Brain Matters

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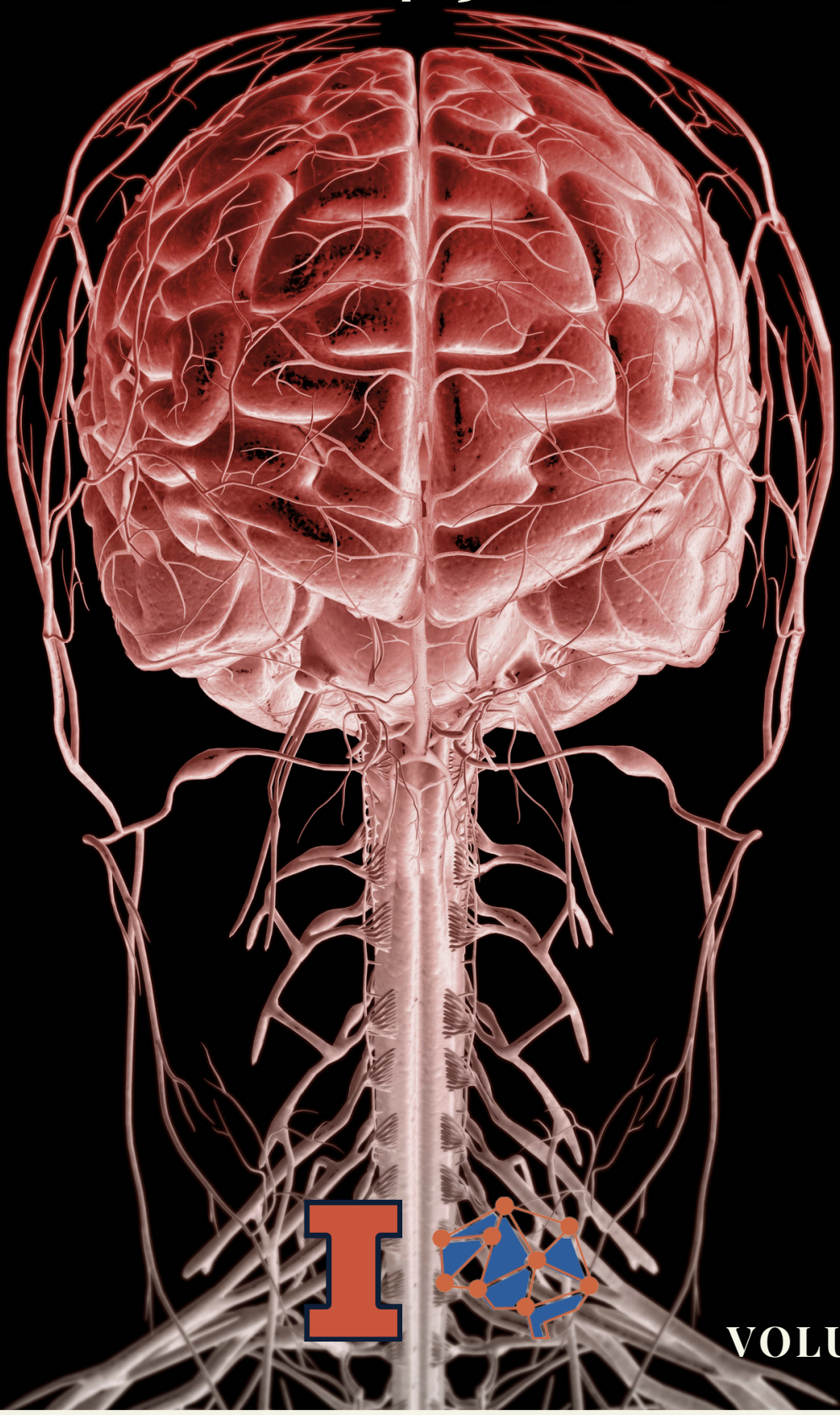

VOLUME VI

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Using Oxytocin as a Therapy For Individuals with Autism Spectrum Disorder

Alisha Babu

Abstract

Autism Spectrum Disorder (ASD) is a disorder with many symptoms ranging from a lack of social skills and communication to repetitive actions and behaviors. . The disorder is characterized by a large spectrum, making it difficult to diagnose, due to the wide variety of symptoms it can portray in affected people. ASD poses a challenge on a worldwide scale due to lack of information regarding causes or curative treatment. Though there are no acknowledged cures, there are many types of therapies for children with ASD - all aimed at improving their symptoms ("Autism spectrum disorder", 2022). One possible treatment option that is being researched is 'Oxytocin Therapy'. Oxytocin therapy utilizes oxytocin -a hormone/chemical messenger that promotes qualities of recognition, trust, and bonding which leads to its positive enforcement of social interactions in people (DeAngelis, 2008). These qualities are what led to the development of a hypothesis that this hormone could be administered in a therapeutic form to improve the social functioning in those diagnosed with ASD (Ford, n.d.). This neuropeptide is administered intranasally and has been researched mostly in young children and teenagers. The results from these studies prove to be controversial as they display both positive as well as negative findings. Hence, further research needs to be conducted on oxytocin therapy before a comprehensible conclusion can be made on its outcome.

Introduction

In 2018 it was established that an average of 1 in 4 children are diagnosed with autism spectrum disorder by the CDC ("Data and statistics", 2022). Autism spectrum disorder (also known as ASD) is a neurodevelopmental disorder characterized by difficulties in social communication and interaction ("Autism spectrum disorder", 2022). Patients diagnosed with autism have a large number of symptoms and behavioral abnormalities. These symptoms include: social impairment with communication difficulties along with repetitive and characteristic behaviors. Specifically, signs of this include attention deficits such as failing to respond to one's name when called, lack of eye contact, and an abnormal range of speech (no speech or fluent speech that may be awkward or inappropriate). Repetitive behaviors may include certain bodily or speech ticks as well as an obsessive/deep interest in ideas or concepts which are intriguing to the patient("Autism spectrum disorder", 2022).

Doctors and clinicians categorize the disorder into different types based on these symptoms. One type of ASD is known as high functioning autism (HFA) which is also known as level 1 autism, and another type is known as low functioning Autism (LFA) which is also called level 3 autism. (Fredericks, 2008). Patients with high functioning autism are able to read, write, and speak efficiently and are able to perform basic life skills such as eating and getting dressed. They show incredible persistence, can recognize patterns, and pay attention to detail. However, they experience difficulties with social interaction, are hypersensitive to their environment, display uncoordinated movements, and lack desire for a routine. ("What is Asperger Syndrome?", n.d.). Level 2 includes the same symptoms, but more severe, with marked deficits in social interaction and verbal display. Level 3 is characterized by the most prevalent symptoms which characterizes it as low functioning autism. These symptoms include severe deficits in social interaction and verbal communication ("Autism diagnosis criteria", n.d.). Patients diagnosed with level 3 ASD are typically in need of full time aides and/or intensive therapy (Holland, 2018).

Children and adults with low functioning autism (LFA) will commonly show pronounced symptoms including limited social abilities, repetitive behaviors, and restrained communication skills. Research indicates that 25-50 percent of individuals with LFA will never be able to achieve the skill of functional speech in their lifetime. Patients diagnosed with LFA also tend to have more memory impairments as compared to patients with HFA (Ni Chuileann & Quigley, 2012).

Typically, ASD is diagnosed during childhood. If symptoms are very apparent, diagnoses can be made at the early age of 18 months of age. This early diagnosis can be sought if the child shows signs of ASD at the age of 6 to 12 months. However, it is also possible for autistic symptoms to emerge and subside by the age of 24 months (WebMD Editorial Contributors, n.d.).

Although ASD is not curable, there are many treatments (including medications and a variety of different therapies) that can alleviate its symptoms. One new type of therapy - known as Oxytocin Therapy - has been recently researched and is considered effective in treating individuals with ASD.

Oxytocin - also known as alpha-hypophamine - is a hormone/chemical messenger that is produced in the hypothalamus and is transported and stored in the posterior pituitary gland. Subsequently, the pituitary releases the hormone into the bloodstream in response to a trigger. The secretion of oxytocin from the pituitary gland relies on the activity of neurons within the hypothalamus - excitation of these neurons leads to the release of oxytocin into the

bloodstream (“Oxytocin”, n.d.).

The roles of oxytocin span in variety. One significant role of the hormone is specifically to trigger contractions of the uterine wall and lactation during childbirth. Not only does oxytocin stimulate the muscles within the uterus to contract but also boosts production of prostaglandins - which sustain these contractions. The psychological effects of these increased levels of oxytocin during childbirth can lead to “reducing pain and anxiety, enhancing well-being, and promoting interaction and bonding with the child” (Doherty, n.d.). Oxytocin is also known to play a role in facilitating social-interactions with others and can encourage their ability to affiliate with others. Stressful situations can also boost levels of oxytocin in the body. This response has been linked with low norepinephrine levels, blood pressure, and heart rate (DeAngelis, 2008). The hormone is capable of enhancing trust or suspicion, affiliation or aggression, sexual arousal, and learning and memory (Ford, n.d.). The role oxytocin has within social bonding and stress regulation is what led researchers to hypothesize that oxytocin could be utilized as an effective therapy for those with ASD (DeAngelis, 2022).

Oxytocin Therapy for Autism Spectrum Disorder

Oxytocin therapy aims to optimize the circuits that underlie social deficits in those with ASD while improving reward, motivation, and learning in them (Guastella, 2016). Nature Reviews Neurology states that, “oxytocin increases the salience of social stimuli and fine-tunes neural processes so that an organism can better attend and respond to those stimuli”(Ford, n.d.). Specifically, oxytocin facilitates the flow of social information from incoming sensory signals. This information is encoded in the regions involved with cognitive processes such as reward, learning, and memory.

The method of administration of this treatment would be through a nasal spray. This method of therapy was observed and analyzed through many different studies and trials. One randomized double-blind clinical trial studied oxytocin’s effect on children with ASD conducted by Yatawara et al. In this trial, 31 children aged 3-8 and affected with ASD were used as participants. These participants were randomly assigned drug kits which either had an oxytocin nasal spray or a placebo spray. The first dose started with 3 IU (International Units) twice a day and gradually increased to 12 IU twice a day (full dose) by day 7. 15 of the participants had ‘oxytocin then placebo’ and 16 had ‘placebo then oxytocin’. This treatment lasted for a total of 5 weeks. The participants’ oxytocin levels were measured before and after the treatment and their behavior was observed (Yatawara et al., 2015).

Results of this experiment revealed that children aged 3-8 with autism had an improved social responsiveness - as rated by their care-giver - over a 5 week course of oxytocin treatment. This study shows how there can be significant improvements caused by this new form of therapy, however another study experimenting with the effects of oxytocin with individuals with autism did not show as promising results.

Another study published in the New England Journal of Medicine was conducted using 290 participants aged 3-17 years diagnosed with autism spectrum disorder. These participants were administered 24-40 international units of intranasal oxytocin or placebo twice a day for a maximum of 24 weeks. Clinical questionnaires were completed by the parents/guardians of the participants in 4 week intervals. The data provided by 277/290 participants had shown that the administration of oxytocin had no effect on ASD symptoms (Sikich et al., 2021).

The ability of oxytocin to penetrate through the blood/brain barrier and diffuse intracerebrally has been questioned due to its short half-life. Instead of the chronic supplementation route, researchers wonder if enhancing oxytocin signaling could be a promising treatment. In addition to solely supplying the participants with doses of oxytocin, researchers speculate whether pairing this intranasal dose with cognitive and behavioral therapy would prove to be an effective method (Ford, n.d.).

Another randomized, double-blind, placebo-controlled study utilized 19 adult participants diagnosed with high functioning autism or Asperger’s disorder - 16 males. These participants were aged 33 years with a standard deviation of 13. The subjects were randomized to a dose of 24 IU (6 puffs) intranasal oxytocin twice daily for 6 weeks. Their social and cognitive function was measured using the Diagnostic Analysis of nonverbal Accuracy, and repetitive behaviors were measured through Repetitive Behavior Scale Revised. Molecular Autism states that “secondary measures included the Social Responsiveness Scale, Reading-the-Mind-in-the-Eyes Test and the Yale Brown Obsessive Compulsive Scale – compulsion subscale and quality of life (World Health Organization Quality of Life Questionnaire – emotional/social subscales). These tests were conducted every 2 weeks. Results showed that based on the scores of the measurement scales, improvements occurred in social cognition and quality of life after the full 6 weeks of dosage (Anagnostou et al., 2012).

Conclusion

The skewed results obtained from the research conducted so far indicates that utilizing oxytocin as a therapy needs to continue being researched. A multi-level meta-analysis conducted by Huong et al and published in The Journal of Neuroscience and Biobehavioral Reviews highlights the promise of using oxytocin as a new generation therapeutic to address core social impairments in ASD (Huang, 2021). There is still much that needs to be studied about the direct effects of oxytocin on one’s actions and attitudes before a clear determination can be made on whether this therapy will be useful in improving the symptoms in those diagnosed with ASD. Future studies should involve larger numbers of participants with wider spectrums of race, age, and gender represented in order to see if these traits affect the results oxytocin therapy can have on its user with ASD. There must be a wider pool of participants with diversity in age as well as gender to see if these traits affect the results oxytocin can have on its user with ASD.

References

1. Anagnostou, E. (2012, December 12). *Intranasal oxytocin versus placebo in the treatment of adults with autism spectrum disorders: A randomized controlled trial*. Molecular Autism. Retrieved May 1, 2022, from https://molecularautism.biomedcentral.com/articles/10.1186/2040-2392-3-16
2. Chuileann, S. N. (2012, October 30). *Assessing recollection and familiarity in low functioning autism*. Springer Link. Retrieved May 1, 2022, from https://link.springer.com/article/10.1007/s10803-012-1697-3
3. DeAngelis, T. (2008, February). *The two faces of oxytocin*. American Psychological Association. Retrieved March 26, 2022, from https://www.apa.org/monitor/feb08/oxytocin
4. Doherty, C. (2021, January 7). *What is Oxytocin?* VeryWell Health. Retrieved March 23, 2022, from https://www.verywellhealth.com/what-is-oxytocin-5090160
5. Ford, C. L. (n.d.). *Refining oxytocin therapy for autism: Context is key*. Nature Reviews Neurology. Retrieved April 29, 2022, from https://www.nature.com/articles/s41582-021-00602-9
6. Guastella, A. J. (2016, February). *Oxytocin Treatment, Circuitry, and Autism: A Critical Review of the Literature Placing Oxytocin Into the Autism Context*. Science Direct. Retrieved March 27, 2022, from https://www.sciencedirect.com/science/article/pii/S0006322315005430
7. Hoffman, M. (2020, December 6). *What are the types of autism spectrum disorders?* WebMD. Retrieved April 28, 2022, from https://www.webmd.com/brain/autism/autism-spectrum-disorders
8. Holland, K. (n.d.). *High-functioning autism*. Healthline. Retrieved April 28, 2022, from https://www.healthline.com/health/high-functioning-autism#asperger's-syndrome.
9. Huang, Y. (2021). Intranasal oxytocin in the treatment of autism spectrum disorders: A multilevel meta-analysis. *Neuroscience & Biobehavioral Reviews*, *122*, 18-27. https://doi.org/10.1016/j.neubiorev.2020.12.028
10. Low functioning autism ? symptoms, signs, treatments, and more. (n.d.). AngelSense. Retrieved May 1, 2022, from https://www.angelsense.com/blog/low-functioning-autism/
11. *Oxytocin*. (n.d.). You and Your Hormones. Retrieved March 23, 2022, from https://www.yourhormones.info/hormones/oxytocin/
12. Sikich, L. (2021). Intranasal oxytocin in children and adolescents with autism spectrum disorder. *New England Journal of Medicine*, *385*(16), 1462-1473. https://doi.org/10.1056/NEJMoa2103583
13. Quigley, J., and S. Ni Chuileann. "Assessing Recollection and Familiarity in Low Functioning Autism." Journal of Autism and Developmental Disorders, vol. 23, pp. 1406-22. MEDLINE with Full Text, eds.a.ebscohost.com/eds/detail/detail?vid=5&sid=de746ea2-cccd-4198-b309-7cdc1d3e060d%40sessionmgr4007&bdata=JkF1dGhUeXBlPWNvb2tpZSxnZW8sdXJsLGlwJmdlb2N1c3RpZD1zODQ3NTc0MSZzaXRlPWVkcy1saXZlJnNjb3BlPXNpdGU%3d#db=mnh&AN=23108988. Accessed 1 May 2022.
14. Sikich, L. (2021). Intranasal oxytocin in children and adolescents with autism spectrum disorder. New England Journal of Medicine, 385(16), 1462-1473. https://doi.org/10.1056/NEJMoa2103583
15. What is asperger syndrome? (n.d.). What Is Asperger Syndrome? Retrieved April 30, 2022, from https://www.autismspeaks.org/types-autism-what-asperger-syndrome
16. Yatawara, C. J. (2015, October 27). The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: a randomized clinical crossover trial. Nature. Retrieved March 27, 2022, from https://www.nature.com/articles/mp2015162

Implications of GPCRs in Alzheimer's

Katilyn Simmons

Abstract

G-protein coupled receptors, or GPCRs, are a large, diverse group of receptors found in all eukaryotes. GPCRs, as their name suggests, interact with G-proteins in the cell in order to carry out a variety of cellular responses. Most of these cellular responses are related to sensory functions such as pheromone signaling, taste, light perception, and other processes in the brain (Azam et al., 2020). For this reason, GPCRs are a very promising target for drugs that treat disorders affecting these processes. These disorders include many neurodegenerative CNS disorders, such as Alzheimer's disease. While many current drugs and therapies treat symptoms of these disorders, drugs that target GPCRs more directly would focus on the cause of the disorders at their roots (Huang et al., 2017). Insight into the mechanisms involved in signal transduction pathways in disorders such as those in Alzheimer's would lead us to new discoveries that could alter the course of these and many other disorders of the CNS.

Why are Receptors Important?

The neurons in your brain, as well as other cells in your body, are constantly sending signals in all directions to any neuron that will listen and respond. These neighboring cells need a way to "listen" to these communications and interpret them in meaningful ways so that the cell can respond accordingly. An example of one way that the cell does this is through receptors. When a cell fires, it releases a signaling molecule – typically a hormone or a neurotransmitter – called a ligand, which then binds to the receptor. While some signals do result in direct cellular responses, such as in the case of a ligand binding to an intracellular receptor, signals usually initiate some type of cellular response through a series of steps called a signal transduction pathway (Brooker et al., 2022). This pathway consists of a series of changes that lead to the production of a secondary signaling molecule which can lead to various cellular responses, such as altering enzymatic activity, altering protein function, or altering the function of transcription factors which activate gene expression – essentially turning a gene on or off. The proper functioning of any receptor is vital to the normal everyday bodily processes that are happening constantly in your body.

What are GPCRs?

One especially important group of receptors that are specifically relevant in the neuropathology realm are GPCRs, or G-protein coupled receptors. To put things into scope, there are over 370 non-sensory GPCRs currently identified, and 90% of those 370 receptors are expressed in the brain (Azam et al., 2020). GPCRs are a remarkably diverse group of receptors that bind a vast variety of different signaling molecules, and therefore perform a variety of difference functions in your body and brain. In the brain, they are responsible for things like taste and appetite, pheromone signaling and mood, vision and light perception, immune regulation, and more general functions like cognition and synaptic transmission (Huang et al., 2017). It is for this reason that regulation of GPCRs is a common target for drugs that treat disorders of such functions.

How are GPCRs Structured?

Being able to answer questions about how something is structured can often give us some clue as to how it works. GPCRs typically have seven domains, or segments, that are membrane-spanning, meaning that they wind back and forth across the plasma membrane of the cell. They also contain extracellular loops that contain components that stabilize the structure. GPCRs interact with G-proteins, named for their ability to bind to GTP and GDP. The G-protein is a lipid-anchored protein, which means that it is attached to the intracellular side of the membrane and consists of an alpha subunit and a β/gamma dimer. In its inactivated state, the G-protein binds GDP (Brooker et al., 2022).

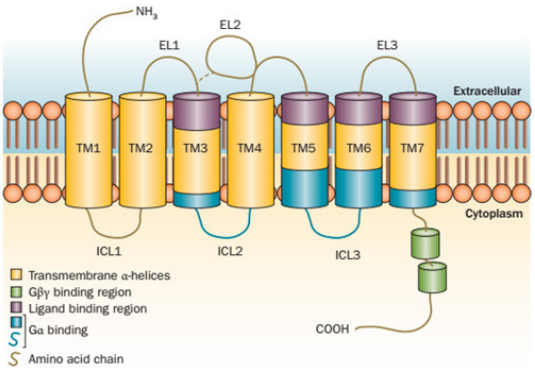


Figure 1. Schematic Diagram of GPCR Structure (Neumann et al., 2014).

How do GPCRs Function?

Now that we have a basic understanding of how the GPCR and G-protein are structured, let us examine how they function to carry out cellular responses when they are functional. To begin the signal transduction pathway, a ligand, or signaling molecule such as a hormone, peptide, or growth factor binds to the extracellular portion of the receptor. This causes a conformational change which allows the receptor to bind to a G-protein. Once bound to the receptor, the G-protein a subunit and β/g dimer separate, releasing GDP. This allows the alpha subunit to bind GTP.

The two components of the G-protein can both play separate, very important roles in eliciting cellular responses. For example, the a subunit can activate enzymes in the cell that lead, in a chain reaction, to the increased or decreased production of important energy sources such as glucose. The b/g dimer is also important, as it can play a role in the regulation of ion channels (Brooker et al., 2022).

