Brain Matters

UNDERGRADUATE NEUROSCIENCE | JOURNAL

VOLUME V

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Brain Matters Board

Chief Editor

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

Assistant Chief Editor

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

Public Relations Chair

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

Editors

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

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

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

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

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

Design Board*

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

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

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 is a Junior in Brain in Cognitive Science, soon to be an MCB major with a certificate in neuroscience! She is interested in cellular neuroscience and neuropathology. Apart from her role in Brain Matters as a writer, and recently appointed Design Team member and Editor, She is a research assistant in the Physical Activity and Neurocognitive Health Lab, as well as the Evolutionary Immunology and Genomics Laboratory. After undergrad, she plans to attend grad school to conduct her own research in cellular neuroscience!

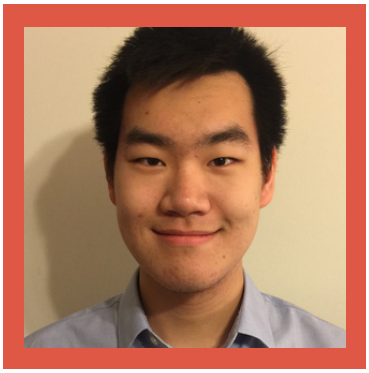
Zainab Hashmi is a sophomore pursuing a dual degree in Psychology and Information Science with a minor in computer science. Previously a writer for Brain Matters, she joined the Design board this year. She's involved in research at the Adaptive Cognition and Interaction Design Lab at UIUC, is Design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

*Due to publishing delays, Volume 5 was designed by the design board team from the 2022-2023 academic year

Brain Matters Writers

My name is Karishma Patel and I am an incoming senior studying psychology with a concentration in cognitive neuroscience. My article investigates the impact early life stress can have on child development. This paper highlights the neurodevelopmental/neurobiological changes that occur in the brain due to stressful events and circumstances early in development. Furthermore, this essay assesses how the relationship between children and their caregivers can modulate the activity of stress hormones in early life.

Apurva is a Senior majoring in Molecular and Cellular Biology with minors in Sociology and Chemistry on the pre-med track. She currently works on campus as a Research Assistant in the Physical Activity and Neurocognitive Health Lab and is a student worker at McKinley. She is excited to be a part of this volume of Brain Matters to increase discussion.



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

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

Nabiha Javed is a Student at the University of Illinois, Urbana-Champaign, who is double-majoring in political science and history. She is the author of the article, 'The Life Cycle of Neurons'.

Life Cycle of Neurons

Nabiha Javed

Neurons are one of the most important cells in the human body; they are used to signal other parts of our body to start or stop processes vital for sustaining life. Despite all of our somatic cells being bound to the process that is the cell cycle, the life cycle of neurons is something that is quite different from other cells in the human body. Our somatic cells go through the life cycle of becoming differentiated, carrying out their respective jobs, and then undergoing apoptosis once they are worn out or damaged. The majority of neurons we have in our brains are present by the time of birth, however there is evidence that neurogenesis is a lifelong process, which is a belief contrasting starkly to the previous thought that humans are born with all the neurons they were going to ever have.

Once cells in our body die, they are destroyed and are consequently replaced by new cells. Neurogenesis replaces neurons that have died, however, are not replaced by new cells in the way that other specialized cells in our body are. Neurons are limited in their capacity to proliferate. When neurons die unnaturally, the brain suffers ramifications, making way for neurological and neurodegenerative diseases such as types of dementias. In order to better understand the causes and effects of such neurological and neurodegenerative disorders, we must examine the life cycle of a neuron, from neurogenesis to death. We must also understand what the structure and function of a neuron is, and why neurons are so important to the human brain and the human body at large.

The majority of cells undergo these cycles, on average, 40 to 60 times in their lifetime; this is quite different from neurons, who often remain in a phase known as G0. G0 is a nondividing and nonreIn order to understand what the life cycle of a neuron is, it is fundamental to first acknowledge the cell cycle and its implications on the neuron's development and eventual death. The cell cycle has four main phases: G1, S, G2, and M (1). In eukaryotes, somatic cells undergo mitosis, which is where the parent cell duplicates its genetic material and splits into two subsequent daughter cells identical to its initial composition. This creates two new cells that are genetically identical to the mothering cell. Mitosis consists of 4 phases: prophase, metaphase, anaphase, and cytokinesis. After all four steps of mitosis are complete, the two resulting daughter cells are functional and complete. plicating phase of the cell cycle. Progression through the cell cycle is closely monitored by checkpoints resulting from the activation of different signalling pathways, leading to inhibition of CDK (2) and cyclin complexes. Each cell must complete the phases in order before progressing to the next one. If any defect is detected by proteins involved in regulating the cell cycle, the proteins halt the progression of the cycle until this defect is addressed. This makes it nearly impossible for a defective cell to make it past the cell cycle without being corrected, if possible, or sent into programmed cell death if the defect is too extensive to be fixed.

