October 18). National Institute on Aging. https://www.nia.nih.gov/health/alzheimers-symptoms-and-diagnosis/what-are-signs-alzheimers-disease#:~:text=For%20most%20people%20with%20Alzheimer

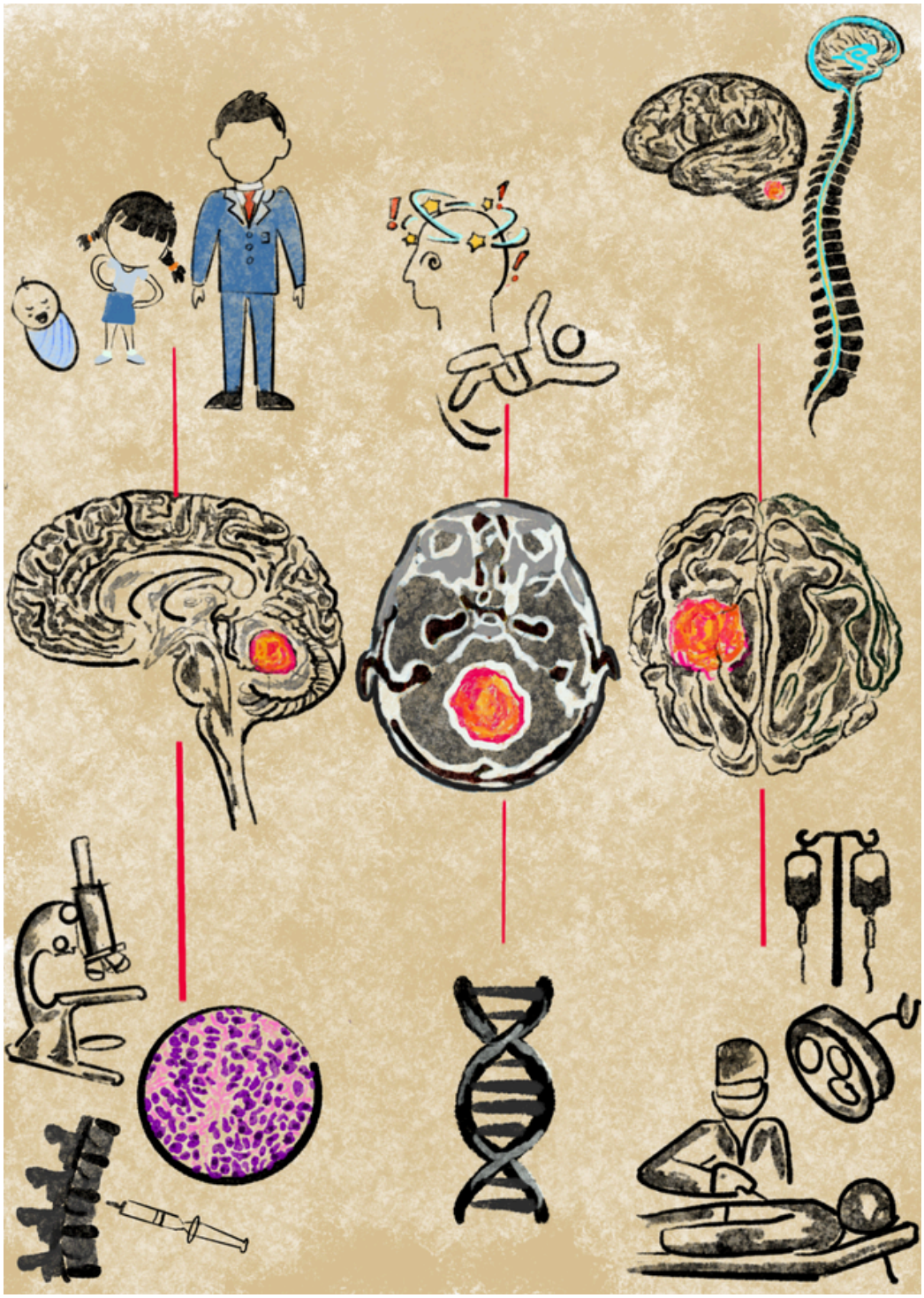
Medulloblastoma

Karthyayani Ramesh, Honours Life Sciences *Class of 2023*

Artist Statement

The image depicted is a graphical representation of relevant information regarding Medulloblastoma. Medulloblastoma is a rare type of pediatric brain cancer, which as depicted on the top left corner, mainly impacts children under the age of 16, but can also occasionally impact adults. The top middle graphics depict some of the symptoms associated with this disease, like dizziness and a negative impact on one's motor coordination. The top right corner depicts where the cancer can be identified. This brain cancer is often be found growing in the cerebellum but can also spread to other locations within the brain and spine via the cerebral spinal fluid (shown in blue). The bottom left corner represents when/how the cancer is identified by a healthcare professional. Medulloblastoma is identified when health care professionals conduct MRI Scans, CT scans, a spinal tap, or conduct biopsies on samples obtained from the patient. The bottom middle depicts why Medulloblastoma occurs. Unlike other cancers, Medulloblastoma is not considered to be a cancer that occurs due to lifestyle habits, and to date, research shows that there are no effective preventative methods. Medulloblastoma, however, is more likely to occur in children who have a family history of cancer, genetic conditions like mutations within specific genes, and have inherited conditions like Turcot or Gorlin Syndrome. Lastly, the bottom right corner depicts how Medulloblastoma is treated which includes methods such as surgery, radiation therapy, and or chemotherapy. A combination of three, additionally, is shown to result in a 75% chance of the pediatric patient surviving into adulthood.

1. Medulloblastoma [Internet]. 9500 Euclid Avenue, Cleveland, Ohio: Cleveland Clinic. Available from:https://my.clevelandclinic.org/health/diseases/22591-medulloblastoma
2. Medulloblastoma [Internet]. Jacksonville, Florida. Available from: https://kidshealth.org/en/parents/medulloblastoma.html
3. Medulloblastoma [Internet]. Baltimore Maryland. Available from:https://www.hopkinsmedicine.org/health/conditions-and-diseases/brain-tumor/medulloblastoma
4. Medulloblastoma [Internet]. Los Angeles, California. Available from: https://www.cedars-sinai.org/health-library/diseases-and-conditions/m/medulloblastoma.html
5. Medulloblastoma [Internet]. United Kingdom. Available from: https://www.cancerresearchuk.org/about-cancer/childrens-cancer/brain-tumours/types/medulloblastoma



Medulloblastoma