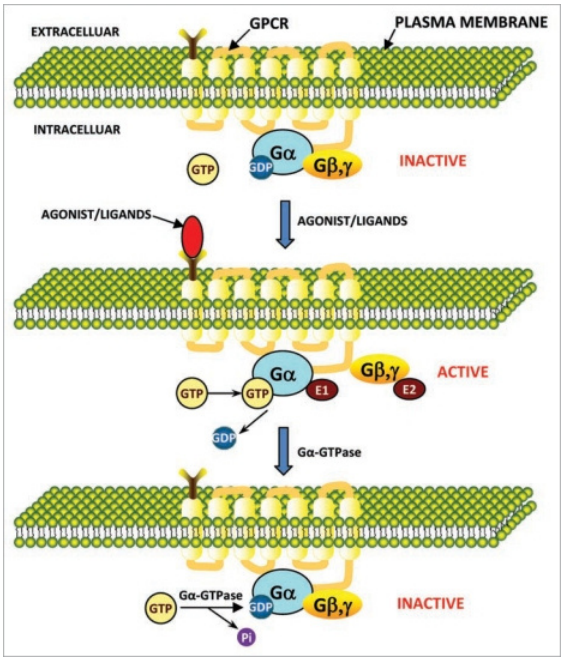


Figure 2. Diagram of General Signal Transduction Pathway of GPCRs (Tuteja, 2005).

How Do GPCRs Relate to Alzheimer's?

Alzheimer's disease (AD) is a neurodegenerative disorder associated with reduced cognitive function, loss of synapses, and neurofibrillary degeneration, or the formation of tangles of fibers within nerve cells, due to a buildup of plaques in the brain. These plaque buildups are accumulations of β-amyloid peptide (Aβ), which is formed from a protein called amyloid protein precursor (APP) (Zhao et al., 2016). As stated before, GPCRs are involved in the normal functioning of many important cellular processes in the brain. One example of this is demonstrated in GPCRs' role in the development of AD through the processing of APP.

GPCRs and the Regulation of APP Through BACE1 Downregulation

BACE1 is an enzyme that is essential for the processing of APP and generation of b-amyloid. In patients with AD, BACE1 has been found to be overactive, but not in excess (Zhao et al., 2016). Research suggests that GPCRs (specifically the M1 AChR, δ-opioid receptor, and A2A receptors) are involved in the regulation of BACE1 (Zhao et al., 2016). There are also a number of different proteins that are responsible for the regulation of GPCRs, and therefore may be responsible for regulating BACE1 activity. It has been shown that a loss of function in these enzymes is also connected to the progression of AD in some way or another (Zhao et al., 2016). For example, the upregulation of small GTPases such as RABs has been connected to cognitive impairment in AD (Ginsberg et al., 2010). Although there is evidence for a linkage of GPCRs to the regulation of BACE1, it is not currently known exactly the mechanism through which it is done.

GPCRs and the Regulation of APP Through Degradation of BACE1

Another possibility for a mechanism of regulation of APP by GPCRs is related to the degradation of BACE1. There is evidence that mAChR, which was previously mentioned as a possible component of BACE1 downregulation, could be involved in the degradation of BACE1 (Jiang et al., 2012). The mechanism through which this is done is not clear to researchers and is a continuing topic of discovery.

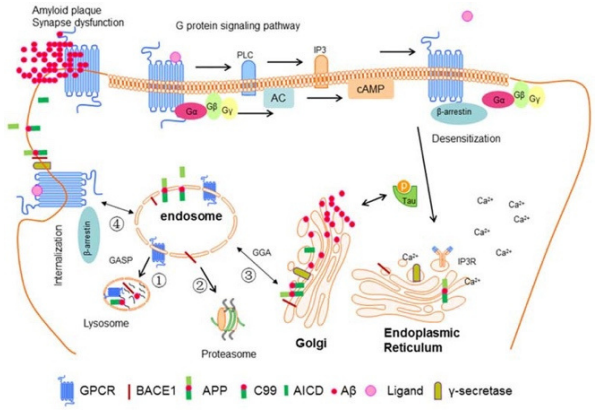


Figure 3. Proposed Signal Transduction Pathway and Interaction Between GPCR and BACE1 (Zhao et al., 2016).

Why is Determining These Mechanisms Hard, but Also So Important?

Currently, the drugs used for the treatment of AD only scratch the surface of the problem. Current treatments such as acetylcholinesterase inhibitors and memantine treat only the symptoms of AD. Acetylcholinesterase inhibitors simply inhibit the breakdown of acetylcholine, which is in short supply in the brains of AD patients. Similarly, memantine prevents excitotoxicity due to overstimulation (Huang et al., 2017). These treatments, while helpful, leave the root of the problem unchecked. If the mechanisms behind the role of GPCRs in the processing of APP are further studied, better therapies and even a possible cure for Alzheimer's may be on the horizon. The problem, however, is that there are a few difficult tasks standing in the way of our understanding of these mechanisms. First, inhibiting BACE1 would not come without side effects. Inhibiting BACE1 may prevent unnecessary Aβ production, but this does not come without consequences in application in the body. There is a strong possibility that BACE1 is related to the production of many other enzymes, so inhibiting it would affect enzymes that were not meant to be affected. This could lead to unwanted effects such as impaired spatial reference and working memory, as well as problems with temporal associative memory (Cole & Vassar, 2007).

Conclusion

Receptors in general are vital to the function of many bodily and brain processes. Even more specifically, GPCRs are vital to our understanding of the body, as they make up a large chunk of all receptors, especially in the brain. Further research into the functions of GPCRs and GPCR signal transduction pathways in relation to BACE1 and other enzymes would open the door, not only to potential treatments and maybe even a cure for Alzheimer's, but also to several treatments for CNS disorders such as Parkinson's and Huntington's disease.

Therefore, a partial, rather than full, inhibition of this enzymatic activity may be beneficial, although the percentage of BACE1 inhibition required to significantly delay amyloid pathology and the associated cognitive changes, remains to be determined.

References

1. Azam, S., Haque, M. E., Jakaria, M., Jo, S. H., Kim, I. S., & Choi, D. K. (2020). G-Protein-Coupled Receptors in CNS: A Potential Therapeutic Target for Intervention in Neurodegenerative Disorders and Associated Cognitive Deficits. Cells, 9(2), 506. https://doi.org/10.3390/cells9020506
2. Brooker, R. J., Widmaier, E. P., Graham, L. E., & Stiling, P. D. (2022). Cell Communication. In Biology (pp. 85–92). essay, McGraw Hill LLC.
3. Cole, S.L., Vassar, R. The Alzheimer's disease β-secretase enzyme, BACE1. Mol Neurodegeneration 2, 22 (2007). https://doi.org/10.1186/1750-1326-2-22
4. Ginsberg, S. D., Alldred, M. J., Counts, S. E., Cataldo, A. M., Neve, R. L., Jiang, Y., Wuu, J., Chao, M. V., Mufson, E. J., Nixon, R. A., & Che, S. (2010). Microarray analysis of hippocampal CA1 neurons implicates early endosomal dysfunction during Alzheimer's disease progression. Biological psychiatry, 68(10), 885–893. https://doi.org/10.1016/j.biopsych.2010.05.030
5. GPCR | Learn Science at Scitable. (n.d.). Scitable. Retrieved February 26, 2022, from https://www.nature.com/scitable/topicpage/gpcr-14047471/?error=cookies_not_supported&code=4f65e9e1-a4a2-46fa-a388-b0b489fbf9c4
6. Huang, Y., Todd, N., & Thathiah, A. (2017). The role of GPCRs in neurodegenerative diseases: avenues for therapeutic intervention. Current Opinion in Pharmacology, 32, 96–110. https://doi.org/10.1016/j.coph.2017.02.001
7. Jiang, S., Wang, Y., Ma, Q., Zhou, A., Zhang, X., & Zhang, Y. W. (2012). M1 muscarinic acetylcholine receptor interacts with BACE1 and regulates its proteosomal degradation. Neuroscience letters, 515(2), 125–130. https://doi.org/10.1016/j.neulet.2012.03.026
8. Neumann, E., Khawaja, K., & Müller-Ladner, U. (2014). G protein-coupled receptors in rheumatology. Nature reviews. Rheumatology, 10(7), 429–436. https://doi.org/10.1038/nrrheum.2014.62
9. Tuteja N. (2009). Signaling through G protein coupled receptors. Plant signaling & behavior, 4(10), 942–947. https://doi.org/10.4161/psb.4.10.9530
10. Zhao, J., Deng, Y., Jiang, Z., & Qing, H. (2016). G Protein-Coupled Receptors (GPCRs) in Alzheimer's Disease: A Focus on BACE1 Related GPCRs. Frontiers in aging neuroscience, 8, 58. https://doi.org/10.3389/fnagi.2016.00058

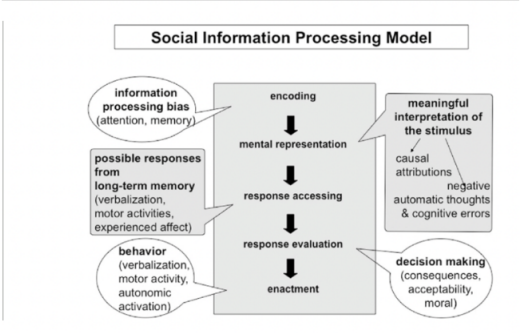
The Neurobiology Behind the Making of the Antisocial Personality Type

Vyapti Patel

The antisocial personality type is a particular type that is full of mysteries, but with the assistance of more advanced technology, and the exploration of this personality type, more knowledge upon it is slowly being gained. It is known that the diagnosis of this personality type is more common in males than it is in females, “total prevalence rate of 4.5% in community samples” (Fitzgerald, 2007). There is so much more to this personality type than what the media presents, and by exploring the brain science behind the antisocial type, more equipped decisions to help these individuals can be made before unfortunate events occur. The antisocial personality type is also closely tied with the legal system, and for years has been causing turmoil upon individuals and their families; whether the individual themselves have this personality type or they themselves have been affected by someone who has this personality type. This personality type “stems from brain abnormalities” and has a lot to do with “dysfunctions in select parts of the brain” according to the research suggested in the article, The neuropsychology of antisocial personality disorder (Fitzgerald, 2007). The antisocial personality type has a lot to do with the genetics and the biological aspect of oneself, but when tied with ‘nurture’, the making of a dangerous individual can be amplified. Treating individuals with the antisocial personality type can be difficult as they themselves do not have the desire to change, most probably due to their lack of empathy when inflicting pain upon others. Although change can be brought upon these individuals; through the exploration of the antisocial personality type in terms of the neurological as well as the psychological aspect, a more deep understanding of this personality type can be gained, which in turn can help eradicate the chaos and destruction that this personality type brings into society as well as save the lives of those experiencing this personality type.

The development of the child plays a significant role in the emergence of the antisocial personality type. It is actually considered normal for children to express aggression and certain antisocial behavior when they are young, because they have yet to get a sense of the world around them, and understand what is socially appropriate and what is not. For example, a young child may take another child's toy and not give it back, but they do not know that this is not appropriate. Contrary to that, this becomes a problem when aggression and antisocial behavior prospers long term. There tends to be signs at an early age with what type of turnout will come about the child; as an infant these individuals have a more ‘difficult temperament’ (Rudolph, 2022). Then as they progress to preschool, they may be more prone to throw tantrums, be more stubborn as well as more physically aggressive. Onward to their childhoods, they may engage in fighting, bullying, while also having academic and social difficulties, but a big give away can be showing signs of animal cruelty. Then as they develop into their adolescence they continue on with these behaviors on a bit of an extreme scale. Finally the problem can lead to adulthood and this is when the individual becomes more involved with the legal system, while juggling a chaotic life, which may include broken relationships, psychiatric problems, unable to parent well, etc. (Rudolph, 2022).

These children tend to process social information differently compared to the majority of the children. According to the Social Information Processing Model carried out by psychologist Ken Dodge, a scenario was given to some of the children in order to determine the social processing steps the individual with a more aggressive nature went through. The scenario consisted of the child at a cafeteria, who had milk spilled over them, but prior to that when the child was waiting in line they had two children behind them, one making a goofy face and one smiling at them. When asked to explain what had happened to the child, the child with the personality disorder viewed the actions of the other children as purposefully malicious. This relates to the hostile attributional bias - the tendency for the child to interpret the behaviors of others to have malintent towards them - where the child is asked how they would want to react to this, and they say that they will get back at the other kid. This child is not afraid of the consequences, and they do not feel fear at the normal level that an average person would. So fulfilling a hostile goal in order to either assert dominance and/or get revenge does not require much doubt. These kids think that there will be a positive outcome to this and think they are going to be good at this. The child is not able to think of all things that could go wrong, and they are unable to see this as an accident, as they have internalized it.

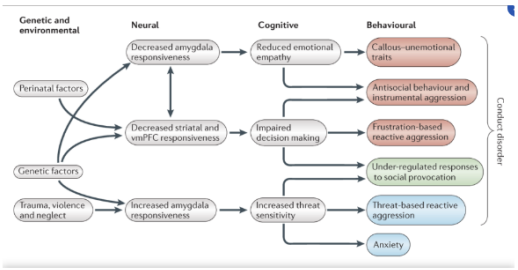


Dodge's Social Information Processing Model (1993)

Geared towards hostile behaviors, (Verhoef, 2021)

Figure 1.

This type of development involves not only the neurological aspect within the individual but the family/environment plays a huge role in fueling these behaviors. First of all, it can be genetically passed down from a family member which can result in a more negative temperament. Adding onto that, the parenting style that these individuals have grown up with can play a big factor; there can be a 'power assertion' where one of the parents makes the child feel unimportant, with punishments involved. Another parenting type can be the low monitoring parent, one that practically neglects the child, leading the child to be more deviant. Although, parenting is not the only cause for these behaviors. A child is at school for most of their lives, so if the child experiences peer rejection either due to academics or social reasons, the child may steer from the normative group of children and become more involved in a deviant group of children, or isolate themselves. This only leads to more of a feeling of ostracism, and this coupled with early genetic deficits as well as neurological/cognitive deficits results in the child to go down a more deviant pathway.



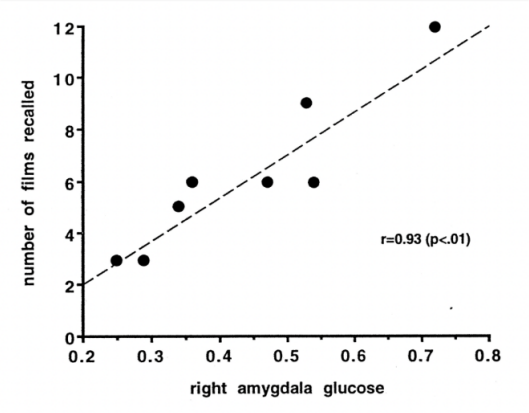
Framework of Conduct Disorder - Child shows antisocial behavior (Blair, 1970)

Figure 2.

An individual born into a low socioeconomic family can also facilitate antisocial personality traits. When exposed to neighborhood violence at a young age, the child does not know any better than from what they have seen and experienced. At a young age, they seem to understand that this is normal for them. They also become 'desensitized to violence' (Rudolph, 2022). The parent may also not be so involved in their lives because they are busy handling multiple jobs or are not in a state to provide much for their child. All this can lead the child to partake in deviant activities with deviant peers and find a sense of belonging even though it is not safe for them. A lot of this can be avoided if the schools the children attended facilitated them into being more busy and involved within the community, but these institutions themselves are lacking in resources to provide. The schools either do not have enough funding to support the children or they do not have enough extracurriculars for the children to get involved in, which only leaves the children to pass time in their neighborhood. If these children already are biologically prone to the antisocial personality disorder, this sort of environment will only facilitate them towards the direction of atypical behavior within the community, which may result in delinquent activities.

Empathy and callousness play a prominent role in the development of an individual with the antisocial personality disorder. Empathy relates to the ability for one to put themselves in the place of another, and callousness is the opposite where the individual is insensitive to the feelings of others. By exploring the neural and peripheral physiology of an individual with the antisocial personality disorder, more insight upon the significance that empathy and callousness holds upon these individuals will be revealed. Empathy plays a significant role in promoting prosocial behavior, without it the connection between individuals is lost, causing disconnect and isolation amongst an individual, when paired with callousness and unemotional traits (CU), which are "traits related to maladaptive social information processing" (Shirtcliff, 2009). The development of psychopathy emerges, which is closely affiliated with the antisocial personality type. Alterations in the neural circuitry as well as the limbic system plays a huge role in relation to empathy and CU traits. The amygdala, an almond-shaped region within the brain, allows for emotions and arousal to be detected within the individual. This region is critical when it comes to responding to outside stimuli relating to arousal, and stress; low levels of it can indicate indifference to the outside environment. Individuals with high levels of the CU traits 'often show reduced amygdala activation' which suggests amygdala hypo-responsivity; this affiliates closely with the 'neurobiology of callousness.' A study upon this has been conducted by Marsh and colleagues according to Shirtcliff as mentioned in her article. The study required the observation of youths with CU traits in comparison to youths without the CU traits. What was found through this study was that, "youth with high levels of CU traits showed similar [reduced] amygdala activation to fearful, angry or neutral faces while healthy comparison or youth with ADHD displayed the typical enhancement of amygdala activation in response to fear" (Shirtcliff, 2009). These findings conclude that those with amygdala hypo-responsivity to emotional stimuli are associated with the antisocial personality type. The amygdala not only is associated with emotions but stores memories acquired through emotions. The amygdala usually does not go hand in hand with memory but it does get involved when it is 'activated by emotional arousal'. Without this function, it is hard to understand how to go on about combatting a situation similar to a previous situation in the future. This is supported by an experiment performed by Cahill where he performed a procedure similar to Nielson and Jenson: psychologists from another study, in order to determine whether the amygdala is correlated with long-term memory by showing 12 slides with narrations to human individuals being tested. At this step of the procedure he found that, "emotional arousal did not enhance long-term memory in a subject with bilateral degenerative lesions of the amygdala" (McGaugh, 1996). This finding indicates that damage to the amygdala impairs memory dealing with certain emotional events. He then goes onto a third study using a positron-emission tomography scan in order to assess for 'cerebral glucose metabolism in healthy volunteers' in which one session consisted of viewing emotionally arousing film clips, while the other session consisted of the individuals watching an emotionally neutral film clip. Three weeks had gone by and then memory of the clips they had seen was recalled and tested for.

It was found that, the glucose metabolic rate of the right amygdala was “induced by viewing the emotional film clips, [it] was highly correlated (+0.93) with the number of films recalled” (McGaugh, 1996). It is therefore concluded by this study that the amygdala is in correlation with emotional memory storage. So those that have a healthy functioning amygdala are able to understand social cues and recognize emotions in others in comparison to those that do not. Supporting the idea, healthy individuals are able to reduce the distress of others by following through with actions learned in the past, but those with low activation of the amygdala are unable to reduce another's distress because they themselves are unable to feel the distress of the situation. Helping another individual relates to moral decision making. When an individual has poor amygdala activation, they are also unable to make moral decisions which is associated with the impulsivity of those with the antisocial personality type.



The role of the amygdala in long-term memory, specifically its correlation to emotional memory recall (McGaugh,1996)

Figure 3.

Not only does the amygdala play a key role in the empathy/callousness aspect of the antisocial personality type, but so do certain other factors such as the anterior cingulate cortex as well as the insular cortex which are considered to be a part of the paralimbic system. Both of these cortices are regions of the medial pain system which play a trivial role regarding empathy (Medford, 2010). The ACC and insula are activated across a range of emotion-related tasks (Shirtcliff, 2009). It was found by Sterzer and colleagues that there is a reduction of insular gray matter in children with low levels of empathy and high levels of aggression. This reduction indicates the inability to understand social emotions, which reduces the human-to-human connection. A study was conducted which detected the activation of the ACC and insula in fear conditioning. It was found that “control participants activated the insula and the ACC as they paired neutral faces with pain, but psychopathic patients did not” (Shirtcliff, 2009). This is a big indication that those with the antisocial personality type are unable to feel empathy the way others can. Through the inability to feel empathy towards others and heightened callousness, a physical and emotional connection between individuals is lost. This loss of connection breeds individuals who are unable to digest the consequences they are to face when deciding to thrust themselves upon impulsive and aggressive tasks. Understanding the paralimbic and limbic systems and their relation to empathy and callousness helps those wanting to make an impact understand the basis of where the antisocial personality type stems from. Through digesting the main roots affiliated with this personality type, more research can be conducted upon this, and with the aid of new knowledge, more steps can be taken to prevent thesendividuals from causing chaos in our society while also helping them live a more suitable life.

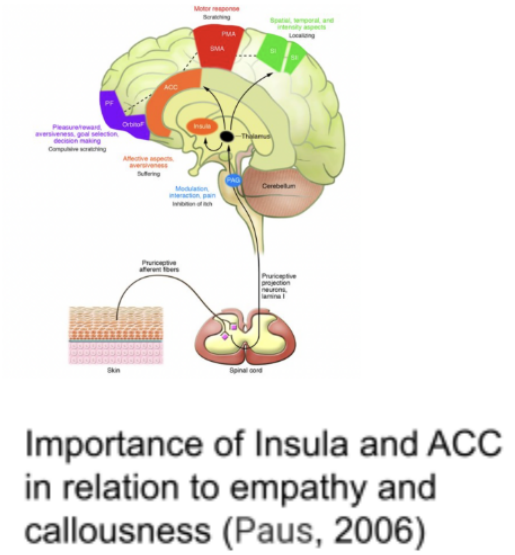


Figure 4.

The antisocial personality disorder has a lot to do with brain dysfunctions and impairments, whether it be genetic or due to a traumatic event. There are many types of psychopathic qualities that have emerged innately. The frontal lobe dysfunction theory speaks of an impairment in the executive functioning system. The damaging of the frontal lobe can lead to “distractibility, lack of guilt, periodic mood disorders, and increased sensitivity to alcohol” (Fitzgerald, 2007). These are all characteristics of an individual with the antisocial personality type; they are rash and execute plans that have uncertain outcomes. The dysfunctioning of the frontal lobe is possibly innate or it can occur in individuals later in life. Take the case study of Phineas Gage: he was known to be an energetic and a good businessman but after damaging his frontal lobe due to a railroad incident, his persona entirely shifted. He “became impulsive, irresponsible, profane, indifferent to social properties, childlike in intellectual capacity, and behaved more primitively following the accident” (Fitzgerald, 2007). The hard blow that his head took completely molded his brain another way, and those regions affiliated with decision making and impulsivity changed drastically, developing in him the antisocial personality type. In this case, the brain impairments Gage went through were not innate but happened due to the brain suffering from trauma. Another factor that is associated with the antisocial personality type is the impairment of the amygdala. This is highly associated with the risk of aggressive behavior as ”lesions in the amygdala have

been shown to impair the effects of aversive classical conditioning, lower automatic response to cues that predict shock, and impair passive avoidance learning' (Fitzgerald, 2007). This is very common amongst those with the antisocial personality disorder; they are not able to feel the fear and arousal of what the environment has to present, making it easier for them to act as predators because they see what they want, and go after it, and afterwards carry on to do the same without remorse. Those with high or low attention tasks associate well with the risk that they take when plotting a risky venture. In the gambling task done by Bechara, it was found that inmates in prison that had poor attention "performed poorly and made more risky choices more frequently," not thinking about the consequences that they would have to face when caught (Fitzgerald, 2007). The inmates were more likely to get prison time and get caught than those with high attention, who are also associated with the antisocial personality disorder but are not caught so easily. The amygdala as well as the frontal lobe play a huge role with the development of the antisocial personality disorder, and with new and improved technology, we may be able to repair some impaired portions of the brain, allowing for these innate born individuals to live a life that we all live.