The central nervous system, composed of the brain and spinal-cord, is made up of 2 basic cell types, one of these types being neurons. In order to understand the functions of a neuron, it is necessary to understand the structure of a neuron. Neurons vary in their morphology depending on what variety of neuron they are, however, they all have basic structure similarities with one another. All neurons contain four distinct regions: the cell body, dendrites, axon, and axon terminals. All four of these regions serve distinct and different purposes that are vital to the function of a neuron in terms of it being a messenger cell. The cell body of a neuron, also known as the soma, contains the nucleus, which is the control center and the 'brain' of the neuron. Essentially all neuronal proteins and membranes are synthesized in the nuclei of neurons. From this cell body, the dendrites and axon branch out from the left and right, respectively. In order to communicate with each other, neurons send messages across the synapse, a gap between one neuron's dendrites and the other's axon. Most neurons have multiple dendrites, which serve to receive chemical signals originating from the axon terminals of other nearby neurons. Neurons' axons do not contain any ribosomes, and thus do not synthesize proteins. Axons are the channel by which action potential travels over a neuron, from the dendrites all the way to the end of the axon terminals of a neuron. Neurons are the cells that help our central nervous system relay messages all over our body. This makes our organ systems do what they do, and helps us respond to our environment in the ways we react.

Despite there being the previous belief of neurons dying off and not being replaced by subsequent neurons after the fact, there is now evidence neurogenesis does happen over the span of a person's lifetime. Neurogenesis, or the birth of neurons, is the process by which new neurons are created and introduced into the human body for use. Neurons are born in areas in the brain rich with neural stem cells; neural stem cells have the ability to create most, if not all, of the varieties of neurons and glial cells found in the brain and spinal cord.

After the birth of a neuron, migration occurs. Migration is the process by which neurons go to parts of the braion or spinal cord that need their services. Migration is the part of a neuron's life cycle where a lot of neurons do end up dying off, despite neurons being the longest living cells in the human body. Scientists speculate that only a third of neurons make it to their destination.

Once a neuron reaches its destination, it will differentiate in order to become a specialized neuron specific to the job it will be carrying out. Neurons are responsible for the uptake of neurotransmitters, chemicals that relay messages to the brain, and thus differentiation is an important component of a neuron's function. Unlike most other cells, neurons are believed to lose their ability to proliferate once.

This means that neurons cannot divide and make more of themselves after they have undergone the process of differentiation.

Differentiation is the process by which neurons become specialized to do specific jobs around the brain and nervous system. The ramifications of adult neurons dying leads to many neurological and neurodegenerative diseases we see, such as varieties of dementias or Parkinson's disease. Although neurogenesis is indeed a lifelong process, adult neurons have challenges in proliferating and being replaced after dying in development and migration. Neurons can die in a variety of ways, but the unnatural neuronal death that occurs occasionally in a human brain can lead to diseases and disorders. The progressive death of specific neuron populations is what is characteristic of neurodegenerative disorders. For example, Alzheimer's disease, the most common cause of dementia, is characterized by neurons reentering the cell cycle. Research has further suggested that Alzheimers involves a dysfunction in this cell cycle reentry, leading to what is known as the two-hit hypothesis of Alzheimer's disease. The first hit in this hypothesis is abnormal cell cycle reentry, typically resulting in neuronal apoptosis and thus a prevention of Alzheimer's disease in the brain. The second hit, however, involves chronic oxidative damage that prevents apoptosis of the neurons, leading to the plaques and tangles characteristic of an Alzheimer's brain. Neurons are quite apt to oxidative stress as a result of the high oxidative metabolism rate in the brain, which explains this chronic damage. Oxidative stress is also seen as a major damage to genetic material. Cells with extensively damaged DNA often will be destroyed via apoptosis to prevent complications from arising, as seen by neuronal apoptosis in the first hit in the two hit hypothesis. Other unnatural causes of neuronal death are stress, head trauma, strokes, or physical illnesses. Glucocorticoids are hormones that are released when we are stressed, and extended exposure to these substances can damage the brain, making our neurons more exposed to neurological injuries. Preventing stress in day to day life may make our brains more resistant to strokes, forms of dementias, and other types of neurological disorders.