The antisocial personality type in itself can be dangerous, but when paired with a difficult development into adulthood, the psychopathy of the individual is heightened. It all starts when the individuals are still infants, even though the child is unable to remember their youth and the treatment they received. The neurobiology of the children captures the treatment the children received at a young age. It was found in this study reported by Hane and Fox that "maternal sensitivity and intrusiveness [affects] infants' social interactions," so when this is lacking, the infants show "less interest" in social interactions (Frazier, 2010). This embarks their isolation and doubts upon trusting others. The children's neurological differences are well associated with their neurobiology during a critical point in development. There seems to be a biological association with neglect in association with the neurotransmitter dopamine. According to the analysis done by Pruessner et al., it was reported that there is "increased dopamine and cortisol release during stressful situations in individuals who reported low-quality relationships with caregivers in childhood" (Frazier, 2010). This increase in dopamine results in an individual being more aggressive and competitive; these are traits found more intensively in individuals with antisocial personality disorder. Along with that, another critical aspect of development occurs in the right hemisphere during the first 3 years of development, which is involved in emotional and social processing. Furthermore, longitudinal and cross-sectional brain imaging studies chronic stress, deprivation, or maltreatment in the first 3 years of life have been shown to cause brain volume reductions and significant brain development abnormalities in affected 3-year-olds" (Frazier, 2010). These developing abnormalities due to one's environment results in these children to begin adulthood not knowing what it means to be cared for, and their genetic predisposition of the development of the antisocial personality type prolongs into adulthood.

The antisocial personality type in specific is one that has many circulating questions, but through experiments, and the use of the technology we are given, the mysteries of this personality type can be gradually uncovered. This personality type has many factors that affect not only its developmental, but more so neurological and physiological impairments and also include the environment that one is born in. Those with a low socioeconomic status are more likely to strengthen this personality type. Through learning about this personality type, the lives of these individuals can be saved as well as the others that may be a victim to these individuals.

References

1. Shirtcliff, E. A., Zahn-Waxler, C., Merz, J. L., Gostisha, A. J., Graf, A. R., & Vitacco, M. J. (2009, August 20). Neurobiology of empathy and callousness: Implications for the ... National Library of Medicine. Retrieved April 30, 2022, from https://onlinelibrary.wiley.com/doi/10.1002/bsl.862
2. Fitzgerald KL, Demakis GJ. The neuropsychology of antisocial personality disorder. Dis Mon. 2007 Mar;53(3):177-83. doi: 10.1016/j.disamonth.2007.04.010. PMID: 17544650.
3. Frazier, A., Ferreira, P., & Gonzales, J. (2019). Born this way? A review of neurobiological and environmental evidence for the etiology of psychopathy. Personality Neuroscience, 2, E8. doi:10.1017/pen.2019.7
4. Medford, N., & Critchley, H. D. (2010). Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain structure & function, 214(5-6), 535–549. https://doi.org/10.1007/s00429-010-0265-x
5. Rudolph, K. (2022). Aggression and Antisocial Behavior. [Lecture powerpoint] https://learn.illinois.edu/course/view.php?id=66118
6. McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996, November 26). Involvement of the amygdala in memory storage: Interaction with other Brain Systems. Proceedings of the National Academy of Sciences of the United States of America. Retrieved June 5, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC33638/
7. Team, H. J., & Team, H. J. (2019, April 11). Amygdala function, location & what happens when amygdala is damaged. Health Jade. Retrieved April 29, 2022, from https://healthjade.net/amygdala/
8. Blair, R. (1970, January 1). The neurobiology of psychopathic traits in youths: Semantic scholar. undefined. Retrieved April 29, 2022, from https://www.semanticscholar.org/paper/The-neurobiology-of-psychopathic-traits-in-youths-Blair/c0263a8e1fc53aa3209a3a590cd5979be0b00218
9. Paus, R., Steinhoff, M., Bíró, T., & Schmelz, M. (2006). Frontiers in pruritus research: Scratching the brain for more effective itch therapy. JCI. Retrieved April 29, 2022, from https://www.jci.org/articles/view/28553/figure/2

10. Verhoef, R. E. J., Dijk, A. van, & Castro, B. O. (2021, April 6). A Dual-Mode Social-Information-Processing Model to Explain Individual Differences in Children's Aggressive Behavior. Research Gate. Retrieved May 10, 2022, from https://www.researchgate.net/publication/352204344_A_Dual-Mode_Social-Information-Processing_Model_to_Explain_Individual_Differences_in_Children's_Aggressive_Behavior/fulltext/60beceb892851cb13d88cea8/A-Dual-Mode-Social-Information-Processing-Model-to-Explain-Individual-Differences-in-Childrens-Aggressive-Behavior.pdf

Can Gene Editing Be The Key to Treating Alzheimers?

Saani Kulkarni

Commonly known as the most complex part of the human body, the brain contains millions of neurons, each with the ability to send and receive unique messages utilizing electrochemical signals. However, in individuals with Alzheimers and other neurodegenerative diseases, the typical function of neurons is impaired greatly. The lifespan of a neuron is dependent upon 3 primary factors: communication, metabolism, and its ability to repair itself. Without proper signaling, neurons are unable to access their target cells and gain access to necessary trophic factors. Moreover, neurons require adequate nutrients and chemicals to operate, gaining their energy through oxygen and glucose from the blood; the lack of these necessities will result in the death of the neuron. They must also be able to maintain a healthy state throughout their lifespan; while other human body cells may die quickly, neurons are observed to be able to live beyond 100 years of age in the human body.

While in a healthy human brain neurons may possess all these qualities, the opposite can be said for the brain in regards to Alzheimers; eventually, many neurons stop functioning and die out. Due to this, essential connections at the synapse may be broken down, impairing an individual from receiving necessary signals to carry out tasks. While researchers continue to investigate all causes behind Alzheimers, the beta-amyloid protein is commonly known as a major factor in the development of the disease. The cause of the cleavage of the amyloid precursor protein (APP), the presence of the beta-amyloid protein is originally beneficial, as it plays a significant part in neural growth and neural repair. However, a form of beta-amyloid known as beta-amyloid peptide 42 has been proven to be significantly toxic to the human body. Almost plaque-like, beta-amyloid 42 begins to gather in large quantities between neurons, damaging their functioning and breaking down their connections. Alongside b-amyloid 42, a protein known by tau that functions as a stabilizer for microtubules by attaching to them is often found in the human body as well. However, tau can separate and connects to other tau molecules instead, creating numerous knots and disruptions inside the neuron and ultimately affecting their ability to communicate. Researchers have found a positive correlation between an increased presence of tau and that of beta-amyloid, hinting at the fact that there are multiple mechanisms intertwined in the progression of Alzheimers.

Once neuronal networks begin to disappear, the memory of the individual, with parts of the brain such as the hippocampus and entorhinal cortex, is the first to be affected. As the disease spreads, the cerebral cortex of the brain is next, and ultimately individuals may be unable to carry out many basic behaviors independently. With such an extreme increase in severity, researchers have attempted to devise methods that will be able to treat Alzheimers and be able to reduce the symptoms gained as a result of it.

While originally researchers believed that a type of anti-beta amyloid drug would be a viable solution, it was soon understood that the state of the disease was already at a level of severity where simply treating it by affecting the amount of beta-amyloid protein in the brain would not necessarily result in a major change of quality of life nor health. In order to target the protein, the protein accumulation is removed as efficiently and quickly as possible in order to preserve the remaining parts of the brain.

Due to the precision of gene editing and the nature of the disease, teams worldwide have been examining the potential to treat Alzheimers using a variety of gene editing techniques. A significant positive towards gene editing would be the failure of other treatments to surpass the blood-brain barrier; however, gene therapy has the ability to surpass such obstructions. Despite this, many experiments regarding gene editing have not yet resulted in effects that would be considered noteworthy to the point of a fixed treatment. Researchers wish to continue experimentation by altering the type of viral vector, target for the therapeutic gene, and the route through which the vector should take. Viral vectors are considered one of the most effective ways for gene delivery to any target cells. When done ex-vivo, the target cells are drawn out from the organism's body, then introduced to the therapeutic gene, and planted back into the organism; in-vivo requires the process to be done within the organism itself. This can result in either gene silencing or overexpression, all of which is dependent on the target cell itself. Considering the wide range in virus shapes and structures, many types of viral vectors are utilized in order to attain precision and efficacy.

In treatments for Alzheimers, researchers have traditionally experimented with adeno-associated virus (AAV) vectors, due to their non-toxic and non-pathogenic nature. Taking into account the possibility of mutagenesis in the body, it is essential that the viral vector must possess these two qualities. Researchers identified around 100 AV variants with a range of 13 serotypes; although multiple have been deemed adequate for experimentation, AAV2 is used most frequently due to its high level of safety and sustained expression of the therapeutic gene within the neuron. Along with the identified AAVs, a genetically engineered AAV capsid (AAV-PHP.B) has been utilized in studies and expresses the ability to deliver a greater capacity of AAV

genomes to the central nervous system (CNS) and convert more than 50% of astrocytes and neurons (Chen, W., Hu, Y., & Ju, D, 2020).

While the selection of a vector is critical, researchers globally have experimented with AAV vectors and various targets in the body to treat Alzheimers; without choosing the proper target, the therapeutic gene may simply diminish symptoms slightly while possessing no contribution to the treatment and root cause of Alzheimers. Endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) has been extensively studied, as the majority of neurodegenerative diseases are correlated with an accumulation of misfolded proteins, which contributes to stress and eventual breakdown of the ER. Additionally, beta-amyloid oligomers are a source of destabilization to the calcium of the ER and its homeostasis, resulting in the death of neurons. By potentially being able to reduce the amount of stress affecting the ER, researchers have begun to experiment with a method to target the unfolded protein response (UPR) signaling in the hopes that the signaling pathway may be amplified for improvement in protein folding through gene editing. Notably, a positive correlation between the overregulation of the UPR pathway and glioblastoma invasion has been discovered, therefore being a safety concern when experimenting with this pathway. Another potential target for researchers has been the mTOR pathway, which deals with the regulation of mammalian metabolism and has also been known to play a role in neurodegeneration; when being abnormally regulated, protein accumulation is unable to be removed. In 2017, Chen et. al previously demonstrated that the delivery of mTOR positive regulators to the retina via the AAV vector resulted in a decrease of ganglion cell death and CNS axon regeneration; a variety of other studies have also reported positive effects on neuron regeneration in mouse models, highlighting the potential for the mTOR pathway to be an ideal target. Researchers have also devised methods for autophagy to be used through gene editing; in 2012, Gorbatyuk et. al demonstrated that the overexpression of a kinase through AAV2 resulted in the autophagy of dysfunctional mitochondria. In doing so, mitochondrial function that was lost as a result of b-amyloid oligomers was regained (Chen et.al, 2020). Similarly, microglia and astrocyte function has been brought to light as potential targets, considering the great importance of microglia within the neuroimmune system, and the damaging of their functions resulting in the neuron destruction witnessed in Alzheimers. The re-regulation of microglia function has been considered a potential treatment; multiple studies have reviewed the ability of the overexpression of the receptor TREM2 on myeloids to assist beta amyloid destruction and microglial movement. Through this process, the plaque formation and eventual disruption of neurons caused by b-amyloids is reduced, and spatial memory abilities are increased.

In recent years, studies with clustered, regularly interspaced short palindromic repeats and the CRISPR-associated protein 9 (CRISPR-Cas9) have increased significantly, and yielded optimistic results. Targeted to specific genes and highly precise, gene-editing techniques and therapies have improved greatly as a result of this technology. Comprised of a singular enzyme (Cas9) and a single guide RNA (sgRNA), the target DNA sequence is registered and recognized by the sgRNA, and cleaved by the Cas9 endonuclease, resulting in either a replacing of the mutated sequence or the insertion and deletion of sequences for inactivation. Considering that genetic mutations only comprise around 1% of familial Alzheimer's cases, CRISPR's role in helping patients with AD may be limited to changing symptom expression by manipulating b-amyloid metabolism (Bhardwaj, S., Kesari, K. K., Rachamalla, M., Mani, S, et. al, 2021).

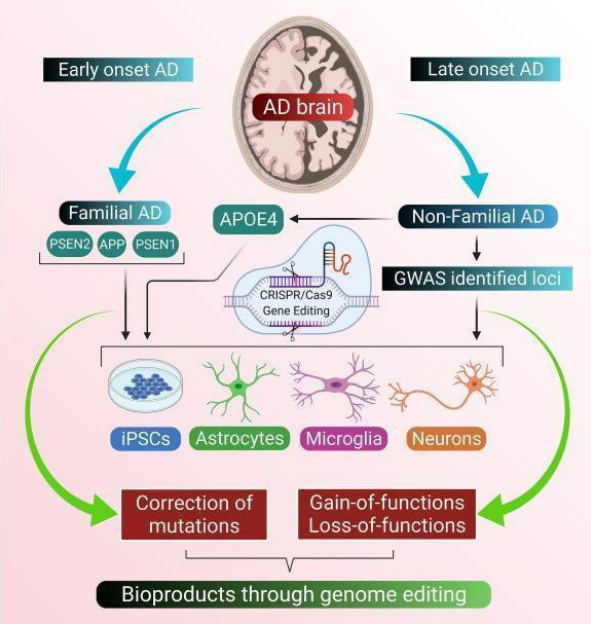


Figure 1. Proposed CRISPR Cas-9 gene editing approaches to types of Alzheimer's Disease. Adapted from "CRISPR-Cas9 gene editing : New hope for Alzheimer's disease therapeutics," by Bhardwaj, S. et al, 2021, Journal of Advanced Research (https://doi.org/10.1016/j.jare.2021.07.001). CC BY 4.0.

While the variety of findings in regards to gene editing and the treatment of Alzheimer's disease are promising, much work is needed to ensure the safety of procedures on the human brain and their efficacy. Host responses to viral vectors may prove to be dangerous, as is the concern of patients with high-functioning immune systems creating antibodies with the purpose of neutralizing the inserted vectors. Additionally, the ethics and viability of a supposed treatment must be taken into consideration; factors such as cost, effectiveness, and availability all must be regarded. Improved knowledge of the mechanisms behind Alzheimer's and their connection to various parts of the human body will undoubtedly improve the potential prospects for treatment. In combination with the continued efforts to find suitable vectors and outline target genes, many scientists and doctors are hopeful that gene-editing techniques may be a potential means to find a conclusive treatment to a disease that has affected millions of people worldwide.

References

1. Bhardwaj, S., Kesari, K. K., Rachamalla, M., Mani, S., Ashraf, G. M., Jha, S. K., Kumar, P., Ambasta, R. K., Dureja, H., Devkota, H. P., Gupta, G., Chellappan, D. K., Singh, S. K., Dua, K., Ruokolainen, J., Kamal, M. A., Ojha, S., & Jha, N. K. (2021). CRISPR/Cas9 gene editing: New hope for alzheimer's disease therapeutics. Journal of Advanced Research. https://doi.org/10.1016/j.jare.2021.07.001
2. Chen, W., Hu, Y., & Ju, D. (2020). Gene therapy for neurodegenerative disorders: Advances, insights and prospects. Acta Pharmaceutica Sinica B, 10(8), 1347–1359. https://doi.org/10.1016/j.apsb.2020.01.015
3. Gaj, T., Sirk, S. J., Shui, S.-lan, & Liu, J. (2016). Genome-editing technologies: Principles and applications. Cold Spring Harbor Perspectives in Biology, 8(12). https://doi.org/10.1101/cshperspect.a023754
4. Warnock, J. N., Daigre, C., & Al-Rubeai, M. (2011). Introduction to viral vectors. Methods in Molecular Biology, 1–25. https://doi.org/10.1007/978-1-61779-095-9_1
5. U.S. Department of Health and Human Services. (n.d.). What happens to the brain in alzheimer's disease? National Institute on Aging. Retrieved April 25, 2022, from https://www.nia.nih.gov/health/what-happens-brain-alzheimers-disease

The Mind-body Problem and Cognitive Neuroscience: A Brief History and Outlook

Alex Ball

Abstract

Cognitive neuroscience investigates the relationship between mental processes (such as perception, attention, thought, and memory) and physical states of the nervous system. This relationship gives rise to the mind-body problem, which has long been the subject of debate in philosophy. Over the last century, discussion of the problem has been informed by a deluge of empirical evidence from brain and mind sciences. While promising as a method of inquiry, cognitive neuroscience runs into an exceptional difficulty in explaining how non-conscious physical systems gain the ability to have an internal, first-person conscious experience that is characteristic of a mind. The challenge of this gap in explanation is commonly known as the "hard problem" of consciousness. Unlike the conceivably resolvable "easy problems" for cognitive neuroscience, such as merely correlating specific brain states with wakeful mental states, the "hard problem" does not have a readily apparent path to solving it. This article will explore early conceptualizations of consciousness, how cognitive neuroscience and related fields have changed how we think about conscious mental states, and what future possibilities there are for achieving a complete understanding of the conscious mind.

The Challenge of Consciousness

The mind-body problem is a long-standing question in philosophy: what exactly is the causal relationship between the properties of the mind, particularly conscious experience, and the physical brain? Consciousness, while a notoriously contentious term, generally means possessing subjective experience with varying levels of wakefulness. A person, animal, or thing is said to be conscious when they are in some capacity phenomenally aware of the contents of their cognition, such as thoughts, perceptions, beliefs, and emotions. Such contents are referred to as mental states in philosophy of mind, and a person possesses conscious mental states in wakeful life or when dreaming and is seemingly absent of them when in deep dreamless sleep, a coma (Laureys, 2005), or under sufficient general anesthesia (Alkire et al., 2008; Pavel et al., 2020).

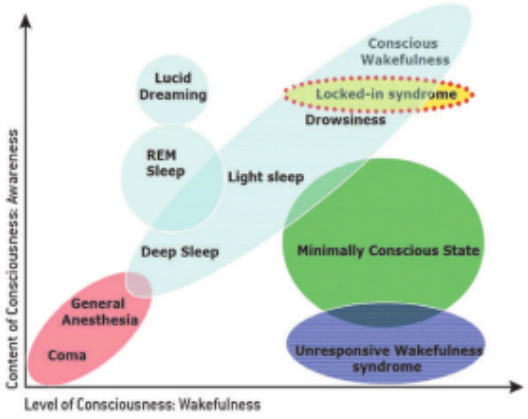


Figure 1. Schematic Diagram of GPCR Structure (Neumann et al., 2014).Figure 1. Schematic Diagram of GPCR Structure (Neumann et al., 2014).

Conscious mental states are considered to be part of the mind; they are mental phenomena. For cognitive neuroscience, the challenge of the mind-body problem lies in explaining the precise relationship between such mental properties and the physical brain in an objective manner to establish a unified scientific understanding of both mind and body. Intuitively, the mental is separate from the physical. There is an apparent difference between the third-person objectivity of the world examined by the sciences and the first-person subjective nature of conscious mental states, which has historically led to the mind and body being thought of as fundamentally separate (but related) phenomena.

Historical Origin of the Problem and Mind-body Dualism

The mind-body problem may have earlier conceptual origins in western philosophy, but the most influential early attempt to resolve it came from rationalist philosopher René Descartes. Descartes posited that mental and physical activity occurred in a fundamentally separate, but connected view called substance dualism. He claimed that there are two fundamental aspects to reality: the substance of matter, which is spatially extended in the world and includes the physical body, and the substance of mind (or soul), which is immaterial and non-spatial (Descartes, 1641/1986). Descartes speculated that the pineal gland, recognized today as a melatonin-secreting endocrine organ (Axelrod, 1974), facilitated the interaction between mind and body as the "seat of the soul." While research into the pineal gland has failed to support such a hypothesis of interaction, Descartes' idea of the body as a purely physical system paved the way for further objective scientific inquiry into human biology, as immaterial causes were localized to only mental activity and the body largely lost its sacred status (Shapin, 2000). Mind-body dualism continues to be a popular notion in folk psychology. Regardless, the view has fallen out of favor as a viable theory of the mind due to the lack of a coherent explanation for interaction between substances and, chiefly, in light of our modern understanding of the nervous system.

The Mind-Body Relationship Today: Contributions From Cognitive Neuroscience

Dominant philosophical theories of the underlying nature of consciousness, and the most relevant for cognitive neuroscience, are under the umbrella of physicalism: the doctrine that reality, including the mind, fundamentally consists of only physical things. Contrary to substance dualism, only the material substance exists. The popularity of physicalist theories of the mind can be attributed to the empirical study of the brain indicating that the instantiation of the mind is dependent on physical systems, and that its mental processes can be disrupted by physical alteration. For Descartes (1649/1989), the ability to think and to reason was a facet of an immaterial and rational soul. Contrarily, conscious mental processes have been shown to be just as functionally indebted to the physical structure of the brain as the unconscious regulation of the heartbeat, respiration, and digestion. One such example is working memory (WM), which is critical for the conscious manipulation of information.

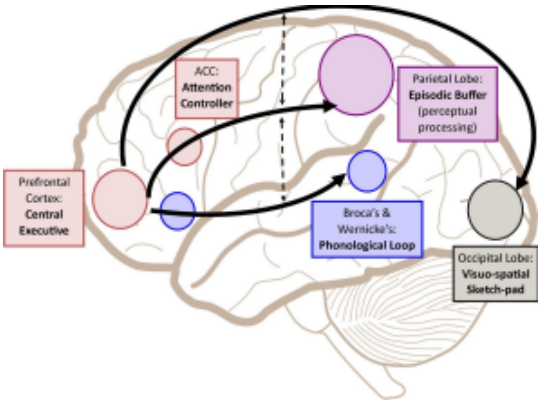


Figure 2. Simplified illustration of Baddeley's (2010) multicomponent model of working memory, demonstrating multiple cortical structures thought to be involved in various tasks (Chai et al., 2018).

Neuroimaging techniques have discovered that the frontoparietal network and regions such as Broca's and Wernicke's areas, the basal ganglia, the thalamus, and the caudate nucleus variously activate depending on the WM tasks performed (Chai et al., 2018). Lesions following traumatic brain injury to such regions (often in the frontal lobe) consistently impair WM tasks (Owen et al.,1990; Barbey et al., 2013).

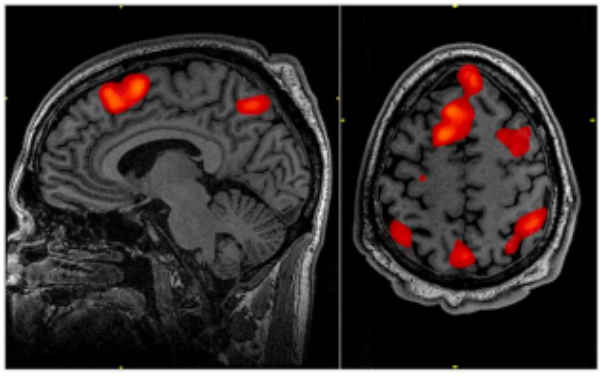


Figure 3. Highlighted regions of an fMRI scan display activity during two different working memory tasks (Graner et al., 2013).

Additionally, WM can be further explored at the genetic and molecular levels. For example, Hsiao et al.'s (2020) findings suggest that boosting or hampering the expression of the gene Gpr12, which encodes the G-protein-coupled receptor GPR12 in mammals, has substantial effects on WM. The researchers associated a higher concentration of GPR12 proteins in the thalamus of mice with better performance in WM tasks in mice, and found that performance suffered when the encoding gene was underexpressed. GPR12 is an orphan G-protein-coupled receptor, meaning its exact endogenous ligand is presently unidentified, but the path to a molecular understanding of WM is entirely conceivable. At first glance, it seems possible for cognitive neuroscience to provide an explanation of the entire causal relationship between particular states of the brain and the functioning of WM and countless other mental processes in the future. However, in the above scientific theories, something vitally important has been left out of the picture. WM is a conscious mental process, and the phenomenal awareness of mental content – one of the most basic properties that separate a conscious state from a non-conscious one – has managed to evade a reductive explanation.

The Explanatory Gap

Physicalism is often thought of in its reductive form, in which a higher-level property (such as heat) can be functionally explained in the terms of its lower-level properties (molecular motion). A reductive physicalist theory of the mind maintains that the basic elements of consciousness, subjective conscious mental states, can be translated into lower-level properties. A completely reductive understanding of the mind needs to take mental phenomena and reduce them to the language of biology, which can be further translated to chemistry and physics, neatly fitting consciousness with our best scientific theories about the world. Reductive physicalist theories of the mind have increasingly come under fire, including from other physicalists who propose that reducing subjective experience to physical terms is an impossible task. Such perspectives emphasize the epistemological limits of science, irrespective of the ontological status of the mind as physical. Nagel's (1974) widely influential article "What is it like to be a bat?" argues that consciousness means there is "something that it is like" to undergo mental states for organisms, such as bats, and that such an internal experience is inaccessible to understanding from the outside. According to Nagel, a human cannot understand what it is like to be a bat just by understanding every physical fact about the animal. Levine (1983) highlights that while we can find certain biological correlates for conscious perceptions such as pain, a scientific explanation for the actual subjective feeling of something like the slow nociceptive pain that seems to result from the activation of C-nerve fibers is nowhere to be found. The central element to these arguments against reductive physicalism is the idea of qualia: a conscious mental state has a qualitative, subjective feeling that is experienced, such as the redness of an apple or the sourness of a lemon. Perceptions like color can be reduced to physical explanations in the objective sense by understanding electromagnetism and how the nervous system converts photons into neural activity, but the

explanation lacks subjective quality, instances of which are called qualia. Trying to explain redness to a congenitally blind person is fruitless because there is, supposedly, no explanatory means to understand qualia without actually experiencing them. If non-reductive accounts of the mind are true, then the intractability of subjectivity is concerning for reductive physicalism and broader hopes that cognitive neuroscience can resolve the mind-body problem.

The gap between explaining physical systems and explaining the capacity for qualia is an important point of the contemporary debate over the mind-body problem. Some reject the commonsense idea of qualia, viewing the concept as a category mistake that requires further progress in neuroscience to truly understand (Churchland, 1985; Dennett, 1988); others posit that qualia are (however rudimentarily) a fundamental aspect of some or all physical things (Strawson, 2017). Regardless, bridging the explanatory gap is what Chalmers (1995) has coined "the hard problem" of consciousness, which every complete theory of mind must address in some capacity. The "easy problems" of consciousness, according to Chalmers, are those that are conceptually possible for a physicalist inquiry into the mind, such as a complete understanding of only the neural correlates of consciousness. As the above arguments from philosophy of mind have demonstrated, finding a place for the phenomenal awareness aspect of consciousness alongside our reductive explanations of the natural world seems to require a radical reconsideration of either qualia or reality itself.

Concluding remarks

Cognitive neuroscience has contributed to the debate surrounding the mind-body problem by narrowing the realm of possibility through the scientific study of the mind's relationship with the body. When it comes to consciousness, cognitive neuroscience may only be capable of fully explaining the far from trivial "easy problems," leaving the explanatory gap unbridged. The fundamental nature of the mind and consciousness may always remain an unsolvable mystery. Alternatively, the present difficulty in reconciling reductive physicalism with certain properties of consciousness may open the door to entirely new ways of thinking about the mind that have yet to be known or even conceptualized. Whether the mind-body problem can be ultimately solved or not, cognitive neuroscience and related fields provide valuable and practical insights into the mental processes of the elusive conscious mind.

References

1. Alkire, M. T., Hudetz, A. G., & Tononi, G. (2008). Consciousness and anesthesia. *Science, 322*(5903), 876–880. https://doi.org/10.1126/science.1149213
2. Axelrod, J. (1974). The pineal gland: A neurochemical transducer. Science, 184(4144), 1341–1348.
3. Baddeley, A. (2010). Working memory. Current Biology, 20(4), 136-140. https://doi.org/10.1016/j.cub.2009.12.014
4. Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. *Cortex, 49*(5), 1195-1205.
5. Chai, W. J., Abd Hamid, A. I., & Abdullah, J. M. (2018). Working memory from the psychological and neurosciences perspectives: a review. *Frontiers in Psychology, 9*, 401.
6. Chalmers, D. J. (1995). Facing up to the problem of consciousness. *Journal of Consciousness Studies, 2*(3), 200-219.
7. Churchland, P. M. (1985). Reduction, qualia, and the direct introspection of brain states. *The Journal of Philosophy, 82*(1), 8-28. https://doi.org/10.2307/2026509
8. Dennett, D. C. (1988). Quining qualia. In Consciousness in Modern Science. Oxford University Press.
9. Descartes, R. (1986). Meditations on first philosophy: with selections from the objections and replies (J. Cottingham, Trans). Cambridge University Press. (Original work published 1641)
10. Descartes, R. (1989). Passions of the soul. (S. Voss, Trans). Hackett Publishing. (Original work published 1649)
11. Graner, J. L., Oakes, T. R., French, L. M., & Riedy, G. (2013). Functional MRI in the investigation of blast-related traumatic brain injury. Frontiers in Neurology, 4, 16.
12. Hsiao, K., Noble, C., Pitman, W., Yadav, N., Kumar, S., Keele, G. R., Terceros, A., Kanke, M., Conniff, T., Cheleuitte-Nieves, C., Tolwani, R., & Rajasethupathy, P. (2020). A Thalamic Orphan Receptor Drives Variability in Short-Term Memory. Cell, 183(2), 522-536.
13. Jöhr, J., Pignat, J. M., & Diserens, K. (2015). Neurobehavioural evaluation of disorders of consciousness. Schweizer Archiv für Neurologie und Psychiatrie, 166(5), 163-169.
14. Nagel, T. (1974). What is it like to be a bat? The Philosophical Review, 83(4), 435-450. https://doi.org/10.2307/
15. Laureys, S. (2005). The neural correlate of (un) awareness: lessons from the vegetative state. Trends in Cognitive Sciences, 9(12), 556-559. https://doi.org/10.1016/j.tics.2005.10.010
16. Levine, J. (1983). Materialism and qualia: The explanatory gap. *Pacific Philosophical Quarterly, 64*(4), 354-361.
17. Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia, 28*(10), 1021-1034.
18. Pavel, M. A., Petersen, E. N., Wang, H., Lerner, R. A., & Hansen, S. B. (2020). Studies on the mechanism of general anesthesia. *Proceedings of the National Academy of Sciences, 117*(24), 13757-13766.
19. Shapin, S. (2000). Descartes the doctor: Rationalism and its therapies. *The British Journal for the History of Science, 33*(2), 131-154.

20. Strawson, G. (2017). Physicalist panpsychism. In The Blackwell Companion to Consciousness, 2nd edition. New York: Wiley-Blackwell, 374-90.

Deep Brain Stimulation - Advancements in Clinical Medicine, Innovation in Cutting-Edge Technology

Bilal Karim

Introduction

Scientific innovation has been incredibly influential, leading to countless breakthroughs, especially in surgical technology. These discoveries have revolutionized access to quality patient care and adequate treatment. We have seen new creations and developments in Artificial Intelligence, leading to optimized support and management for triage, and efficient reviewing of electronic health records (EHR). However, a relatively new remedy called Deep Brain Stimulation has become more prominent in the treatment of several debilitating neurological symptoms. This procedure is most commonly used to treat diseases like Parkinsons, Essential Tremors, and Epilepsy (especially focal epilepsy which originates in the frontal, occipital, temporal, and parietal part of the brain). These diseases are characterized by tremors, rigidity, stiffness, and slowed movement (National Institute for Health, 2017). DBS is considered a plausible treatment option for movement disorders, and is generally performed when medications have become less effective and begin interfering with daily life activities (UI Hospitals).

Anatomy of Deep Brain Stimulation

DBS uses a surgically implanted, battery-operated medical device called the implantable pulse generator (IPG), which is placed deep into a central location in the brain. The IPG is similar to that of a heart pacemaker, and dimensions are approximately similar to that of a stopwatch. DBS is designed to deliver electrical stimulation to localized regions of the brain that control movement, which ultimately block or inhibit the nerve signals that cause the symptoms. DBS consists of three components: the lead, the extension and the IPG. The lead (commonly known as the electrode), is a thin, insulated wire that is inserted through a small opening in the skull and positioned in the brain. Next, we have the extension component, which is an insulated wire that is passed underneath the skin, and connects the lead to the IPG. Lastly, the IPG (our “battery pack”) is the third and final part that is implanted under the skin near the collarbone. The length of the wire and the distance between the electrode will determine the ideal placement at which the IPG can be planted.

Mechanisms of DBS

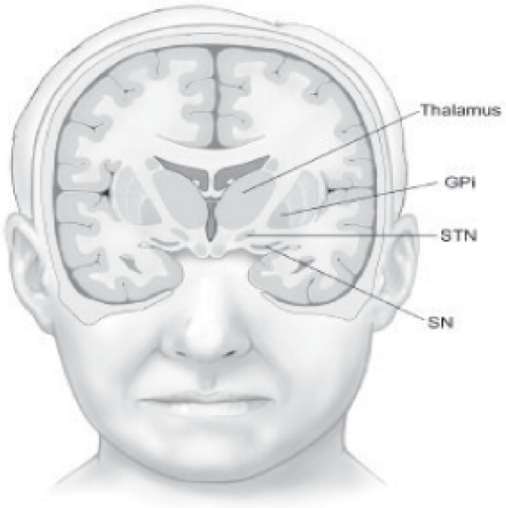
Implants have become widely accepted over the last few years and research has led to the development of several advanced designs and blueprints for them. All modern Implantable Pulse Generators (IPG) contain a radiofrequency antenna, which leads to increased usability, and enables clinicians to deploy external programming devices to monitor for impedence and for editing stored data. In ‘closed-loop’ or ‘adaptive’ DBS, the stimulator is able to measure neural activity while synchronously stimulating the target zone. These devices are increasingly taking the form of ‘apps’ on consumer-grade mobile devices such as smartphones and tablets. IPGs use proprietary radio communication protocols. More recently, sumer-grade mechanisms such as bluetooth are being utilized in order to facilitate over-the-air modifications and remote connections.

As for diagnoses, neurologists and other clinicians use powerful magnetic imaging to make a clear and concise decision regarding the exact target for surgical implantation within the brain. These regions include the subthalamic nucleus, the thalamus, and the globus pallidus. During the operation, surgeons are able to use microelectrode monitoring to improve the overall condition of the patient.

In most circumstances, DBS has been approved for a wide variety of conditions and has shown to be remarkably safe and effective (Cleveland Clinic, 2020). While symptoms may not be eliminated, they can be reduced to a tolerable amount. The results are widely dependent on the appropriate selection of patients, stimulation of the correct brain region, and precise positioning of the electrode during surgery, and evidence-based programming and medical management.

Functionality & Implementation

Parkinson’s Disease is closely linked with a significant loss in functionality of dopaminergic cells within the substantia nigra pars compacta (SNc). These dopaminergic cells also project to the striatum - a major arc of the basal ganglia (American Association of Neurological Surgery). Dopaminergic regions primarily consist of motor, cognitive, and limbic loops. The SNc has connections to locations of the brain that control both motor and non-motor functions. Two important regions, the subthalamic nucleus (STN) and the globus pallidus internus (GPi) have proven to be powerful targets for managing abnormal electrical circuits. They alleviate the symptoms of bradykinesia, motor fluctuations, and dyskinesia (John Gardner, SagePub, 2013). Following activation, the lead and electricity it emits will work to normalize brain signals, resulting in a smoother response to medication. DBS has proven to be an exciting and effective tool for treating a large spectrum of conditions, but there is a good reason that the field is only beginning to recognize its full potential. Subsequently, use of a powerful technology for modulation purposes will inevitably lead to dire consequences and serious negative risk in the case of poor implementation.



Programming Adjustment

The programming of the stimulator system is usually performed in an outpatient setting, but in some circumstances, it may be activated before the patient's discharge from the treatment facility. Generally, there is an immediate improvement in some PD symptoms, however, some patients may take up to a week or a month to notice improvements. Patients may also be admitted to a rehabilitation center, allowing clinicians to closely evaluate and monitor their response to DBS and adjust medication as needed. The endless combinations and configurations of DBS make it difficult to find a setting which is best suited to the individual. Each DBS electrode has four leads within it, of which two are activated. The lifespan of the battery should last anywhere from two to five years. A DBS programmer should regularly check on the device to ensure that there is no loss of therapy efficacy.

Research Obligations & Ethical Validity

DBS faces several prominent concerns due to its widespread adoption and establishment. A complete investigation pointed to many complexities, which have acted as impediments to the continued progression of DBS. The successful translation and interpretation of research into clinical use is thwarted by obscurity in adopting suitable clinical trials. For most experiments, blinding is unachievable, as patients are actively awake during the stimulation. Nonetheless, performing well blinded trials is easier to achieve in comparison to traditional ablation surgeries, as neurostimulators can be activated and manipulated without the need for unnecessary surgery. Additionally, DBS is an expensive tool to use and maintain. DBS is game-changing and life-saving; however, it should only be used in extremely rare and heightened emergencies due to the non-trivial risks associated with surgery (University of Virginia Health, 2021). This expense is problematic in the real world, as very few people have the resources to afford the treatment and hardware, even if the treatment warrants consideration. Increased production of low-cost IPGs would be logical, although the lack of surgical centers and providers still create barriers.

Nowadays, DBS systems rely on stimulation parameters set forth by a neurophysiologist, clinician, or even the patient. The system will remain static until manually modified. The rollout of DBS has been limited due to a wide variety of challenges in optimizing each component of the feedback (John Gardner, SagePub, 2013). IPG designs have also improved in terms of their ability to network with other devices. This networking may occur between smartphones and tablets, leading to wider accessibility. Nonetheless, the inherent cybersecurity risk does increase with wirelessly communicating electronic devices. Attackers who could potentially gain access to the IPG could cause considerable harm to patients and their clinical state.

Potential Advancements for Treatment

Refinement of DBS gives way to changes in medical applications and furthers the spectrum of improved technology. In the future, technological advancements may allow the implantation of several electrodes in the brain. This can enable the treatment and diagnosis of multiple symptoms at once, or the synergistic treatment of one symptom via multiple apparatuses. Currently, a few IPGs are highly capable of stimulating up to two different frequencies simultaneously. However, newer devices may allow new stimulation protocols to be established for each parameter that involves electrode contact with the respective region (Cedars-Sinai Medical Center, 2016). It is important to remember that DBS does not restore one's previous quality of life; it will only allow one to achieve more independence in one's daily life.

Conclusion & Constraints

As we strengthen our perspective surrounding neurophysiological contraptions, we gain a stronger perspective on how we can successfully target multiple structures in the brain for electrical modulation via DBS. DBS has single-handedly drawn out curiosity in both scientists and the general public by offering a humanitarian and scientific perspective. The indicators for DBS will continue to expand to cover a wider range of disorders. The development of more effective paradigms such as closed-loop simulations will enhance refractory movement disorders, resulting in stronger microelectrode mapping. The increase in fundamental knowledge concerning human health and mechanisms of disease have made it easier to invest in biological advancements and innovation. The next few years of modernization will be crucial, and should spark an uptick of growth, leading to a scientific revolution of sorts.

References

1. *Deep Brain Stimulation (DBS)*. Cleveland Clinic. (n.d.). Retrieved November 5, 2021, from https://my.clevelandclinic.org/health/treatments/21088-deep-brain-stimulation
2. Deep Brain stimulation. Deep Brain Stimulation | UVA Health. (n.d.). Retrieved November 7, 2021, from https://uvahealth.com/services/parkinsons-movement-disorders/deep-brain-stimulation

3. Gardner J. (2013). A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools. Social Studies of Science, 43(5), 707–728. https://doi.org/10.1177/0306312713483678
4. Pycroft, L., Stein, J., & Aziz, T. (2018). Deep brain stimulation: An overview of history, methods, and future developments. Brain and Neuroscience Advances. https://doi.org/10.1177/2398212818816017
5. U.S. Department of Health and Human Services. (2017, June 20). A noninvasive deep brain stimulation technique. National Institutes of Health. Retrieved November 11, 2021, from https://www.nih.gov/news-events/nih-research-matters/noninvasive-deep-brain-stimulation-technique
6. Spine, M. B. &. (n.d.). DBS. mayfieldclinic.com. Retrieved November 12, 2021, from https://mayfieldclinic.com/pe-dbs.htm
7. Towards the next generation of deep brain stimulation therapies: Technological advancements, computational methods, and new targets. Frontiers. (n.d.). Retrieved October 14, 2021, from https://www.frontiersin.org/research-topics/9483/towards-the-next-generation-of-deep-brain-stimulation-therapies-technological-advancements-computati
8. Update on current technologies for deep brain stimulation in parkinson's disease. Journal of Movement Disorders. (n.d.). Retrieved December 5, 2021, from https://www.e-jmd.org/journal/view.php?number=302
9. M;, D. O. M. K. J. R. U. T. (2016, August 11). Subthalamic nuclei deep brain stimulation improves color vision in patients with parkinson's disease. Brain stimulation. Retrieved January 2, 2022, from https://pubmed.ncbi.nlm.nih.gov/27591893/

The Overlap Between Neuroscience and Psychiatry: An Exploration of the Effectiveness of Neurological Applications in Treating Psychiatric Disorders

Michelle Bishka

Abstract

Neuroscience and psychiatry, once indistinguishable fields, had developed into their own disciplines over the course of the 20th century. By the end of the 20th century and the beginning of the 21st century, however, developments in neuroscience that enable psychiatric disorders to be treated in terms of structural abnormalities of the brain have led to a possible reunification between the two fields, though the fields still remain separate today.

Neuroscience and psychiatry have a historically complicated dynamic, originating as the unified field of neuropsychiatry and later diverging into two separate fields of study. Neuroscience is the study of the nervous system and the brain. A critical branch of neuroscience that is concerned with the nervous system and brain-related diseases is neurology. Psychiatry, like neurology, is also concerned with brain abnormalities, but, unlike neurology, psychiatry is the study of mental illnesses. Mental illnesses differ from neurological disorders in that they cannot be solely identified and treated through somatic, physical, symptoms and their mediation. This is because mental disorders are often associated with environmentally-induced trauma. However, as research in neuroscience develops, there is evidence to suggest that certain psychiatric disorders can be linked to structural abnormalities, like chemical imbalances in the brain, intertwining the fields of neuroscience and psychiatry once again (Baker et al., 2002). Though a trend towards reunification between the two disciplines has been established, neuroscience and psychiatry remain distinct but work in tandem for the most effective treatment of psychiatric disorders.