The brain is made up of tissues, composed of various kinds of cells. Of these cells are neurons, which are the messengers and signal relayers of our brain. From birth, migration, differentiation, to death, a neuron carries out several important tasks for our wellbeing, such as taking up neurotransmitters and signaling other parts of the body on when to start and stop processes vital to the processes of living.

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Impact of Gestational Period Stress and Early Life Stressors on Child Development

Karishma Patel

Abstract

Neurobiological/neuroanatomical differences that impact development often manifest from physical defects, genetic diseases, physical trauma, and other internal factors. However, external factors have also been discovered to have a significant effect on brain structure, brain function, cognition, and emotion. This paper in particular will focus on the way gestational period stress on the mother can negatively impact a child's development in connection with the increased neurotrophic factors, depressed development, and social anxiety that forms within the child. To continue, children who undergo early life stressors, whether that be in the form of a traumatic disorder or the struggles of low socioeconomic standing show developmental changes in brain anatomy that hinder memory, emotional control, and reward pathways. Furthermore, the consequences of early childhood/prenatal stressors on development are most modulated by maternal nurturing.

Introduction

Prenatal stressors are experienced by the fetus through the intermediate of the placenta, a fetal organ with dramatic endocrine properties. While prenatal stress can enhance child development, it is the nature, magnitude, chronicity, timing of the stress, and the pregnant mother's biological/psychological response to the stress that will determine it as deleterious or not (Buss et al., 2012). During a high stress pregnancy, an increased presence of maternal cortisol can lead to a dysregulation of a placental enzyme by the name of 11-B hydroxysteroid dehydrogenase type 2 (11B-HSD2). This enzyme converts the cortisol to cortisone, thus inhibiting the amount of cortisol that crosses the placenta and reaches the developing fetus. Thus, dysregulation of this enzyme can expose the developing fetus to greater levels of cortisol (Nieves et al., 2020). Furthermore, these elevated cortisol levels that not only influence the developing fetus, but also young children who are exposed to high stress environments, act on glucocorticoid receptors that are richly abundant in areas of prolonged postnatal development, such as the hippocampus and prefrontal cortex (Pechtel et al., 2010). The glucocorticoid receptors can impair neural plasticity in these specialized brain structures, leading to deficits in cognition in specialized areas such as language, aspects of memory, executive function and emotions (Katsnelson, 2015). The relationship that children have with their caregivers is also imperative in modulating stress hormones in the early years of life.

Discussion

To begin, mothers who suffer from high stress levels in the gestational period tend to release increased placental corticotropin releasing hormone (CRH) and maternal cortisol, which in turn results in impaired fetal maturation, infant mental/motor development, and infant temperament (Buss et al., 2012). These damaging impairments include neuroendocrine dysregulation, social anxiety, and internalizing behaviors (problematic internal feelings, such as anxiety, sadness, reticence, fearfulness, and oversensitivity). A reduction in gray matter volume due to high levels of cortisol inhibiting the growth and differentiation of the developing nervous system, consequently leading to detriments in executive function, attention, learning, memory, motor control, balance, precision, coordination, is further examined in fetuses whose mothers experienced high levels of anxiety in the second trimester of pregnancy (Buss et al., 2012). The children of women who experienced high pregnancy specific anxiety levels during the early second trimester showed volume reductions in the prefrontal cortex, premotor cortex, medial temporal lobe, lateral temporal cortex, and cerebellum. These brain structures are imperative for a variety of cognitive functions such as reasoning, planning, attention, working memory, some aspects of language, and social and emotional processing including recognition and semantic memory (Buss et al., 2012). Furthermore, a study by Francheska M. Merced Nieves and colleagues suggest a potential disadvantageous effect of maternal stress on visual attention. Increased neuroendocrine responses might also condition the fetus and eventual child to have heightened enhancement for predator detection and avoidance mechanisms. While this response can prepare the fetus for any external socioeconomic stressors it may face, such as an unstable family and dangerous neighborhood, it can also increase a child's susceptibility to mental disorders such as PTSD and depression (Buss et al., 2012). To continue, elevated levels of maternal anxiety and depression have been related with an increased prevalence of fearful temperament among infants (Buss et al., 2012).

While maternal stress can negatively impact the developing fetus in a plethora of ways, stress experienced in childhood, whether due to severe traumatic events or socioeconomic standing, can also be detrimental to development. The amygdala, in particular, is highly susceptible to sensitivity due to early life stressors that these children experience. Furthermore, children who experience early life stressors show significant deficits in the affective domain and in brain regions with extended postnatal development such as the hippocampus, amygdala, and prefrontal cortex (Pechtel et al., 2010). Early life stressors seem to interfere with the neurogenesis, synaptic overproduction, and pruning of synapses/receptors, thus impairing neural plasticity and growth in the critical brain areas listed above

(Pechtel et al., 2010). To continue, dopamine cell bodies in the ventral tegmental area project to the nucleus accumbens, therefore firing reward and unpredictable rewards. Chronic stressors and early hostile rearing environments contribute to anhedonia-like behavior, low energy, and apathy in a child, and in turn resulting in blunted mesolimbic dopamine transmission. This disrupted mechanism leads to dysfunction in reward related brain activation in children exposed to early life stress (Pechtel et al., 2010). Researchers also recognized deterioration in the cerebellum as a result of early life stress to children, resulting in impaired motor learning, balance, coordination, language, visual spatial learning, and working memory (Pechtel et al., 2010).

To continue, maternal love/caregiving support has an extreme impact on reducing stress levels in young children and in preventing adverse brain changes. The detrimental effects of poverty on a child's hippocampus can be mediated by this caregiving support. Reduced hippocampal volume in children can also be attributed to a lack of maternal compassion and love (Luby et al., 2013). To continue, children with a healthy and stable relationship with their caregivers have a controlled stress hormone reaction to frightening or upsetting stimuli. Contrarily, children who are devoid of such stability and are subject to an insecure and disorganized relationship with their parents experience high cortisol levels even after the incidence of mild stressors. To continue, those who live in conditions of chronic poverty and thus experience a culmination of unfortunate conditions (such as separation from parents, family turmoil, etc.) show even more elevated stress hormone levels. Even after moving to a safer home,
young children who are neglected and abused still show abnormal patterns of cortisol production. Certain components of prenatal care, including parental discipline, parent child verbal communication, and sensitivity to the needs of the child can mediate the effects of socioeconomic standing on emotional and cognitive functioning in children.

Conclusion

The detrimental effects of gestational stress on the developing fetus, and external stress on young children (as represented by early life stressors, trauma, or socioeconomic conditions), have intense adverse effects on emotional regulation, reward response, memory, brain plasticity, and gray volume matter in the brain. However, these negative consequences can be overturned with proper maternal/parental care, support, and nurturing. Therefore, it is essential that resources to inspire and endorse support for both expectant mothers and parents that are in impoverished communities are readily available to create an enriching and supportive environment for the healthy development of the fetus and child.

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Antisense Oligonucleotides Mediated Therapy for Neurodegenerative Disease

Apurva Nayak

Abstract

Many neurodegenerative diseases like Alzheimer's disease, Huntington's disease, Duchenne's muscular dystrophy and spinal muscular atrophy are linked to aggregated, toxic proteins. Antisense oligonucleotide-based strategies (ASOs) are the most direct method of targeting gene expression. Synthetic oligonucleotides bind to the target mRNA by Watson-Crick hybridization and can either promote the degradation of RNA or inhibit it. In 2016, two ASO therapies for spinal muscular atrophy and Duchenne muscular dystrophy were approved by the FDA.

Introduction

Many neurodegenerative diseases: Alzheimer's disease, Huntington's disease, Duchenne's muscular dystrophy, and spinal muscular atrophy, are linked to the aggregation of toxic proteins in the nervous system. Although significant strides have been made in studying the mechanisms of neurodegenerative diseases, the consequent advancements in therapies for treating them have been slower. Antisense oligonucleotide-based strategies (ASOs) are the most direct method of targeting gene expression. ASO strategies utilize synthetic oligonucleotides which bind to the target mRNA by Watson-Crick hybridization and can either promote or inhibit the degradation of this RNA, leading to a knock down of gene expression.