The treatment of psychiatric disorders in a neurological context could be seen in the 20th century with electroconvulsive therapy (ECT). The first documented case of ECT was recorded in the 1930s, known as shock therapy (Shorter, 2008). As broken down by Mayo Clinic (2018), ECT passes electrical currents through the brain to trigger a short seizure and reconfigure its chemistry in such a way that relieves the symptoms of certain mental illnesses. Controversy around ECT stems from its initial implementation, which unsafely sent high doses of electricity through the brains of patients without anesthesia, potentially leading to confusion, memory loss, broken bones, or heart complications in the patient. Developments in anesthesia eventually made ECT safer in treating psychiatric disorders, though the stigma of ECT still remains. In contrast, modern-day ECT occurs in a highly-controlled environment where the brain, heart, blood pressure, and oxygen levels of the patient are monitored as they are under anesthesia (Mayo Clinic, 2018). ECT is considered highly effective in patients who have severe depression that remained unaffected by other treatment methods, with more than 50% of severely depressed individuals experiencing improvement in their symptoms (Khalid et al., 2008). ECT has also been proven effective in treating schizophrenia, with 77% of schizophrenic individuals responding to ECT (Kaster et al., 2017). Remission post-treatment is common, with many individuals undergoing a series of ECT treatments to manage their symptoms over time (McKenna, 2021). ECT may also be coupled with other methods of treatment, like medication.

Another conversation surrounding the application of neuroscience to psychiatry surfaced with Irwin and Miller's (2007) "Depressive disorders and immunity: 20 years of progress and discovery," which developed the cytokine model of depression. In depression, it is found that signaling proteins that regulate immunity, cytokines, are produced in high concentrations in a pro-inflammatory form. Large amounts of pro-inflammatory cytokines activate enzymes that convert tryptophan, an amino acid of serotonin, into a form that can no longer be used for serotonin synthesis (Miller et al., 2013). The low levels of serotonin seem to be a cause of depression according to the "serotonin hypothesis" (Albert et al., 2012). Therefore, according to Irwin and Miller, a viable method of treating depression is to limit pro-inflammatory cytokine production through medication, as this would increase serotonin production. Depression was first explained in terms of serotonin more than 50 years ago. With new findings, the "serotonin hypothesis" has been met with inconsistencies, as explained by Paul Albert's analysis of it. Individuals without mental disorders who had their serotonin levels experimentally reduced exhibited little to no change in mood. Antidepressants that increase serotonin levels were found to not necessarily work for all individuals with depression, and antidepressants that do not raise serotonin levels can also aid in depression treatment (Albert et al., 2012). This is not to say that the "serotonin hypothesis" is not credible. The most commonly prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), which increase serotonin levels. These antidepressants are about as effective as their competitor, serotonin and norepinephrine reuptake inhibitors, which increase both serotonin and norepinephrine levels (U.S. National Library of Medicine, 2020). A study published by the U.S. National Library of Medicine (2020) evaluated the efficacy of antidepressants, revealing that 40 to 60 people out of the 100 who took antidepressants had their severe depression symptoms alleviated within six to eight weeks, while 20 to 40 people out of the 100 who took a placebo experienced the same result. Although this suggests that antidepressants improve severe

depression symptoms in about 20 people out of 100 within six to eight weeks, there are still a significant number of individuals who did not see any improvement in their severe depression symptoms despite taking antidepressants. As a result, depression is viewed to be caused by a conglomerate of environmental, psychological, biological, and chemical factors. Thus, it is important to note that psychiatry is multidisciplinary and may utilize treatment methods that are not based in neurology.

One such example of a psychiatric treatment method that is not neurologically-founded is psychotherapy, which primarily alleviates the symptoms of mental disorders that are not directly associated with complications in the physical or chemical structure of the brain. Psychotherapy is an opportunity for an individual to learn coping mechanisms for difficult situations and relieve stress that can be amplified by mental illness (Mayo Clinic, 2016). Unlike ECT, the results of psychotherapy are heavily dependent on both the therapist and the patient. According to Per Høglend's "Psychotherapy Research" (1999), an ideal therapist is able to apply psychiatric interventions to their patient and adjust these interventions according to their patient's response. A suitable patient is one that can verbalize their concerns and work well with others. The efficacy of psychotherapy is, therefore, highly contingent on the individuals involved. On average, 63 out of 100 individuals who continually participate in psychotherapy have seen progress with their psychiatric disorder, while only 38 out of 100 individuals under a placebo or minimal treatment experienced the same effect (Høglend, 1999). This indicates that 25 out of 100 people who undergo psychotherapy report a successful outcome.

The effectiveness of common psychiatric disorder treatments, ECT, medication, and psychotherapy, vary among individuals. Both neurologically and non-neurologically-based treatments have their benefits. In general, there is no large discrepancy between the effectiveness of medication and psychotherapy usage surrounding patients with moderate anxiety or depressive disorders, as seen in a study conducted by Alvine Fansi (2015). Despite this, psychotherapy seems to have longer positive effects with a reduced likelihood of relapse (Fansi 2015). According to a study led by Pim Cuijpers (2013), a similar pattern is seen in patients with panic disorder and seasonal affective disorder (seasonal depression), where the effectiveness of psychotherapy and medication parallel each other. A shift occurs with dysthymia, a severe form of chronic depression that is more effectively treated with medication than psychotherapy, and obsessive-compulsive disorder (OCD), a disorder that is more effectively treated with psychotherapy than medication (Cuijpers et al., 2013). ECT is often used as a last resort, to treat disorders that have not been improved by treatments that have lower risk and are easier to access. As demonstrated in a study led by Eric Ross (2018), ECT, in comparison to medication and psychotherapy, is more effective in treating severe depression, but has extremely high relapse rates. There is potential evidence to suggest that the relapse rates and, thus, effectiveness of ECT may improve when ECT treatment is coupled with medication (Youssef & McCall, 2014) or psychotherapy (McClintock et al., 2011), specifically in treating severe depression. Still, further investigation is required to solidify this evidence, as it originated from studies with flawed designs that require refining. Overall, all treatments of psychiatric disorders are helpful in mediating their symptoms, but their effectiveness depends on the individual and their mental illness. Thus, it is important to note that psychiatry is multifaceted. The incorporation of neurological methods in the treatment of psychiatric disorders has proven to be effective for many, but it is overly simplistic to rely solely on medication or ECT as treatment when addressing a disorder that can be better alleviated with psychotherapy or a combination of psychotherapy, medication, and ECT.

References

1. Albert, P. R., Benkelfat, C., Descarries, L. (2012, September 5). The neurobiology of depression--revisiting the serotonin hypothesis. I. Cellular and Molecular Mechanisms. Philosophical transactions of the Royal Society of London. Series B, Biological sciences. Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3405681/
2. Baker, M. G., Kale, R., Menken, M. (2002, June 22). The wall between neurology and psychiatry. BMJ (Clinical research ed.). Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11234283.
3. Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., Reynolds, C. F. (2013, June 4). The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. World psychiatry : official journal of the World Psychiatric Association (WPA). Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3683266/
4. Fansi, A., Jehanno, C., Lapalme, M., Drapeau, M., Bouchard, S. (2015). [effectiveness of psychotherapy compared to pharmacotherapy for the treatment of anxiety and depressive disorders in adults: A literature review]. Sante mentale au Quebec. Retrieved December 24, 2021, from https://pubmed.ncbi.nlm.nih.gov/27203537/
5. Høglend, P. (1999). Psychotherapy research: New findings and implications for training and Practice. The Journal of psychotherapy practice and research. Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3330564/
6. Irwin, M. R., Miller, A. H. (2007, March 13). Depressive Disorders and immunity: 20 years of progress and Discovery. Brain, Behavior, and Immunity. Retrieved December 24, 2021, from https://www.sciencedirect.com/science/article/pii/S08891 5910700027X
7. Kaster, T. S., Daskalakis, Z. J., Blumberger, D. M. (2017, April). Clinical effectiveness and cognitive impact of electroconvulsive therapy for schizophrenia: A large retrospective study. The Journal of clinical psychiatry. Retrieved December 24, 2021, from https://pubmed.ncbi.nlm.nih.gov/28297593/

1. Khalid, N., Kirov, G., Champney-Smith, K., Giles, M., Tredget, J., Atkins, M. (2008, June). The effectiveness of electroconvulsive therapy in treatment-resistant depression: A Naturalistic study. The journal of ECT. Retrieved December 24, 2021, from https://pubmed.ncbi.nlm.nih.gov/18580559/
2. Mayo Foundation for Medical Education and Research. (2016, March 17). Psychotherapy. Mayo Clinic. Retrieved December 24, 2021, from https://www.mayoclinic.org/tests-procedures/psychotherapy/about/pac-20384616
3. Mayo Foundation for Medical Education and Research. (2018, October 12). Electroconvulsive therapy (ECT). Mayo Clinic. Retrieved December 24, 2021, from https://www.mayoclinic.org/tests-procedures/electroconvulsive-therapy/about/pac-20393894
4. McClintock, S. M., Brandon, A. R., Husain, M. M., Jarrett, R. B. (2011, September). A systematic review of the combined use of electroconvulsive therapy and psychotherapy for depression. The journal of ECT. Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3162076/
5. McKenna, J. (2021, February 21). Electroconvulsive therapy (ECT) and mental illness. WebMD. Retrieved December 24, 2021, from https://www.webmd.com/schizophrenia/electroconvulsive-therapy
6. Miller, A. H., Haroon, E., Raison, C. L., Felger, J. C. (2013, March 6). Cytokine targets in the brain: Impact on neurotransmitters and neurocircuits. Depression and anxiety. Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4141874
7. Ross, E. L., Zivin, K., Maixner, D. F. (2018, July 1). Cost-effectiveness of electroconvulsive therapy vs pharmacotherapy/psychotherapy for treatment-resistant depression in the United States. JAMA psychiatry. Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145669/
8. Shorter, E. (2008, November 21). History of psychiatry. Current opinion in psychiatry. Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714299/#R25
9. U.S. National Library of Medicine. (2020, June 18). Depression: How effective are antidepressants? InformedHealth.org [Internet]. Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/books/NBK361016/
10. Youssef, N. A., McCall, W. V. (2014, November). Relapse prevention after index electroconvulsive therapy in treatment-resistant depression. Annals of clinical psychiatry: official journal of the American Academy of Clinical Psychiatrists. Retrieved December 24, 2021, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4420179/

Unlocking the Inner Genius Within

Shireen Aydogan

Abstract

People with savant syndrome are characterized by rare intellectual gifts in one or more specific areas. Acquired savant syndrome occurs, in most cases, after a Traumatic brain injury (TBI) and is associated with the development of frontotemporal dementia (FTD). Specifically damage to the left temporal lobes caused by FTD has been linked to the acquisition of savant skills. The left-right compensation theory explains the process responsible for acquiring new abilities. It explains that the inhibition of pathways on the left side of the brain, specifically the temporal lobes, can cause compensatory growth on the right side of the brain. Allan Synder's experiment utilizing transcranial direct current stimulation (tDCS) demonstrates this theory utilizing low levels of electrical current targeting the left region of the brain to stimulate the formation of new neural connections on the right side. Relatively new technologies and current research is promising to understanding acquired savant syndrome and gives light to possibilities of unlocking one's inner genius.

Introduction

For much of his adolescence Jason Padgett, a college dropout, lived a typical party life and had no interest in education, especially mathematics. All of this changed when he suffered a blow to the back of his head during an attack outside a bar one night. Padgett was rushed to the hospital and diagnosed with a concussion and a bleeding kidney. It was not long after his return home that he noticed his behavior drastically changed and that he was seeing everything from a different perspective. Padgett stated, “water coming down the drain didn’t look like it was a smooth, flowing thing anymore, it looked like these little tangent lines” (Keating, 2020). For the first time in his life, Padgett was observing everything through a peculiar lens and he knew something was quite strange. He turned to the internet with hope of an explanation to the unique vision caused by his trauma, but was unsuccessful. Oddly enough, he was finally able to explain what he was seeing with drawings, which are commonly known as fractals, or repeating geometric patterns. He realized that he acquired a rare talent for physics and mathematics in particular. Most fascinatingly, he is the only person known to date who can not only see, but also draw fractals.

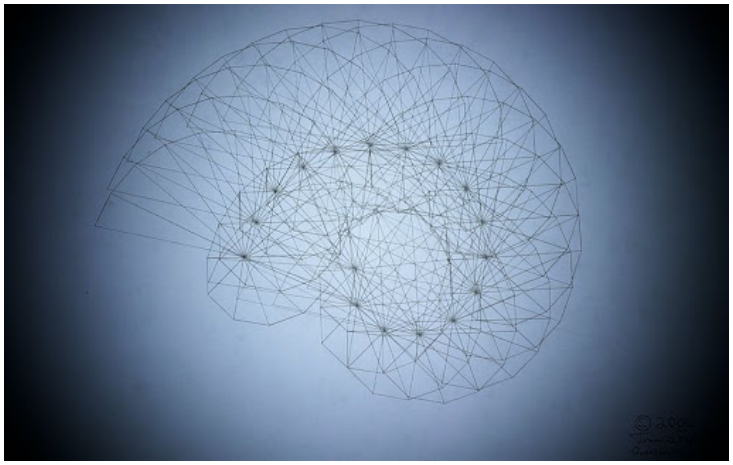


Figure 1. One of Jason Padgett’s hand drawn fractals, Quantum Nautilus. It describes the fact that all things in the universe are in constant motion and rotating around something else (Padgett, 2006)

Savant Syndrome

Jason Padgett is believed to have acquired savant syndrome. Savant syndrome is a rare condition in which people, typically who are mentally impaired, demonstrate remarkable talent. Less than 1% of individuals have been diagnosed with savant syndrome, but it is estimated that 1 in 10 people who have autism have some level of savant abilities. The characteristics of acquired savant syndrome are parallel to people with autism who have savant syndrome. The major difference is that acquired savants discover a prodigious ability that laid dormant after suffering traumatic brain injury (TBI). A TBI is a disruption in the normal function of the brain caused by a sudden injury that causes acute and irreversible damage to the parenchyma (Ng and Lee, 2019). The most severe forms of TBI can cause permanent damage and lingering side effects. Common side effects include headaches and loss of memory as well as consciousness (Argawal et al., 2020).

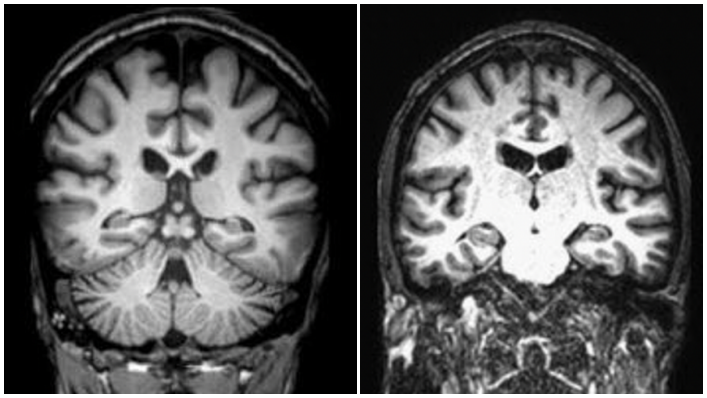


Figure 2. A comparison of coronal MRI scans demonstrating the differences in a savant (right) (Padmanaban et al., 2020) and a non savant (left) (Corrigan et al., 2012), specifically in hippocampi.

Connection between traumatic brain injury and acquired savant syndrome

While many side effects are common with TBIs, it is a particularly high risk factor for developing Frontotemporal Dementia (FTD), a deterioration of the frontal and temporal lobes. The frontal and temporal lobes of the human brain are highly developed and serve as a major differentiator

between the abilities that humans and non-humans have. FTD is typically a language or behavior disorder and affects the anterior temporal lobes (ATLs) which are the center for semantic knowledge or general information that one has acquired. The orbitofrontal cortex which is involved in social and emotional behavior is also targeted by this disease (Young et al., 2017). This specific deterioration has been unexpectedly linked to the acquisition of savant-like talent (Heaton & Wallace, 2004).

Not only is FTD linked to savant syndrome, but it seems that patients with FTD affecting the left-temporal lobe are most likely to acquire savant syndrome. A research study which investigated patients with newly acquired savant-like skills in the early stages of FTD determined that 4 out of 5 patients had the left-temporal variant of FTD. In an earlier research study, the inhibition of certain signals, specifically from the left hemisphere of the temporal lobe, was found responsible for inducing savant-like capabilities (Miller, 1998). A plausible explanation for this occurrence is the left-right compensation theory that states the inhibition of the left hemisphere can cause compensatory growth in the right side of the brain (Snyder, 2009). The formation of the new connections in the right region of the brain fosters new abilities and causes a burst of creativity.

Although savant syndrome activates specific parts of the brain through formation of new neural connections, it destroys others. People who acquire savant syndrome are rare cases of geniuses, yet most have encountered behavioral disorders connected with TBI. In Jason Pagdett's case, his TBI brought on obsessive compulsive disorder, specifically germaphobia and agoraphobia (Keating, 2020). This presents the fundamental question of whether we can tap into and become geniuses without the side effects of TBI. Looking into these possibilities, Allan Snyder, a neuroscientist at the University of Sydney, conducted an experiment using transcranial direct current stimulation (tDCS) to induce changes to cortical excitability of the left hemisphere of the temporal lobe. The subjects were asked to solve a critical thinking puzzle known as the "nine-dot" puzzle before tDCS yet all were unsuccessful. During the tDCS, 40% of participants were able to solve the same intellectual challenge (Chi & Snyder, 2016). Like people who acquired savant syndrome, the participants of this experiment expressed a unique ability that was not present before (Piore, 2013). This experiment not only demonstrated the possibility of localizing regions of the brain responsible for savant-like talents, but it also shed light on the possibility of unlocking one's inner genius.

Figure 3. Professor Allan Synder displays the device used to electrically stimulate the brain, commonly referred to as the "thinking cap" (Wynne, 2011).

Similar to acquired savants, participants of Allan Synders experienced discernible changes in their neural activity. The tDCS forced redistribution of electric circuits in the left hemisphere and in turn allowed stimulation of neurons on the right side. Although for acquired savants, damage to the temporal lobes is what ultimately allows "rewiring" of neural pathways and domination of the right hemisphere (Stan-Missouri, 2019). The ability of the brain to empower neurons to form new connections is known as neuroplasticity. That is what neuroscientists believe is responsible for the expression of a new ability that otherwise was not present, or "hiding".

Currently, tDCS is available online for a fairly cheap price and its popularity is steadily growing. In recent studies, tDCS constitutes a promising therapeutic intervention for psychiatric disorders such as people with major depressive disorder (Bennabi and Haffen, 2018). Commercial headsets have become available as well and are just one click away from users. The headset's stimulation encourages the brain to form new connections enhancing users' process of learning. Professional skiers of the Olympic National team train using electric stimulation headbands known as halo (Yuhas, 2018). Targeted audiences for companies selling tDCS also include the average student who wants to perform better in their next exam although neuroscientists have raised concerns about this practice. There are still many unknowns to what long-term side effects tDCS can have after repeated use as well as how the other regions of the brain will react. Emiliano Santarnecchi, a neurologist at Harvard medical school, also emphasized that each brain is different and that individuals may react differently to the stimulation (Yuhas, 2018).

Figure 4. LIFTiD, a commercial tDCS device available that recommends 20 minutes usage a day to maximize attention, focus, and alertness (RPW Technology, 2022).

Future research and Outlook

Despite this remarkable technology, the tDCS has not allowed people to acquire prodigious capabilities similar to the abilities of people with savant syndrome. With this being said, there are still many things about savants that are yet to be fully elucidated. Given the low prevalence rate of extraordinary savant skills, there have been limited studies including savants. While this is a setback, technology that is more sophisticated, like tDCS has allowed researchers to learn more about the brain functions, thus giving more insight to acquired savant syndrome. Through a relatively new approach to the positron emission tomography (PET) called ambulatory microdose positron emission tomography (AMPET) researchers have been able to understand more about brain activity during various activities (Freeman, 2015).

The AMPET is a wearable scanner that allows for imaging while the patient is able to freely move and perform various tasks. Experiments and innovations like these are not only promising in understanding more about the brain functions but also savant syndrome and in helping people who suffer from brain damage.

The possibilities are endless with new neurotechnology that is being developed. Neuralink corporation founded by Elon Musk is currently testing implantable brain-machine interfaces. This chip's purpose is to help paraplegics perform simple tasks that they otherwise would not have been able to complete. Clinical trials have shown promising results with rodents and monkeys and a study is ongoing with human participants. In the near future, this technology could be revolutionary and the missing piece to helping people "unlock their inner genius."