In 2016, two ASO therapies for spinal muscular atrophy and Duchenne muscular dystrophy were approved by the FDA. This marked a shift in the direction of treatment strategies towards antisense oligonucleotides (ASOs). ASOs can target gene expression through a variety of mechanisms including altering the splicing of pre-mRNA, blocking mRNA translation or preventing the assembly of ribosomal complexes. The main complication in ASO therapies is that oligonucleotides cannot cross the blood brain barrier and thus, require invasive forms of delivery. This article will discuss mechanisms of ASO-therapy, challenges in its clinical applications, FDA-approved ASO therapies, and future development.

Mechanisms of ASO-Therapy

Many neurodegenerative diseases: Alzheimer's disease, Huntington's disease, Duchenne's muscular dystrophy, and spinal muscular atrophy, are linked to the aggregation of toxic proteins in the nervous system. Although significant strides have been made in studying the mechanisms of neurodegenerative diseases, the consequent advancements in therapies for treating them have been slower. Antisense oligonucleotide-based strategies (ASOs) are the most direct method of targeting gene expression. ASO strategies utilize synthetic oligonucleotides which bind to the target mRNA by Watson-Crick hybridization and can either promote or inhibit the degradation of this RNA, leading to a knock down of gene expression.

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While maternal stress can negatively impact the developing fetus in a plethora of ways, stress experienced in childhood, whether due to severe traumatic events or socioeconomic standing, can also be detrimental to development. The amygdala, in particular, is highly susceptible to sensitivity due to early life stressors that these children experience. Furthermore, children who experience early life stressors show significant deficits in the affective domain and in brain regions with extended postnatal development such as the hippocampus, amygdala, and prefrontal cortex (Pechtel et al. 2010). Early life stressors seem to interfere with the neurogenesis, synaptic overproduction, and pruning of synapses/receptors, thus impairing neural plasticity and growth in the critical brain areas listed above (Pechtel et al. 2010). The corpus callosum, which connects various aspects of cognitive, motor, and sensory functioning at different stages across development, decreases in size due to early due to early life stressors.

In addition to recruiting cellular enzymes, ASOs can also directly cleave target RNA if they are designed with their own enzymatic activity. This is usually done by associating DNAzymes and ribozymes with ASOs. ASOs can also modify RNAs to alter their stability and promote or inhibit degradation. ASOs also participate in direct translation inhibition by sterically blocking ribosomes. This steric block is formed when ASOs bind to mRNA and prevent the association of the 40s and 60s ribosomal subunits during translation. Furthermore, ASOs can modulate the splicing of RNA into mature mRNA transcripts. ASOs destabilize splice sites by binding to intron-exon junctions thereby preventing the binding of splice factors. If the disorder is known to be caused by a splicing defect, it is suggested that ASOs with this mechanism of action are used to return to normal function. Usage of ASOs in this case can either promote a return to the original reading frame or can simply exclude the mutated DNA segment of the gene.

Current ASO Therapies

As of 2019, the FDA has approved only 3 ASO-mediated therapies for neurodegenerative diseases:

eteplirsen for Duchenne muscular dystrophy, nusinersen for spinal muscular atrophy and inotersen for familial amyloid neuropathy.

Duchenne muscular dystrophy is caused by a mutation in the gene DMD (human Duchenne Muscular Dystrophy) that codes for the protein dystrophin. Usually, DMD mutations result in a premature truncation of dystrophin. The ASO used by eteplirsen acts on the pre-mRNA of DMD and excludes exon 51. This causes a re-establishment of the reading frame and results in partial restoration of DMD function.

Spinal muscular atrophy (SMA) is the result of a deficiency of the 'Survival of Motor Neuron' (SMN) protein caused by a loss of function mutation in both copies of the SMN1 gene located on chromosome 5. In the treatment of spinal muscular atrophy, the gene SMN2 is targeted to offset the SMN protein deficiency. SMN2 is a homologous gene to SMN1 except it does not contain exon 7. The severity of SMA increases as the copy number of the SMN2 gene decreases. The ASO nusinersen prevents the splicing silencer that removes exon 7 from the SMN2 gene. As a result, the SMN2 gene produces the SMN protein.

Challenges in Clinical Application

While some successful therapies have been developed, one of the main issues in using ASO-mediated therapies for neurodegenerative disorders is effective delivery of the drug to the brain. Antisense oligonucleotides are too large to cross the blood brain barrier. In order to reach the brain, the therapy is delivered through the spinal cord by injection into the cerebrospinal fluid.the spinal cord is the pathway of delivery that must be used. Cerebrospinal fluid (CSF) is produced by the choroid plexus and is stored in cerebral ventricles in the brain as well as in the spinal cord. ASOs can be safely administered by injecting them directly into CSF in the spinal cord. The first phase of human clinical testing of an ASO targeting the gene SOD1 showed that the drug was successfully and safely injected into the CSF but only reduced the mutant SOD1 protein expression by about 12%.

There is also the issue of sustainability for long term usage of ASO-mediated therapies. Chemically modified ASOs can have longer half-lives. For example, the modification 2'-O'methoxyethyl can be added to ASOs. This increases binding affinity to mRNA and has a half life of 6 months or more.

ASO-mediated therapies are still relatively new and many improvements need to be made to existing therapies before they can be considered a standard treatment. Improving the specificity to targets is very important to prevent any off-target effects. During the development of ASOs, two main methods are used to study and improve specificity. The first is quantitative PCR to appraise the mRNA expression when treated with ASOs. This method can be used to study where mismatches occurred and whether or not the mismatched binding to the ASO resulted in any changes in gene expression of the target. The second method is transcriptome analysis or RNA-sequencing of mouse tissues. The tissues extracted from mice do not have the mRNA target and are studied for expression changes when treated with the ASO.

ASO-mediated therapies can also be modified to enhance their pharmacokinetic properties like binding affinity and resistance to endogenous nucleases. For example, Modifications from 2' to 4' positions constrain the sugar and result in stronger binding as well.

It is also important that long-term and side effects are studied before the therapies are implemented. There are two possible reasons for off-target effects, hybridization dependent or independent. As ASOs are streamlined to be more efficient and their effects become more widespread, the off-target effects are likely to pose a larger problem. For example, as ASO sequences get shorter, the risk of mismatched complementary binding rises and this leads to a larger risk of influencing the expression of non-target RNAs.

Future Development

As a new type of therapy, ASOs can still be refined and applied to a broad variety of diseases outside of the few known so far. For example, ASOs mediated by RNase H are the most common mechanism of ASO therapies. However, target RNA suppression can also be achieved by other mechanisms. The modulation of splicing is very promising as an alternative ASO mechanism. In this case, attuning splicing can result in an out-of-frame deletion that consequently causes nonsense decay of the transcript which overall, results in protein knockdown.

Most of the current ASO-mediated therapies work by degrading RNA; the opposite, increasing RNA expression, however, is a much more complicated endeavor. In vivo, increasing the levels of proteins is a delicate task because there are not many genes to which this strategy is applicable. Gene therapy and targeting inhibitory antisense transcripts in a process called antisense-mediated derepression are mechanisms of achieving increased protein levels, in vivo. Liang et al. (2016) used ASOs to increase the efficiency of mRNA translation. This study used ASOs that targeted open reading frames upstream of the target sequence to increase translation and thus increase protein levels.

After the approval of ASO therapies for DMD and SMA, the potential of ASOs has been significantly broadened. For example, ongoing studies are developing ASO-mediated therapies for Huntington's and Alzheimer's. Huntington's disease is caused by repeats of the sequence CAG in the gene HTT that codes for a polyglutamine section in the protein huntingtin. This same polyglutamine section is the site of mutations that lead to a number of other neurodegenerative diseases like spinocerebellar ataxias. ASOs are being developed to silence the CAG section of huntingtin, but the issue with this approach is that it may cause downregulation of nontarget sequences that contain CAG. Other approaches include using ASOs to target the mutated HD allele, specifically polymorphisms of individual nucleotides, that a large majority of HD patients have.

With regard to Alzheimer's, ASOs can be used to target the protein tau. Alzheimer's falls under the category of tauopathies, where tau is hyperphosphorylated and accumulates to form tangles in neurofibers. ASO-mediated approaches are being developed to silence tau by targeting a number of different points in the gene expression pathway.

This includes binding and blocking the start codon, splice factors or sequences. So far, the most successful approach has involved using ASOs to create an out-of-frame deletion by skipping specific exons that ultimately reduces tau protein levels.