References

1. Agarwal, N., Thakkar, R., & Than, K. (2020, March 2). Traumatic brain injury. AANS. Retrieved December 18,2021,fromhttps://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Traumatic-Brain-Injury
2. Chi RP, Snyder AW. (2002, May). Brain stimulation enables the solution of an inherently difficult problem. Neurosci Lett, 515(2), 121-4. doi: 10.1016/j.neulet.2012.03.012.
3. Corrigan, N.M., Richards, T.L., Treffert, D.A. and Dager, S.R. (2012) Toward a Better Understanding of the Savant Brain. Comprehensive Psychiatry, 53, 706-717. https://doi.org/10.1016/j.comppsych.2011.11.006
4. Freeman, T. (2015, October 28) "Portable Brain Scanner Allows PET in Motion". http://medicalphysicsweb.org/cws/article/research/63031
5. Heaton P, Wallace GL. (2004, July). Annotation: the savant syndrome. J Child Psychol Psychiatry, 45(5), 899-911. doi: 10.1111/j.1469-7610.2004.t01-1-00284.x.
6. Keating, S. (2020, July 8). The violent attack that turned a man into a maths genius. BBC Future. Retrieved October 3, 2021, from https://www.bbc.com/future/article/20190411-the-violent-attack-that-turned-a-man-into-a-maths-genius
7. Miller, L. K. (1999). The Savant Syndrome: Intellectual impairment and exceptional skill. Psychological Bulletin, 125(1), 31–46. https://doi.org/10.1037/0033-2909.125.1.31.
8. Padmanaban, S., Thiruvenkadam, K., Thirumalaiselvi, M., & Kumar, R. (2020). A role of medical imaging techniques in human brain tumor treatment. International Journal of Recent Technology and Engineering, 8(4S2), 565–568. https://doi.org/10.35940/ijrte.d1105.1284s219
9. Piore, A. (2013, February 19). The Master Memories of Savants. Popular Science. Retrieved November 25, 2021, from https://www.popsci.com/science/article/2013-02/master-memories-savants/
10. Snyder, A. (2009). Explaining and inducing savant skills: Privileged access to lower level, less-processed information. Philosophical Transactions of the Royal Society B: Biological Sciences, 364(1522), 1399–1405. https://doi.org/10.1098/rstb.2008.0290
11. Emiliano SantarnecchiStann-Missouri, Eric. (2019, November 5). Your brain can rewire itself after traumatic injury. Futurity. Retrieved January 3, 2022, from https://www.futurity.org/traumatic-injury-brains-2202932-2/
12. Treffert, D. A. (2015, January 1). Accidental genius. Scientific American. Retrieved November 17, 2021, from https://www.scientificamerican.com/article/accidental-genius/
13. Wynne, P. (2011, February 11). Brain-zapping 'thinking Cap' just might work. NBCNews.com. Retrieved January 8, 2022, from https://www.nbcnews.com/id/wbna41534303
14. Lindau M, Almkvist O, Kushi J, Boone K, Johansson SE, Wahlund LO, Cummings JL, Miller BL (2000). First symptoms--frontotemporal dementia versus Alzheimer's disease. Dement Geriatr Cogn Disord. 5, 286-93. doi: 10.1159/000017251.
15. Takahata, K., & Mimura, M. (2010). Acquired savant syndrome in frontotemporal dementia. Rinsho Shinkeigaku, 50(11), 1017–1017. https://doi.org/10.5692/clinicalneurol.50.1017.
16. Ng, S. Y., & Lee, A. Y. (2019). Traumatic brain injuries: Pathophysiology and potential therapeutic targets. Frontiers in Cellular Neuroscience, 13. https://doi.org/10.3389/fncel.2019.00528
17. Bennabi, D., & Haffen, E. (2018). Transcranial Direct Current Stimulation (tDCS): A Promising Treatment for Major Depressive Disorder?. Brain sciences, 8(5), 81. https://doi.org/10.3390/brainsci8050081
18. Yuhas, D. (2021, April 8). Students are zapping their brains to get ahead in school - but evidence for the practice is limited. The Hechinger Report. Retrieved January 27, 2022, from https://hechingerreport.org/students-zapping-brains-get-ahead-school-evidence-practice-limited/

Biochemical Mechanisms of Dendritic Nonlinearities and their Application into Computational Models

Matthew Babik

Abstract

While dendritic spines make up only a small portion of the entire neuronal system, multiple intracellular mechanisms are localized to these points to trigger unique signaling pathways. Biochemical interactions of membrane channels, intracellular protein cascades, and spine morphologies all give rise to nonlinear mechanisms of signal transduction. Large branch summation events, in which multiple incoming signals are integrated towards the soma, are mediated by these mechanisms. Information on this topic is utilized within computational studies to create accurate pyramidal neural networks. However, the methods to incorporate these nonlinear mechanisms into programs can be thoroughly debated. The purpose of this paper is to discuss the advantages and disadvantages of current approaches that incorporate nonlinear signal transduction into neuronal models.

Introduction

Dendritic nonlinearities are a signaling method implemented by neurons in the prefrontal cortex (PFC) to increase the computational power of a single neuron. This type of signaling has been associated with learning-related mechanisms and higher-level cognitive functions, such as emotions (Poirazi et al., 2014). Dendrites utilizing nonlinearities tend to propagate incoming signals through vast integrative networks known as dendritic branches. The nonlinearities themselves occur directly at the spines of the dendrite which process the incoming signal and generate dendritic spikes alongside nearby spines (Spruston, 2013). The tendency for a signal to propagate towards the soma occurs by spiking, which has the ability to elicit action potentials based on its strength (Spruston, 2013). Dendritic spikes are caused by the summation of incoming signals from multiple dendritic spines. These signals can be increased or decreased by subcellular memorization mechanisms that take into account previous depolarizations (Poirazi et al., 2014). A variety of biochemical mechanisms mediate these signaling interactions and can occur locally or communally along a particular dendritic branch. Nonlinear mechanisms that are isolated to particular spines tend to occur through interactions with Na+, K+, Ca2+ cation channels (Poirazi et al., 2014). Spatiotemporal relationships between spines regulate signals and the manner in which they are processed communally. These spatial relationships utilize N-methyl D-aspartate (NMDA) receptors and their intracellular effects to regulate synaptic connections (Poirazi et al., 2014). The cyclic adenosine monophosphate response element-binding protein (CREB) transcription factor also acts relative to local signals received by a synapse. This transcription factor helps to produce proteins that induce long-term potentiation at the spine that was depolarized. The coupling of all these biochemical reactions creates the pattern of nonlinearities experienced by the neuronal network.

Biochemical Mechanisms of Dendritic Nonlinearities

Cation Channels

Ion channels on the dendritic spines of PFC neurons exhibit unique biophysical properties and can be controlled by intracellular processes. Certain mRNA are trafficked by chaperone proteins into localized dendritic locations as a consequence of synaptic activity in the area (Bramham & Wells, 2007).

Dendritic spines contain the intracellular machinery to translate these messages, thus modifications are highly regulated and able to be localized to the environment near the postsynaptic area (Bramham & Wells, 2007). These mRNA typically contain information to produce new ion channels in a dynamic system that may lead to the overexpression or underexpression of a particular channel protein.

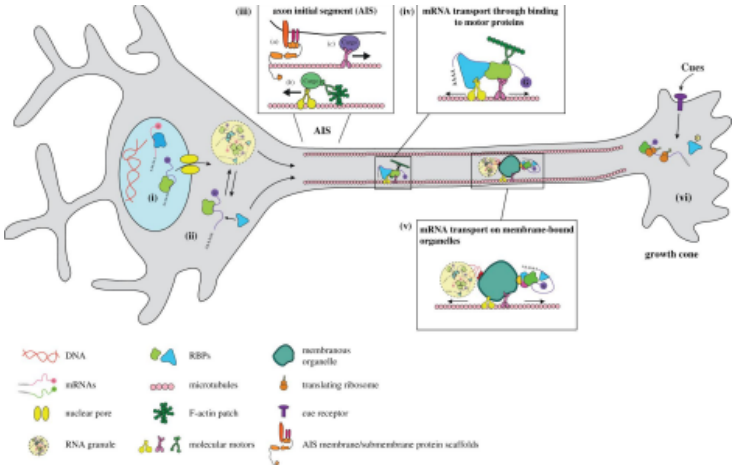


Figure 1. The localization and simulation of mRNA translation within a dendritic spine. (Benita et al., 2020)

If the activity of an ion channel is increased within these locations, the neuron will actively modify the dendrite in response to synaptic activity (Bramham & Wells, 2007). Depolarizations of particular channels are also important to maintain the integrity of the spines. The localized production of the Arg protein expands the actin cytoskeleton, which underlies the morphology of the dendritic spine (Bramham & Wells, 2007; Lo et al., 2020). This protein is transcribed locally in a spine after a depolarization event by Ca2+ions via NMDA receptor channels where it can then exert its effects (Bramham & Wells, 2007). All dendritic spines start from the actin cytoskeleton pushing on the cellular membrane to produce a small bubble. This bubble will begin to localize intracellular machinery and eventually produce a working

dendritic spine. This unique production of the Arg protein acts to maintain the stability of the spine through its interactions with the cytoskeleton and thus also maintains the synaptic connection (Bramham & Wells, 2007; Lo et al., 2020).

Post-translational modifications of ion channels elicit unique activity-dependent responses that allow for nonlinear signal propagation. These changes depend on the type of protein and the mechanism it acts with intracellularly (Shah et al., 2010). Local depolarization and plasticity of the synapse cause changes in the phosphatases and kinases present within the postsynaptic area (Shah et al., 2010). The involvement of cascade proteins creates mechanisms of biochemical backpropagation that tend to act on the ion channels. This type of backpropagation governs the activity of a particular synapse (Shah et al., 2010). For example, in CA1 dendrites, activation of protein kinases A, C, mitogen-activated protein kinase (MAPK), and extracellular signal-regulated kinase (ERK) modify A-type K+ion channels. Modification of these channels can elicit enhanced AP propagation (Hoffman & Johnston, 1998; Shah et al., 2010). A well-studied post-translational modification involves the attachment of the protein calmodulin to the Ca2+ mediated potassium channel “KCa2.2” (Shah et al., 2010). Calmodulin acts as an intermediate to attach Ca2+ and activate the channel, allowing the affinity of the protein to be regulated in order to vary the activity of K+influx (Allen et al., 2007; Xia, 1998). The phosphorylated state of KCa2.2-bound calmodulin is controlled by localized phosphatase (phosphatase 2A) and kinase CK2 (Allen et al., 2007; Shah et al., 2010). Phosphorylation of calmodulin decreases the activity of the channel due to a lower affinity of Ca2+for calmodulin (Allen et al., 2007; Shah et al., 2010; Xia, 1998). Likewise, the removal of this phosphate will increase the affinity for Ca2+. This process leads to bidirectional activation of the channel. In all, the mechanisms presented have the ability to create unique depolarizations and allow for the retention of information relative to the inputs received.

In addition, distributions of ion channels in spines also play a role in nonlinear processing (Remy et al., 2009). The inactivation of Na+ channels strongly regulates spike generation within CA1 pyramidal neurons (Remy et al., 2009; Poirazi et al., 2014). Inactivation of these channels leads to increased dendritic excitability globally in the cell (Remy et al., 2009). This feature thus aids in inducing synaptic plasticity relative to the surrounding neurons. Local distributions of voltage-gated ion channels and their properties tend to be altered after long-term potentiation (LTP) induced excitatory stimulation (Poirazi et al., 2014). These LTP stimulations decrease the peak depolarization required to elicit a dendritic spike. This change leads to a slow but permanent increase in the ability of a dendritic branch to influence the voltage of the soma (Poirazi et al., 2014; Losonczy et al., 2008). This effect is well understood and is known as branch strength potentiation (Poirazi et al., 2014). Overall, this

phenomenon shows that if plasticity is induced on a spine, it will propagate to the surrounding dendrites via A-type currents (A-type currents occur via Ca2+ mediated K+ channels) (Poirazi, 2014) Ionic conductances, particularly those with Ca2+, Na+, and NMDA, have been shown to elicit back and forward propagation of dendritic spikes (Poizari, 2014).

Spatiotemporal Associations of Dendrites

The morphological diversity of dendritic trees is capable of affecting signal conduction towards the soma. Dendritic trees act as large summation devices that will properly conduct a signal once a certain threshold has been reached. This is opposed to linear dendritic signaling which acts through simple transmission pathways (Poirazi et al., 2014). These mechanisms are developed through different voltage-dependent conductance factors, particularly via voltage-dependent ion channels (Losonczy et al., 2008). Although these factors are associated with a biophysical view of dendrites, the biochemical interplay inside the cell allows for nonlinearities to occur. The most notable biochemical system that creates these dendritic properties involves the activation of NMDA spikes. NMDA reception is tied to mechanisms of back and forward propagation of dendritic spikes (Losonczy & Magee, 2006). These methods of propagation assist in signal summation events and strengthen synaptic connections as a form of LTP induction (Remy & Spruston, 2007). However, this type of LTP induction is only performed by Parvalbumin-expressing (PV+) GABAergic interneurons (Remy & Spruston, 2007; Cornford et al., 2019).

NMDA reception can cause dendritic regenerative events known as NMDA spikes. 1 These spikes have much higher amplitude and duration than spikes generated by Na+, A-type K+, or Ca2+ mediated potassium channels (Poirazi et al., 2014). However, these spikes still have a lower amplitude than Ca2+ channel spikes2(Poirazi et al., 2014). NMDA spikes are highly localized, being almost purely confined to the dendritic branch of the overall system (Iacobucci, & Popescu, 2019). As the spike acts both forwards and backwards on the system, it is capable of affecting all the spines of a branch (Iacobucci & Popescu, 2019). This effect is described as spatial coupling and has been investigated as a mechanism for intracellular detection of spines that form a synaptic connection (Iacobucci & Popescu, 2019).

In addition to stimulation of the dendritic branch, receptor activation by NMDA can affect the processing of signals purely within dendritic spines (Iacobucci & Popescu, 2019). Spatial coupling influences the overall activity of all NMDA receptors in a spine after a particular NMDA receptor has allowed Ca2+ions to pass through (Iacobucci & Popescu, 2019). This mechanism acts biochemically through interactions with calmodulin, calcium ions, and the local NMDA receptors within the dendritic spine (Iacobucci & Popescu, 2019; Shah 2010). This form of mediation is inhibitory towards NMDA reception and serves as a method to autoinhibit the movement of Ca2+ across the membrane and prevent oversaturation of the ion (Iacobucci & Popescu, 2019).

CREB transcription factor

CREB is a multipurpose transcription factor that enables nonlinear mechanisms in dendritic spines. This protein acts to stabilize long-term memory (particularly in amygdala-related fear memorization engrams) and alters cellular machinery based on this stabilization (Poirazi et al., 2014;

Poirazi et al., 2019; Zhou, 2009). CREB enables the initiation of multiple cascade events which produce plasticity-related proteins when intracellular conditions permit such connections (Zhou, 2009; Poirazi, 2014). In particular, this transcription factor produces proteins involved in the MAPK and mTOR pathways (Zhou, 2009). Both of these cascades are involved in maintaining synaptic integrity after LTP induction. These plasticity-related proteins will eventually cause higher-level functional changes in the physiology of the amygdala by recruiting neuronal cells for the formation of fear engrams. As CREB changes neuronal conformation, it also acts on particular spines to dictate temporal and spatial synaptic cluster formation (Poirazi, 2014; Poirazi, 2019; Zhou, 2009).

The formation of synaptic clusters by CREB mechanisms also leads to the induction of the effects of NMDA spikes within a particular space of the dendritic tree, further propagating methods of nonlinear integration. Additionally, NMDA Ca 2+ channels are shown to influence the spatial dynamics of synaptic clusters during development (Kastellakis & Poirazi, 2019).

The biochemical mechanisms elicited by the CREB protein allow for compartmentalized dendritic spine generation (Poirazi, 2014; Kastellakis & Poirazi, 2019). Specifically, portions of dendritic branches utilize cluster formation as a method of localized spike induction to a particular section of the neuron (Kastellakis & Poirazi, 2019). In this interaction, the MAPK signaling pathway involves the protein Ras GTPase, which is known to increase spine volume after induction of the cascade (Kastellakis & Poirazi, 2019; Kastellakis, 2015). The number of spines is increased by inducing actin molecules from the cytoskeleton in the dendritic branch to push the membrane upward and form a localized pocket (Kastellakis & Poirazi, 2019; Kastellakis, 2015).

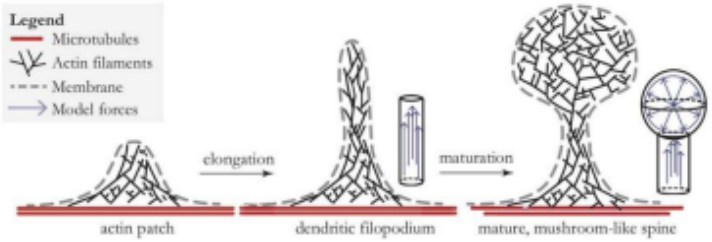


Figure 2. The creation of dendritic spines from actin filaments. (Miermans et al., 2017

An increase in spine volume is integral to synaptic cluster formation, although multiple processes are acting to produce this output (Kastellakis, 2015; Poirazi, 2014).

Modeling dendritic nonlinearities

While mathematical modeling of nonlinear networks has been capable of creating simulations that can process information similar to neurons, networks utilizing functions that integrate known biochemical mechanisms are missing. Higher-order statistical operations, while capable of creating unique integrations (structures beyond simple Hebbian networks), still exhibit faults relative to the biochemical to biophysical interplay (Cox & Adams, 2009; Stöckel & Eliasmith, 2021). Models that give further attention to nonlinear biochemical mechanisms tend to be modeled within single neuron simulations (Poirazi et al., 2003).

These simulations can better account for the large degree of spinal interactions within the “tree-like” networks seen within in vivo cell lines (Stöckel & Eliasmith, 2021; Poirazi & Papoutsi, 2020). Single neuron programs are more capable of modeling spatial and temporal interactions due to the greater ability to model spike firing. The summation of spike inputs is thus able to be based on the biochemical mechanisms mediating spine relationships (Poirazi & Papoutsi, 2020). Due to this complexity on the single-cell level, a wide variety of methods have been proposed for creating multicellular models.

In particular, the transformation functions utilized on the input vectors across neurons in these networks have used non-orthogonal basis functions (multiple correlated independent variables) (Stöckel & Eliasmith, 2021). Networks that use these basis functions linearly combine them to create a processing unit so that the movement of signals is nonlinear (Stöckel & Eliasmith, 2021). Overall, this type of transformation is an attempt to roughly model spikes created by incoming signals and their intracellular properties.

Current models also utilize varying degrees of pre-population versus post-population signal integration (Stöckel & Eliasmith, 2021; Poirazi & Papoutsi, 2020). This variation models biochemical mechanisms utilized for spike integration. Dendritic spines formed by NMDA stimulation produce synaptic clusters capable of being modeled by this population data (Poirazi & Papoutsi, 2020). As this form of integration is commonly utilized within nonlinear neural networks, these models take advantage of dendritic spike summation in order to produce

a possible output (Stöckel & Eliasmith, 2021). This enables nonlinear functions to utilize the connections of the pre-population along with those of the post-population, a property that is mediated by the biochemical mechanisms discussed (Stöckel & Eliasmith, 2021). Overall, this approach of modeling utilizes operations of synaptic filtering to produce nonlinear relationships between somatic input currents and the neural response.

A common challenge within computational neuroscience is building accurate models of the pyramidal tract that can properly integrate excitatory and inhibitory interactions into one signal. A recent method developed to navigate this issue is to separate the two pathways and afterward combine the resulting values using least squares regression optimization to find the updated weights during backpropagation (Stöckel & Eliasmith, 2021). Previous methods utilized inhibitory interneurons that mediate the incoming excitatory signal before progressing. In the new program, the inhibition function is integrated alongside the other nonlinear connections established (Stöckel & Eliasmith, 2021; Drix et al., 2020). The current method not only saves computational space but also prevents loss of signal integrity (Stöckel & Eliasmith, 2021).

Conclusion

Based on current models of dendritic nonlinearities, the ability of current computational models to accurately represent pyramidal neurons shows benefits as well as issues. While these models are capable of gaining insight into higher-order functioning based on the work of biophysical studies since the 1990s, accurate modeling of inhibition is still a problem.

Current neural engineering frameworks integrate inhibition functions with non-orthogonal functions in order to maintain the integrity of the signal. However, this only roughly approximates many of the mechanisms present within the postsynaptic cell. Multiple variables exist on the biochemical level to create the observed patterns of dendritic nonlinearities. These biochemical processes exhibit temporal and spatial relationships relative to the induction of their intracellular mechanisms. These factors lead to variations and randomness that may not be fully accounted for in the final calculation of weights within neuronal models. Due to insufficient information surrounding the biochemical mechanisms that underlie dendritic nonlinearities, it may be a better approach to utilize biophysical models for larger neuronal systems. Strictly adhering to current biochemical knowledge may create limits on the ability of these simulations to portray higher-order functioning.

References

1. Allen, D., Fakler, B., Maylie, J., & Adelman, J.P. (2007). Organization and regulation of small conductance Ca2+-activated K+ channel multiprotein complexes. J Neurosci (9)2369-76.
2. Benita, T., Cinzia, C., & J, Cioni., (2020) Molecular mechanisms behind mRNA localization in axons Open Biol.10, 200177-200177
3. Bramham, C. & Wells, D. (2007). Dendritic mRNA: transport, translation, and function, Nature rev neuroscience, 8(10), 776-89.
4. Cornford, J.H., Mercier, M.S., Leite, M., Magloire, V., Häusser, M., & Kullmann, D.M. (2019) Dendritic NMDA receptors in parvalbumin neurons enable strong and stable neuronal assemblies, *eLife* 8:e49872 DOI: 10.7554/eLife.49872
5. Cox, K. & Adams, P. (2009). Hebbian Crosstalk Prevents Nonlinear Unsupervised Learning, Frontiers in Computational Neuroscience, 3(11).
6. Drix, D., Hafner, V.V., & Schmuker, M. (2020). Sparse coding with Somato-Dendritic Rule. Neural Networks, 131, 37-49.
7. Hoffman, D.A. & Johnston, D. (1998). Downregulation of transient K+ channels in dendrites of hippocampal CA1 pyramidal neurons by activation of PKA and PKC. J Neurosci, 18(10):3521-8.
8. Iacobucci, G. J., & Popescu, G. K. (2019). Spatial Coupling Tunes NMDA Receptor Responses via Ca2+ Diffusion. J Neurosci: the official journal of the Society for Neuroscience, 39(45), 8831–8844.
9. Kastellakis, G. (2015). Synaptic clustering within dendrites: An emerging theory of memory formation. Progress in Neurobiology, 126, 19-35.
10. Kastellakis, G., & Poirazi, P. (2019). Synaptic Clustering and Memory Formation. Frontiers in molecular neuroscience, 12, 300.
11. Lo, L.H., Dong, R., Lyu, Q., & Lai, K. (2020). The Protein Arginine Methyltransferase PRMT8 and Substrate G3BP1 Control Rac1-PAK1 Signaling and Actin Cytoskeleton for Dendritic Spine Maturation. Cell Rep, 10(31).
12. Losonczy, A. & Magee, J.C. (2006). Integrative properties of radial oblique dendrites in hippocampal CA1 pyramidal neurons. Neuron. 50(2):291-307.
13. Losonczy, A., Makara, J.K., & Magee, J.C. (2008). Compartmentalized dendritic plasticity and input feature storage in neurons. Nature, 452(7186):436-41
14. Miermans, C., Kusters, R., Hoogenraad, C., Storm, C., (2017). Biophysical model of the role of actin remodeling on dendritic spine morphology. PLoS ONE, 12(2): e0170113 Poirazi, P., Brannon, T., & Mel, B., (2003) Pyramidal Neuron as Two-Layer Neural Network Neuron, 37, 6, 989-999
15. Poirazi, A., Papoutsi, A., Kastellakis, G., Psarrou, M., & Anastasakis, S. (2014). Coding and decoding with dendrites, Journal of Physiology - Paris, 108, 18-27.
16. Poirazi, P., Tzilivaki, A., & Kastellakis, G., (2019) Challenging the point neuron dogma: FS basket cells as 2-stage nonlinear integrators. Nat Commun, 10, 3664
17. Poirazi, P. & Papoutsi, A., (2020). Illuminating dendritic function with computational models. Nat Rev Neurosci, 21, 303–321.
18. Remy, S. & Spruston, N. (2007). Dendritic spikes induce single-burst long-term potentiation. Proc Natl Acad Sci USA. 104(43):17192-7.
19. Remy, S., Beck, H., & Yaari, Y. (2009). Plasticity of voltage-gated ion channels in pyramidal cell dendrites, Current Opinion in Neurobiology, 20, 503-509.
20. Shah, M. M., Hammond, R. S., & Hoffman, D. A. (2010). Dendritic ion channel trafficking and plasticity. Trends in neurosciences, 33(7), 307–316. https://doi.org/10.1016/j.tins.2010.03.002
21. Spruston, N. (2013). Information Processing in Dendrites and Spines, Fundamental Neuroscience (Fourth Edition), 231-260.
22. Stöckel, A. & Eliasmith, C. (2021). Passive Nonlinear Dendritic Interactions as a Computational Resource in Spiking Neural Networks, Neural computation, 33 (1): 96–128.
23. Xia, X.M., Fakler, B., Rivard, A., Wayman, G., Johnson-Pais, T., Keen, J.E., Ishii, T., Hirschberg, B., Bond, C.T., Lutsenko, S., Maylie, J., & Adelman, J.P. (1998). Mechanism of calcium gating in small-conductance calcium-activated potassium channels. Nature. 395(6701): 503-7.
24. Zhou, Y. (2009). CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala. Nature Neuroscience, 12(11), 1438–1443.