Concluding Statements

ASO-mediated therapies have shown to be a novel approach to treating neurodegenerative diseases. A lot of development and further research needs to be done to broaden the scope of applications of this therapeutic strategy. ASOs, as a new therapy, have a lot of room for improving specificity, efficiency, and rates of activity. Further research needs to be done on enhancing ASO selectivity without increased off-target binding. As ASOs become a more prominent method of treating neurodegenerative diseases, it is important to study its applications to non-neurological disorders.

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How To Improve Memory

Andrew Zhang

Abstract

Memory is important in learning and is built over time and practice. Not all memory strategies are built equally. Recent evidence in both neurological and practical settings suggests that specific strategies can increase memory performance. Compared to traditional block studying, strategies such as the testing effect, spacing effect, interleaving, chunking, and the method of loci significantly improve the efficiency of encoding new memories.

Our abilities to handle novel situations and utilize critical thinking depends heavily on our ever-expanding memory. While activities like problem solving and learning require persistence and effort, studies suggest there are ways to optimize our time and increase our efficiency to remember new things. Since the late 1800's, research has been uncovering how our memory works. Psychological theories on memory paved the road for our understanding of memory, and many classrooms conducted applied research to test the efficacy of different learning techniques. Recently, neurological studies on memory are also corroborating the evidence seen in older psychological studies.

A prominent method for learning is the testing effect, which indicates that practicing knowledge with test-based questions improves learning significantly. While exams may serve as a gauge for people's knowledge in the classroom, researchers have begun to realize their potential as an effective and robust learning method. The testing effect is seen through improved long-term memory, when the memory is retrieved during studying. Studies have shown that short answer questions enhance long-term memory the best, while other testing methods like multiple choice questions or simple recall were not as effective (McDaniel et al., 2007). Methods like repeated studying and rereading proved less valuable than just one intermittent test (Carpenter, 2009).

Recent neurological studies show increased activity in the brain from the testing effect, more so than other studying methods. For example, in learning Dutch-Swahili translations through the testing effect, participants' left inferior parietal and left middle temporal lobes activated in fMRI (van den Broek et al., 2013). The same activity was not seen in traditional studying strategies, like repeating the lesson (van den Broek et al., 2013). In another study, for learning associations between nouns, the testing effect activated hippocampal regions, the prefrontal cortex, and the posterior cingulate cortex, which are brain regions involved in memory retrieval cues (Wing, 2013). On the other hand, these brain regions were much less active in the restudy condition, suggesting that the testing effect is more effective at utilizing brain resources to encode memory (Wing, 2013).

The testing effect proved robust in many different kinds of examinations and different subjects (Agarwal et al., 2008). Even tests that are quite different from the actual examination proved beneficial for memory (Carpenter, 2009). Evidence leads many experts to believe that the testing effect can improve learning and problem solving in addition to memory. When it comes to learning and memorizing new things, a simple test or two can be very helpful. The important implication is that even a bad testing session is more effective than rereading notes or textbooks.

While tests may substantially improve memory, it is not necessary to overload oneself with large exams. Researchers would most likely suggest the opposite, that by spacing material into reasonable learning sessions we can achieve a higher retention for the particular subject. This idea was first proposed by Hermann Ebbinghaus, who suggested that memory follows a forgetting curve, when information fades from memory over time. This loss of retention is best counteracted by learning and reviewing during separate occasions, rather than learning in only one sitting (Ebbinghaus, 1913). This strategy for maximum retention became known as the spacing effect. It is the relationship between memory acquisition and the spacing of time to review the material. When studying is spaced out, information tends to encode better in long term memory. In other words, memory is improved significantly with the help of spacing.

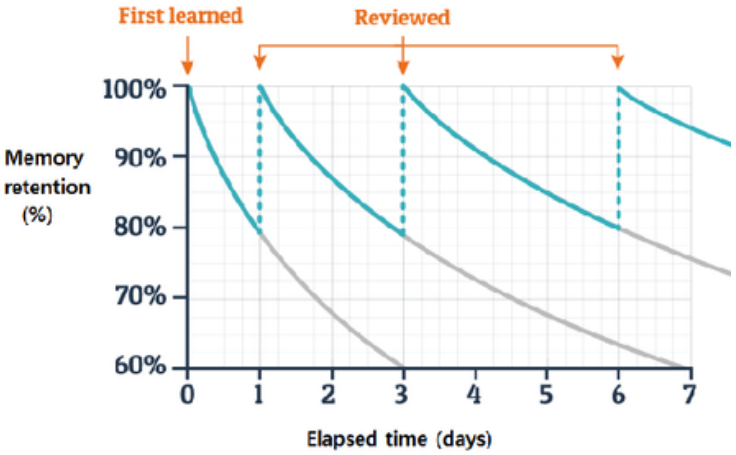

Figure 1. A schematic of the forgetting curve. The curve gradually lengthens with each review session, representing better retention with each review (Chung & Heo, 2018).