Using Cognitive Therapy Methods to Treat Musical Performance Anxiety

Sarah Masud

When it comes to exams, public speaking, and completing tasks in general, performance anxiety appears to be a common experience. However, it can cause significant distress and impairment, even to the point that some consider it to be a subtype of social anxiety disorder. The difference is that social anxiety is broadly concerned with embarrassment and humiliation in social situations while individuals with performance anxiety specifically fear the consequences of performing poorly. Though they aren't the same, applying cognitive behavioral therapy (CBT) shows promising results for both of them. In particular, people with musical performance anxiety (MPA) can benefit from adapted forms of CBT during private lessons.

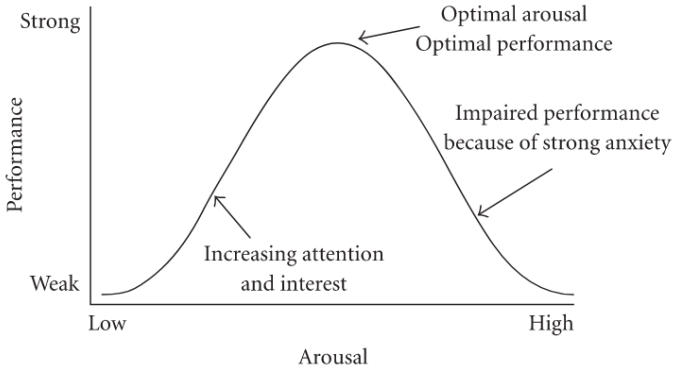


Figure 1. A moderate amount of physiological arousal is optimal for strong performance, but excessive amounts deteriorate performance quality (Wikimedia Commons, 2020).

Performance anxiety has somatic, behavioral, emotional, and cognitive aspects. Some psychologists view somatic symptoms—such as rapid heartbeat, sweaty hands, and muscle tension—as the most important ones. In fact, a study conducted by Zinn et al. (2000) found that these physical symptoms create a chain reaction that leads to anxious thoughts. Once an individual becomes aware that their heart is beating fast and their hands are shaking, it leads to more apprehension about their performance, which only heightens physiological arousal. In contrast, cognitive behaviorists argue that performance anxiety arises because of cognitive assessments of the perceived threatening situation (Bruce & Barlow, 1990). Compared to individuals who don't experience MPA, these judgments are largely negative and disproportional to the actual threat posed. Many studies following Bruce and Barlow's have reinforced that the cognitive and emotional symptoms of MPA are more significant than originally believed. These include a loss of concentration, anxious apprehension, and feelings of helplessness. This is where methods of CBT become helpful: in treating the thought processes associated with MPA.

In *Evidence-Based Practice of Cognitive-Behavioral Therapy*, Dobson and Dobson (2017) discuss how therapists can help their patients work through their negative thoughts by simply educating them about the different types of cognitive distortions and negative thinking patterns. One of the most common distortions is overgeneralization, which involves making a broad judgment based on one bad experience. In the context of MPA, a musician may feel that their performances are never good because they performed poorly one time. A similar distortion is magnification, which is giving one factor more significance than it realistically has. For example, a musician may feel that an entire performance went badly because they messed up on one section. Once these thought patterns are explained to patients, they are asked to record instances when they think these things along with the emotions and behaviors that follow them.

These are thought patterns that can be addressed not only in a clinical setting but in private lessons as well. When teachers are able to pinpoint these cognitive distortions, they can help their students replace negative thoughts with positive ones. This is the goal of CBT, and an alternative thought is meant to be recorded next to each automatic negative thought for future application. An example of a negative thought would be that a student's nerves will always take over and they will be unable to perform well no matter what. The associated emotions and behaviors are feelings of hopelessness and a lack of preparation for the next performance. This could be restructured into a positive thought if the student tries thinking that they're in control of their own thoughts and that they'll become less nervous as they gain more experience. So, the resulting situation is an increase in confidence and motivation to practice and take lessons. This is effective for less remarkably negative thoughts as well. Even replacing the thought of "don't rush this section" with "play slowly and calmly" creates more potential for a good experience.

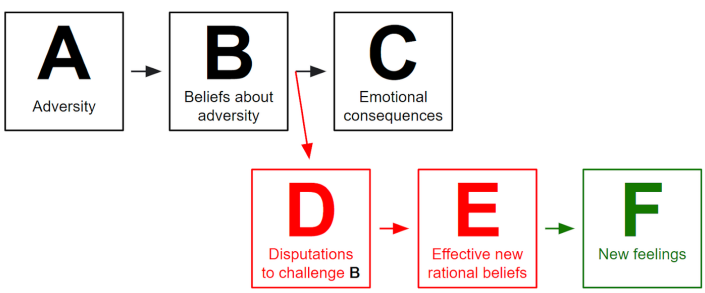


Figure 2. An example of cognitive behavioral therapy working to restructure negative thought patterns and lead to new outcomes (Wikimedia Commons, 2022).

However, it's important to note that this approach won't work for everyone and that CBT has its criticisms. Opposers argue that the methods are too mechanistic and that they fail to consider the whole perspective. Regarding MPA, cognitive appraisals are just one aspect, and addressing them won't guarantee a reduction in anxiety and the physiological and behavioral symptoms associated with it. In a related study conducted by Burns and Spangler (2001), CBT didn't show any significant treatment outcomes for 521 patients with dysfunctional attitudes. Still, many studies show that efforts to reduce negative cognitive assessments may be effective in reducing MPA—one experiment even saw greater improvements in confidence using CBT alone compared to using a combination of CBT and buspirone, an anxiety medication (Clark & Agras, 1991).

Although this adapted form of therapy is a promising approach to treating MPA, further research needs to be done to conclude whether there are more effective treatment methods. Based on current knowledge, it is effective in replacing negative thought processes to reduce the cognitive and emotional symptoms associated with MPA (Cina, 2021). If applied during private music lessons, it could show favorable results that compare to clinical treatment.

References

1. Cina, J. A. (2021). Music Performance Anxiety and Cognitive-Behavioral Therapy: Some Pedagogical Insights. *College Music Symposium*, *61*(2), 53–67. https://www.jstor.org/stable/48645698
2. File:HebbianYerkesDodson.svg. (2020, September 16). Wikimedia Commons. Retrieved 18:33, April 18, 2023 from.https://commons.wikimedia.org/w/index.php?title=File:HebbianYerkesDodson.svg&oldid=460876838.
3. File:REBT Method - Albert Ellis.png. (2022, March 4). *Wikimedia Commons*. Retrieved 18:27, April 18, 2023.from.https://commons.wikimedia.org/w/index.php?title=File:REBT_Method_-_Albert_Ellis.png&oldid=634699703.
4. Gaudiano B. A. (2008). Cognitive-Behavioral Therapies: Achievements and Challenges. *Evidence-Based Mental Health*, *11*(1), 5–7. https://doi.org/10.1136/ebmh.11.1.5

The Neurobiological Basis of the Placebo Effect and Potential Therapeutic Applications

Celeste Acosta

Two patients, Patient A and B, are diagnosed with the same chronic pain condition after a catastrophic car accident. Both patients experience the same type of chronic pain around their neck and lower back. Both patients receive the same prescription from the same doctor, except one bottle of pills does not contain any active drug. Both patients experience pain relief from their symptoms in a few weeks and improve their condition drastically with the treatment. How is this possible if only one of the patients received an active drug compound? The placebo (pla-see-boh) effect, or placebo response, can be described as the “improvement of symptoms” in an individual after receiving a substance under a certain context that is supposed to have no real therapeutic effect (Ortega et al., 2022). But what does this really mean? Is there a neurobiological basis to the placebo effect? Is there an opportunity for the usage of placebo treatments in a clinical setting? In the United States, a country largely influenced by big pharmaceutical companies, delving deeper into the biological basis and further therapeutic application might be seen as a potential threat but nevertheless, a necessary effort to make.

Favorita1987/Shutterstock

Let’s delve a little deeper into how a placebo effect works in the big complex blob that is the human brain. One of the most important factors for a placebo to work is context and setting (Cai and He, 2019). For example, it’s more likely for someone to trust the words of a confident doctor in a white coat than your average joe in a sketchy alley. When you're in the appropriate setting, neurons in your dorsolateral prefrontal cortex begin to fire (Ortega et al., 2022). This area of the brain, located right behind your forehead, is basically like the quality check controller of the brain. If the dorsolateral prefrontal cortex finds good quality information, that likely means it’s important! So this information gets sent off to other areas in the brain, specifically the areas responsible for releasing dopamine and self made opioids (Bennedetti et al., 2005).

The brain can, in fact, produce its own natural opioids called endogenous opioids, and they provide the same level of pain relief as exogenous opioids! From here the brain is releasing feel good chemicals and the placebo effect is in full speed. It can cause even greater changes in the immune system and hormone system (Ortega et al., 2022)

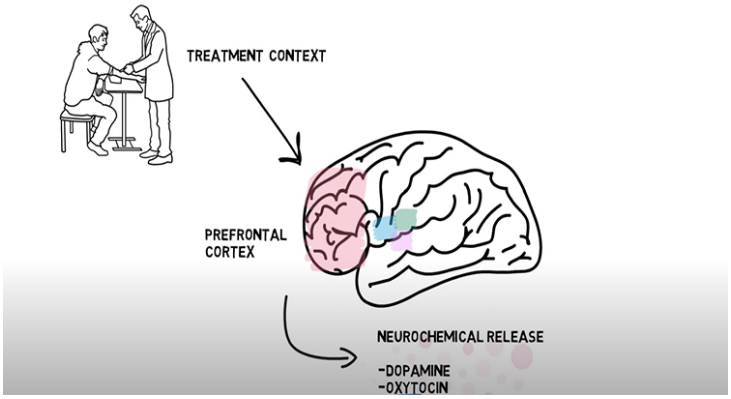


Figure 1. The context in which a placebo treatment is administered is crucial for the corresponding signals to activate the pathways starting from the prefrontal cortex (BrainFacts/SfN).

But if all it takes is to activate that prefrontal cortex, why don’t all placebo treatments work? Well, that answer is a bit more complex but has a lot to do with the context the placebo is received in and the internal beliefs of the person receiving the placebo. Belief also has a major influence on the placebo effect being successful. In fact, the main area of the brain that stores mental representations of the world in order to create our own internal beliefs is the prefrontal cortex (Sathyanarayana Rao et al., 2009). The prefrontal cortex is the area that starts to bring meaning to the signals and stimuli around us, something with meaning can be stored as an internal belief. A “stronger” belief can be correlated to more neurons firing in the prefrontal cortex, and when activated in the right setting, can produce the benefits of the placebo. The more we practice the same connection over and over, the stronger its effects (Sathyanarayana Rao et al., 2009). Similarly, if the belief is negative, and those connections are strengthened, then there won’t be a perceived change overall (“This doesn’t work!”). So, in reality, we really do become what we think.

References

1. Benedetti, F., Mayberg, H. S., Wager, T. D., Stohler, C. S., & Zubieta, J.-K. (2005). Neurobiological mechanisms of the placebo effect. *The Journal of Neuroscience, 25(45)*, 10390–10402. https://doi.org/10.1523/jneurosci.3458-05.2005

2. Cai, L., & He, L. (2019). Placebo effects and the molecular biological components involved. *General Psychiatry*, *32*(5). https://doi.org/10.1136/gpsych-2019-100089
3. Ortega, Á., Salazar, J., Galban, N., Rojas, M., Ariza, D., Chávez-Castillo, M., Nava, M., Riaño-Garzón, M. E., Díaz-Camargo, E. A., Medina-Ortiz, O., & Bermúdez, V. (2022). Psycho-neuro-endocrine-immunological basis of the placebo effect: Potential applications beyond pain therapy. *International Journal of Molecular Sciences*, 23(8), 4196. https://doi.org/10.3390/ijms23084196
4. Sathyanarayana Rao, T. S., Asha, M. R., Jagannatha Rao, K. S., & Vasudevaraju, P. (2009). The biochemistry of belief. Indian journal of psychiatry, 51(4), 239–241. https://doi.org/10.4103/0019-5545.58285

Alzheimer's and Microbes

Casey Meskovich

Introduction

For twenty-five years, professor Ruth Itzhaki's research on microbes as a possible cause of Alzheimer's diseases was dismissed and ridiculed. The idea that there could be a potential bridge between two starkly different fields–virology and neurodegeneration–seemed absurd at the time. Now, Itzhaki's work is the backbone of an ongoing, cutting-edge trial on antiviral treatments for Alzheimer's at Columbia University.

Microbes as Triggers

Evidence supporting Ithaki's theory points to herpes simplex virus 1 (HSV-1) as a driving factor in Alzheimer's disease. HSV-1 is mainly transmitted orally, and causes what is commonly known as cold sores. The mechanism of invasion is as follows: the virus invades the body, burrows into the central nervous system, and remains latent within the brain (Cox, 2023). When activated, it causes an acute inflammatory response. This activation can take place due to periods of stress, including head injuries, immunosuppression, and other comorbid infections. The multiple reactivations lead to sufficient brain damage and inflammation, facilitating the spread of the infection.

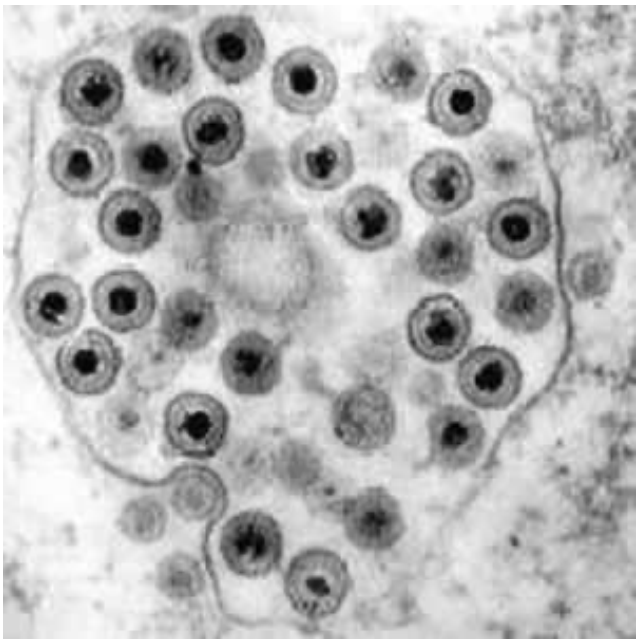


Figure 1. Herpes Simplex Virus (UTMB Home. n.d.).

While any pathogenic microbe can theoretically have a trigger role (and various bacteria have been suspected of this), there are shocking similarities in the brain regions affected by Alzheimer's Disease and the herpes simplex virus 1, leading scientists to believe that it might be implicated in the pathogenesis of Alzheimer's Disease. HSV-1 was found in the temporal, frontal, and hippocampal regions of both AD individuals and individuals only infected with HSV (Tyler, 2021). Additionally, According to Johns Hopkins Medicine, HSV-1 is very common, affecting up to fifty to eighty percent of American adults. The asymptomatic nature of the viral infection often renders it undetectable.

HSV-1 was notably the first microbe to be detected in the human brain, in both patients who were diagnosed with Alzheimer's and those who were not. This is a clear indication that infection by the herpes simplex virus 1 alone is not enough to cause disease, and another factor can determine the degree of damage caused by the virus (Itzhaki, 2022).

The VZV Pathway

A study by Tufts University suggests that another form of herpes virus, varicella zoster virus, may be one of the causative factors (Blanding, 2015). As reported by the National Institute of Health, more than ninety-five percent of people have been infected with varicella zoster virus (abbreviated VZV) before the age of twenty, usually in the form of chickenpox (Tyler, 2021).

To better understand the relationship between HSV-1, VZV, and Alzheimer's disease, Tufts researchers modeled the brain with sponges made of silk and collagen, and populated these sponges with neural stem cells. They found that neurons can be infected with VZV, but that wasn't enough to produce the characteristics of Alzheimer's disease. Interestingly, if HSV-1 was already present in a latent form, the exposure to VZV led to a reactivation of HSV-1 and a dramatic increase in both beta-amyloid proteins and tau proteins, a hallmark of Alzheimer's disease (Cairns et al., 2022).

Amyloid v. Microbial Theory

Until now, researchers have widely accepted what many call the amyloid theory as the cause of Alzheimer's disease. The amyloid theory holds that the disease can result from a buildup of amyloid beta peptides in the space between brain cells. The peptides are then cleaved from this space, allowing them to float freely and aggregate. If left untreated, the clumps aggregate into plaques, one of the defining characteristics of the disease (Cairns et al., 2022). Recent research has proved that the amyloid theory and the microbial theory are not necessarily mutually exclusive.

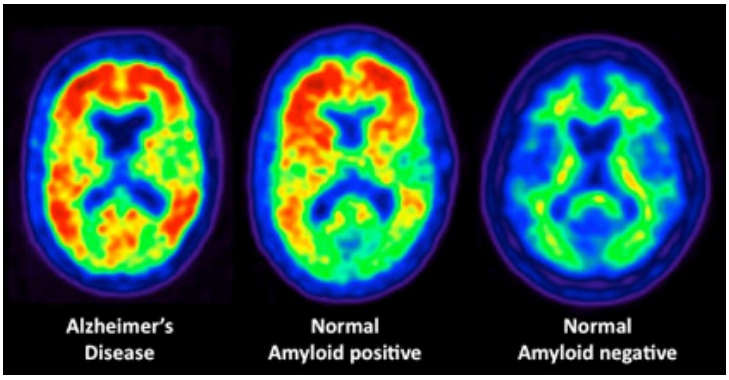


Figure 2. A PET scan by revealing the difference in presence of amyloid plaques between patients with Alzheimer's and those without (Yang, 2012).

A study by neurogeneticist Tanzi and colleagues showed that amyloid-beta has antimicrobial properties. Tanzi's study showed that this peptide was able to kill eight common pathogenic microorganisms, such as Streptococcus pneumoniae and Escherichia coli (Abbott, 2020). By glutinating and trapping various microbes, amyloid-beta is actually the brain's first line of defense, and only poses an issue when allowed to aggregate into plaques.

Aging brings the decreased ability to clear amyloid aggregates from in between neurons, allowing them to trigger a cascade of neuroinflammation. Furthermore, an age-associated waning immune system can allow microbes to proliferate more efficiently, catalyzing the development of the disease. Similarly, lifestyle risk factors of Alzheimer's, such as lack of exercise and social isolation, can also weaken the immune system and further decrease the body's ability to clear plaques (Yang, 2012).

Conclusion

Although the cause of Alzheimer's disease remains largely elusive, recent research into potential microbial origins has offered much-needed insights. Amyloid-beta plaques may be a side effect, rather than an actual cause of Alzheimer's, which could explain the relative ineffectiveness of amyloid-targeting drugs on patients.

Results of the study by Columbia University on valacyclovir, an antiviral treatment for Alzheimer's, are expected in early 2024. However, various studies have already shown the effectiveness of antivirals in preventing Alzheimer's, such as a 2018 study from Taiwan, which showed that people treated with antiviral drugs decreased risk of dementia nine-fold. Current research is now investigating the role of vaccinations in Alzheimer's.

References

1. Abbott, A. (2020, November 04). Are infections seeding some cases of Alzheimer's disease? Nature. Are infections seeding some cases of Alzheimer's disease?
2. Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections-a Nationwide, Population-Based Cohort Study in Taiwan. (n.d.). PubMed. Retrieved March 16, 2023, from https://pubmed.ncbi.nlm.nih.gov/29488144/
3. Blanding, M. (2015, April 1). *Growing the Stuff of Life | Tufts Now*. Tufts Now. Retrieved March 16, 2023, from https://now.tufts.edu/2015/04/01/growing-stuff-life
4. Devanand, D. P., Andrews, H., Kreisl, W. C., Razlighi, Q., Gershon, A., Stern, Y., Mintz, A., Wisniewski, T., Acosta, E., Pollina, J., Katsikoumbas, M., Bell, K. L., Pelton, G. H., Deliyannides, D., Prasad, K. M., & Huey, E. D. (2020). Antiviral therapy: Valacyclovir Treatment of Alzheimer's Disease (VALAD) Trial: protocol for a randomised, double-blind,placebo-controlled, treatment trial. *BMJ Journal, 10(2)*. 10.1136/bmjopen-2019-032112
5. *The innate immunity protein IFITM3 modulates γ-secretase in Alzheimer's disease*. (n.d.). YouTube. Retrieved March 16, 2023, from https://doi.org/10.1038%2Fs41586-020-2681-2
6. Itzhaki, R. (2022, November 15). *My work investigating the links between viruses and Alzheimer's disease was dismissed for years – but now the evidence is building*. The Conversation. Retrieved March 16, 2023, from https://theconversation.com/my-work-investigating-the-links-between-viruses-and-alzheimers-disease-was-dismissed-for-years-but-now-the-evidence-is-building-184201
7. Lay, P., & Cox, D. (2023, February 19). *Could Alzheimer's be caused by an infection?* The Guardian. Retrieved March 16, 2023, from https://www.theguardian.com/society/2023/feb/19/could-alzheimers-be-caused-by-an-infection
8. *Paired Immunoglobulin-like Type 2 Receptor Alpha G78R variant alters ligand binding and confers protection to Alzheimer's disease.* (2018, November 2). PLOS. Retrieved March 16, 2023, from https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1007427
9. *Potential Involvement of Varicella Zoster Virus in Alzheimer's Disease via Reactivation of Quiescent Herpes Simplex Virus Type 1*. (n.d.). PubMed. Retrieved March 16, 2023, from https://pubmed.ncbi.nlm.nih.gov/35754275/
10. Silver, M. (2022, August 2). Common Viruses May Be Triggering the Onset of Alzheimer's Disease. Tufts Now. Retrieved March 16, 2023, from https://now.tufts.edu/2022/08/02/common-viruses-may-be-triggering-onset-alzheimers-disease
11. Tyler, K. L. (2021, September 3). The Link Between Alzheimer Disease and Herpes Simplex Virus Infection: Better Late Than Never, or Better Never Than Late? National Library of Medicine. https://doi.org/10.1007%2Fs13311-021-01112-8

12. *Varicella-Zoster Virus Disease* | NIH. (2022, September 7). Clinical Info HIV.gov. Retrieved April 14, 2023, from https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/varicella-zoster
13. *Viral role in Alzheimer's Disease discovered*. (2022, August 2). University of Oxford. Retrieved March 16, 2023, from https://www.ox.ac.uk/news/2022-08-02-viral-role-alzheimers-disease-discovered
14. Yang, S. (2012, January 23). *Lifelong brain-stimulating habits linked to lower Alzheimer's protein levels* | Research UC Berkeley. Research UC Berkeley. Retrieved March 16, 2023, from https://vcresearch.berkeley.edu/news/lifelong-brain-stimulating-habits-linked-lower-alzheimers-protein-levels

Hippocampus Structure and Functions

Violet Wang

The distinction and consistency of the Dorsal and Ventral Hippocampus's functions.

"What is the name of the mythical creature with the upper body of a horse and the lower body of a fish that came with Poseidon?"
"It is Hippokampos!"

In Greek mythology, Hippokampos means seahorse, and it was later morphed into the English word hippocampus. Hippocampus, a part of the brain, gets its name because of its shape.

Figure 1. Comparison of the human hippocampus and seahorse

The hippocampus is a small seahorse-shaped structure located in the medial temporal lobe of the brain. As part of the limbic system, it is well known for its function of declarative memory formation, consolidation, and retrieval (Squire, 1992). Damage or dysfunction of the hippocampus can lead to a variety of memory impairments, such as amnesia (Zola-Morgan et al., 1986). The hippocampus is a highly intricate and multifaceted brain region that is not limited to memory processing, but also encompasses a range of other important human functions, including emotional regulation.

Let's go back to the structure of the hippocampus. According to the analysis by Moser and Moser (1998), the hippocampus may not be a single entity, but rather, the dorsal and ventral regions may have different roles. Dorsal and ventral are anatomical terms used to describe the relative positions of structures in the body or brain. Dorsal refers to the upper or back side, while ventral refers to the lower or front side. In the hippocampus, the dorsal portion is the septal pole, which is closer to the top of the brain, while the ventral portion is the temporal pole, which is closer to the bottom (Moser & Moser, 1998). Moreover, previous studies of anatomy revealed that the input and output connections of the dorsal hippocampus and ventral hippocampus are different (Swanson & Cowan, 1977).

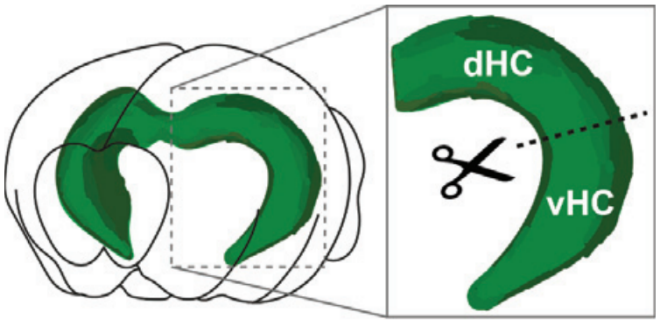


Figure 2. The diagram of the hippocampus. The hippocampus is divided in the middle into dorsal hippocampus and ventral hippocampus.

The dorsal hippocampus is associated with episodic memory and spatial navigation. In a study by Maguire et al. (1997), taxi drivers recalling complex routes through the city showed different activation patterns in the right posterior hippocampus compared to the anterior hippocampus, while language materials preferentially activated the human posterior hippocampus over the anterior hippocampus, with greater activation in the left side (Greicius et al., 2003). Anatomically, the dorsal CA1 is linked to the postpressive and anterior cingulate cortex (Cenquizca & Swanson, 2007; Vogt & Miller, 1983), two cortical regions primarily involved in cognitive processing of visuospatial information and memory, and environmental exploration (Maguire et al., 2006; Spiers & Maguire, 2006). Overall, the dorsal region of the hippocampus is more associated with cognitive processes.

The ventral hippocampus is responsible for emotions, such as anxiety and fear. Kjelstrup et al. (2002) found that lesions to the most ventral quarter of the rats‘ hippocampus led to reduced defecation in brightly lit chambers, indicating a reduction in anxiety. Additionally, studies indicate that animals with the ventral hippocampus removed tend to disregard cues associated with fear (Koh et al., 2009). In human research, the ventral hippocampus is involved across conditions of threat, safety, and conditioned inhibition, using the pairing of threat and safety cue (Meyer et al., 2019) . In terms of neuronal connectivity of the ventral hippocampus, it communicates bidirectionally with the amygdala via glutamate signaling, projecting responses to fear cues (Jimenez et al., 2018). Due to this anatomical feature, the ventral hippocampus is more associated with emotions.

Although the dorsal hippocampus is thought to be more important for spatial processing and memory, and the ventral hippocampus is primarily responsible for fear and anxious behavior, anatomical connections suggest a flow of information between the dorsal and ventral regions (Lee et al. 2019). It was found that in spatial performance, the dorsal hippocampus was mainly involved in the formation of spatial maps, while the ventral hippocampus was involved in spatial flexibility and the ability to update spatial maps (Lee et al. 2019). When dealing with fear, the dorsal CA3 results in the formation of a generalized fear response; the ventral CA3 leads to fear discrimination between the fear-inducing and safe contexts (Besnard et al.,2020). In practice, the dorsal and ventral hippocampus function as a single integrated structure.

In summary, both the dorsal and ventral regions of the hippocampus, which are "the head and tail" of the hippocampus, work separately and together to facilitate various cognitive functions to enhance quality of life.

References

1. Besnard, A., Miller, S. M., & Sahay, A. (2020). Distinct dorsal and ventral hippocampal CA3 outputs govern contextual fear discrimination. *Cell reports*, 30(7), 2360-2373.
2. Cenquizca, L. A., & Swanson, L. W. (2007). Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. *Brain research reviews*, *56*(1), 1-26.
3. Fanselow, M. S., & Dong, H. W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures?. *Neuron*, *65*(1), 7-19.
4. Greicius, M. D., Krasnow, B., Boyett-Anderson, J. M., Eliez, S., Schatzberg, A. F., Reiss, A. L., & Menon, V. (2003). Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI study. *Hippocampus*, *13*(1), 164-174.
5. Jimenez, J. C., Su, K., Goldberg, A. R., Luna, V. M., Biane, J. S., Ordek, G., ... & Kheirbek, M. A. (2018). Anxiety cells in a hippocampal-hypothalamic circuit. *Neuron*, *97*(3), 670-683.
6. Kjelstrup, K. G., Tuvnes, F. A., Steffenach, H. A., Murison, R., Moser, E. I., & Moser, M. B. (2002). Reduced fear expression after lesions of the ventral hippocampus. *Proceedings of the National Academy of Sciences*, *99*(16), 10825-10830.
7. Koh, M. T., Wheeler, D. S., & Gallagher, M. (2009). Hippocampal lesions interfere with long-trace taste aversion conditioning. *Physiology & behavior*, *98*(1-2), 103-107.
8. Lee, S. L., Lew, D., Wickenheisser, V., & Markus, E. J. (2019). Interdependence between dorsal and ventral hippocampus during spatial navigation. *Brain and behavior*, *9*(10), e01410.
9. Maguire, E. A., Nannery, R., & Spiers, H. J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain, 129*(11), 2894-2907.
10. Meyer, H. C., Odriozola, P., Cohodes, E. M., Mandell, J. D., Li, A., Yang, R., ... & Gee, D. G. (2019). Ventral hippocampus interacts with prelimbic cortex during inhibition of threat response via learned safety in both mice and humans. *Proceedings of the National Academy of Sciences, 116*(52), 26970-26979.
11. Moser, M. B., & Moser, E. I. (1998). Functional differentiation in the hippocampus. *Hippocampus, 8*(6), 608-619.
12. Moser, M. B., Moser, E. I., Forrest, E., Andersen, P., & Morris, R. (1995). Spatial learning with a minislab in the dorsal hippocampus. *Proceedings of the National Academy of Sciences, 92*(21), 9697-9701.
13. Spiers, H. J., & Maguire, E. A. (2006). Thoughts, behaviour, and brain dynamics during navigation in the real world. *Neuroimage*, *31*(4), 1826-1840.
14. Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review, 99*(2), 195–231.
15. Swanson, L. W., & Cowan, W. M. (1977). An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. *Journal of Comparative Neurology, 172*(1), 49-84.
16. Vogt, B. A., & Miller, M. W. (1983). Cortical connections between rat cingulate cortex and visual, motor, and postsubicular cortices. *Journal of Comparative Neurology, 216*(2), 192-210.
17. Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience, 6*(10), 2950–2967.

Social Media Effect on Brain Plasticity

Neha Bashir

The school bell rings amongst the sounds of high-pitched chattering of a suburban high school. Lucy, a young freshman, was the type of student to arrive to class five minutes early, already starting the assigned homework for the day. Hardworking and persistent, Lucy always achieved high grades in her studies. However, her infatuation for social media began to affect how well she was doing in class.

Every day, Lucy scrolled through her social media feeds for hours on end. Even if she had an exam the next morning, she would stay up late at night, hooked to the colorful apps of her phone. With no willpower to study anymore, her grades started to decline. She had trouble concentrating in class, and her schoolwork reflected her lack of motivation. Lucy's addiction to social media provides insight on brain plasticity and the effect social media exposure has on it. Brain plasticity refers to the brain's way of changing and adapting to new experiences, where it grows new networks of functional change from learning (Cherry, 2022). National statistics show that the average person spends roughly 3 hours on social media every day, and teenagers spend about 8 hours of phone screen time (Georgiev, 2023). By studying the correlation between excessive exposure to social media on brain plasticity we can possibly discern the real negative effects of mindlessly scrolling on attention and memory deficits.

Most high school students hone their ability to memorize facts quickly and efficiently in an effort to retain the most important information from a lesson. However, when social media excessively consumes a person's thoughts, they try using their multitasking skills to accomplish all the requirements social media demands. Studies have shown that multitasking leads to a decrease in concentration and reduction of absorption in experiences, causing memories to fade (Tamir et al, 2018). Similarly, social media has introduced the use of shorthand typing, where statements like "LOL" take place of "laughing out loud." These quick mnemonics are labeled "crutch" and are harmful in offloading relevant information and then forgetting the important information (Tamir et al, 2018). Memory has shown to have a negative relationship with social media, as it hinders people's abilities to remember information.

However, memory is not the sole victim of social media, as attention decreases just as easily from social media influence. A study was performed to determine the correlation between social media and psychological distress of attention control, where it was concluded that social media has a positive relationship with lower levels of attention control (Mahalingham et al., 2021). Using social media provides people access to control how long they want to pay attention to a certain video, picture, or text message. The brain then translates this control and applies it to other aspects of life, like being in a class where the information could be presented in a boring way. The brain can stop paying attention and focus on other things because the brain is already conditioned to be in control of how little time a person must spend on something. The figure below shows a decrease in memory consistent through the study, as well as an increase in mind wandering. As social media allows people control to swipe as fast away from a certain screen image, the brain shortens its attention span for all life events.

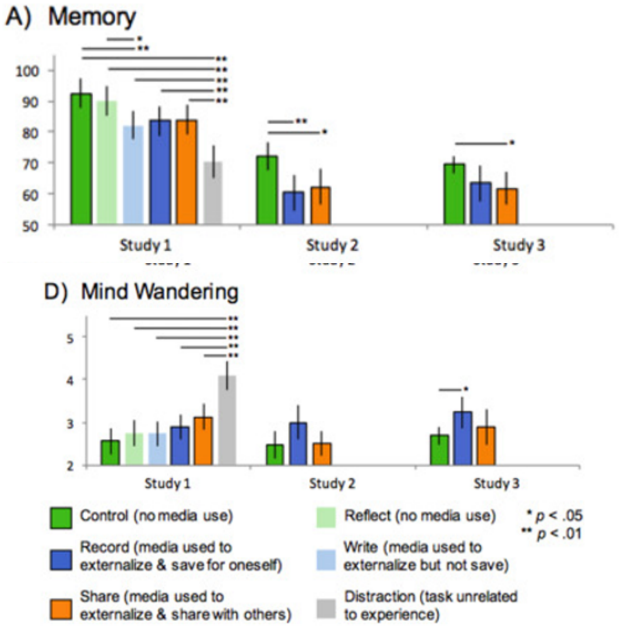


Figure 1. The figure above shows the correlation between social media use and Memory and mind wandering. Given three studies, a positive control of no media use, and two experimental of recording and sharing, it can be noted that there is a discrepancy between the three groups in memory and mind wandering. There is a decrease in memory for both experimental groups and an increase in mind wandering in recording group generally and in one case for sharing as well.

Social media platforms continue to enthrall millions of people, but it is important to note the detrimental effects it could have on brain plasticity. Social media has proven to be a useful tool to remain connected, however excessive screen time has detrimental effects on the brain, but consider just the mechanisms behind social medias affect on memory and how to mitigate the outcome.

References

1. Cherry, Kendra. (2022). “How Brain Neurons Change over Time from Life Experience.” Verywell Mind, https://www.verywellmind.com/what-is-brain-plasticity-2794886.
2. Georgiev, Deyan. (2023).“How Much Time Do People Spend on Social Media in 2023?” Techjury, https://techjury.net/blog/time-spent-on-social-media/#gref.
3. Tamir, D, et al. (2018). “Media Usage Diminishes Memory for Experiences.” Journal of Experimental Social Psychology, Academic Press, https://www.sciencedirect.com /science/article/pii/S002210311730505X.
4. Mahalingham, Tamsin, et al. (2021). “Attention Control Moderates the Relationship between Social Media Use and Psychological Distress.” Journal of Affective Disorders, https://www.sciencedirect.com/science/article/pii/S0165032721011563.

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.

Hi! My name is Sneha Mittal and I am the Treasurer and an Editor for Brain Matters. I am currently a sophomore majoring in Biochemistry on the pre-med track. Outside of Brain Matters, I work as an EMT and serve as the advocacy chair for the UNICEF branch on campus. When I am not working I enjoy spending time with my friends and exploring new things (I plan on going skydiving in a couple of weeks).

My name is Reilly Ruzella and I was an editor on Brain Matters. I graduated from University of Illinois Urbana Champaign in May 2022 with a double major in Molecular & Cellular Biology and Brain & Cognitive Science, and a certificate in Health Technology. I am currently pursuing a Master's degree in Kinesiology, which I will complete in May 2023. In Fall 2023, I plan to attend SUNY College of Optometry in New York.

Rajvi Javeri is a Junior 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 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 Evolution of Intelligent Systems 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!

Michelle is a sophomore pursuing a major in Chemistry and a minor in Computer Science. Aside from being a part of the journal, Michelle is currently working in the Silverman Lab as an undergraduate researcher. She is excited to explore the field of neuroscience by writing for Brain Matters.

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

Brain Matters Writers

My name is Alisha, and I am a sophomore majoring in brain and cognitive sciences as well as minoring in chemistry and psychology. My major allows me to learn how intelligent systems work and this includes intelligent computer systems. I get to intertwine subjects of psychology with cs and learn how they can be used together to understand the world of artificial intelligence and the idea of "what is a mind". I am also a research assistant in the Brain and Cognitive Development lab where we study the basic perceptual and cognitive abilities one is born with. We observe the development in children which can inform us on how early brain organization can inform theories of conceptual development. My personal interests in research delve into neurodivergent disorders such Austism Spectrum Disorder in children and what could possibly be utilized as a therapy for them.

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 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 Evolution of Intelligent Systems 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!

Vyapti is a Freshman majoring in psychology. She is interested in neurobiology and the workings of the mind and its connection to psychology. Outside of the academic realm, she enjoys spending time reading books and sketching. She enjoys researching topics about the brain that are both fascinating and that help bring awareness, which the “Brain Matters’ organization allows her to do. She has currently written an article on the Makings of the Antisocial Behavior type, which not only educates others on the situational and biological aspect of those with the Antisocial Behavior type, but also brings awareness, so that these cases can be better resolved, and prevented from causing chaos.

Saani Kulkarni is a rising junior majoring in Bioengineering with a minor in Computer Science. Outside of academics, she is passionate about learning from different cultures and travel, choosing to further her knowledge by working as a Global Engineering Ambassador for the school. She hopes to combine her interest in neuroscience with her skills in order to promote student awareness on campus in regard to neurodegenerative disorders.

Alex graduated from the University of Illinois Urbana-Champaign in 2023, where he majored in psychology with a concentration in cognitive neuroscience. He was a member of the Undergraduate Psychology Association and LGBTQ+ KiKi and is currently a research assistant in the Learning and Language Lab at UIUC under Dr. Jon Willits. In his free time, Alex enjoys reading and local music. He is passionate about approaching science from a philosophically informed perspective and hopes that his writing in Brain Matters will spark an interest in this point of view for others interested in neuroscience.

Bilal is an undergraduate student currently studying Biomolecular Engineering on a pre-med track. He is currently involved with a few organizations on campus: IDEA Institute, Cancer Center at Illinois, and the Carle Illinois College of Medicine. His interests align with tissue engineering, translational sciences, and the use of health technology. Additionally, he is pursuing a minor in Computer Science. Bilal is active in the research community and hopes to use more of machine learning and artificial intelligence to further automate human interaction. He loves to run, hang with friends, and listen to podcasts in his spare time. You can usually catch him on the quad going for a nice stroll.

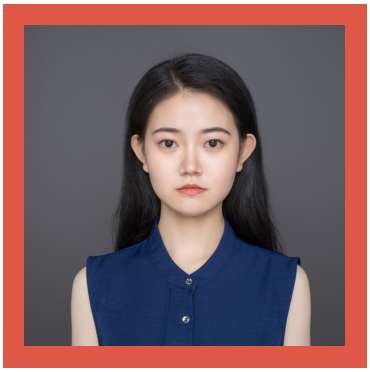
Michelle is a sophomore pursuing a major in Chemistry and a minor in Computer Science. Aside from being a part of the journal, Michelle is currently working in the Silverman Lab as an undergraduate researcher. She is excited to explore the field of neuroscience by writing for Brain Matters.

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

Matthew Babik is a sophomore in the Biochemistry major. He is pursuing an MD. Ph.D. where he hopes to study neuronal mapping techniques as a scientist and perform in utero spina bifida treatments as a medical doctor. During the fall 2021 semester, Matthew worked in UIUC's Roger Adams Laboratory where he researched yeast vacuole proteins and their potential use as homologous models for higher eukaryotic vesicles. Since high school, he has been interested in the topic of dendritic nonlinearities and neuroscience as a whole. He found that writing for the journal was a great outlet for exploring this interest.

Sarah Masud is a freshman pursuing a dual degree in Psychology and Information Sciences. She also plans to minor in Art & Design. Some of her academic interests include cognitive science, human-computer interaction, and psychiatric disorders. She enjoys drawing and visiting coffee shops as well! Outside of Brain Matters, she is also involved in the Undergraduate Psychology Association and Stitching Illini. She hopes to continue furthering her understanding of neuroscience through writing for the journal.

Hello! My name is Celeste Acosta and I'm a Senior in Molecular and Cellular Biology and Psychology! I'm from Cicero, Illinois. I'm currently training to work at the Physical and Neurocognitive Health Lab with Dr. Dominika Pindus and her team on campus. I love learning about the brain and it's wonderful ability to constantly change itself even in the most challenging circumstances! In the future I'd like to apply what I've learned about Neuroscience in a clinical setting as a Child and Adolescent Psychiatrist. In my free time I like to take pictures, read, play Animal Crossing, and spend time with my family back home!



Ruibin (Violet) Wang is a senior student at the University of Illinois Urbana-Champaign, where she is pursuing a major in Psychology with a concentration in Behavioral Neuroscience. Her passion for the field of Neuroscience and Psychology Research is reflected in her various experiences, including her current role as an Undergraduate Research Assistant in the Juraska Lab, where she studies the effect of phthalates on rats' hippocampus.

Neha Bashir is majoring in MCB Honors on the pre-med track, with a minor in Business. Her interests include neuroscience and cognitive health. She is a writer for Brain Matters, which allows her the opportunity to learn about pursue new information about the brain and nervous system. She first became interested with the brain in high school when she was provided the opportunity to hold a cadaver brain, and became inspired as she traced her fingers along the sulci and gyri. Additional to being a writer in Brain Matters, she is involved in cultural and medical clubs at UIUC, as well as being an undergraduate research assistant in the Physical Activity and Neurocognitive Health Lab. After graduating from UIUC, she hopes to attend medical school and achieve a career as a pediatric neurologist.

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.