Spacing has seen success in a variety of practical situations, especially the classroom setting. For example, in a study conducted on 5th graders, students were required to learn difficult English vocabulary in one of two strategies: one taught in mass study (everything at once) while the other re-taught (spaced repetition) after a 7-day gap (Sobel & Kapler, 2010). The students performed equally well after the first session of learning, but 5 weeks after the last learning session, those with spaced repetition performed significantly better (Sobel & Kapler, 2010). Another example was seen in a study with children who were tasked to remember certain toys.

Children who were allowed to play in between learning each toy were able to memorize the toys at a significantly better rate compared to children who learned the toys all at once (Vlach et al., 2008). Despite greater distraction for children playing between each learning session, their brains were able to consolidate information better (Vlach et al., 2008).

Recently, neurologists have studied memory, like the forgetting curve and the spacing effect, in the brains of animals. The hippocampus appears to be crucial in retaining memory. In one experiment (Snyder et al., 2005), rats were tested on a water maze. They were required to learn and memorize the location of a platform in the maze. Rats were also injected with 5-bromo-2-deoxyuridine (BrdU), which labels newly synthesized cells. Compared to normal rats, those with their hippocampus damaged through irradiation performed significantly worse in the water maze only after a few weeks, and showed decreases in BrdU in neurons, meaning less formation of new neurons (Snyder et al., 2005). It is hypothesized that new neurons in the hippocampus were not necessary for learning, since mice with a damaged hippocampus performed equally well with normal rats (Snyder et al., 2005). However, new neurons are necessary for retention of memory, as seen by a drastic forgetting curve without them. A second experiment was conducted, where two groups of rats either learned a water maze in either a single mass session (all at once) or with spacing. The rats with spaced learning performed significantly better than those without, and spaced repetition were correlated with more BrdU labeled cells in the hippocampus, suggesting neurological changes due to the spacing effect (Sisti et al., 2007). Overall, these studies point to the impact of the spacing effect on the preservation of new neurons, which in turn helps retain more information.

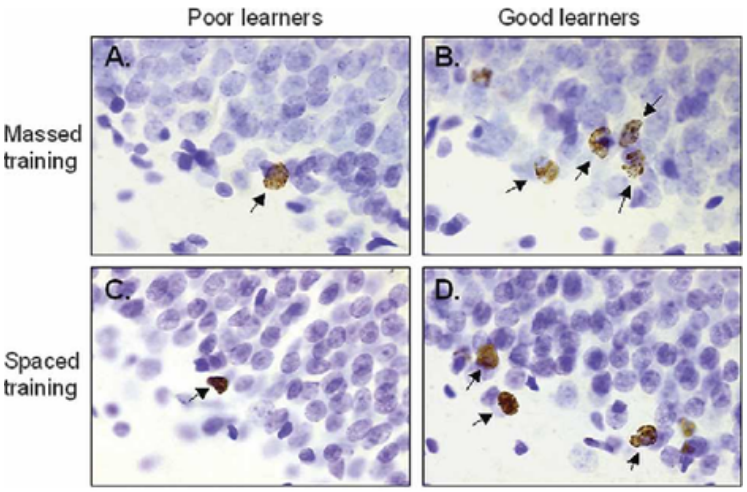

Figure 2. Learning correlated with BrdU-labeled cells (Sisti et al., 2007).

In recent years, it is found that even the spacing effect can be further improved upon in strategies that make learning and memory consolidation more efficient. A similar but relatively new approach of learning is interleaving, or mixing subjects together while learning. For example, one can learn both math and English concepts in the same hour, alternating between the two subjects every couple of minutes. Many interleaving techniques inevitably introduce spacing effects. Concepts from one subject are separated in time in order to sandwich concepts from a different subject. However, even while controlling for spacing, studies suggest that interleaving promotes stronger associations with similar concepts and stronger differentiation between different concepts (Kange & Pashler, 2011). Basically, interleaving helps improve and sharpen memory.

In one study, subjects were tasked to learn and identify paintings by the artists. One group was shown 6 paintings of each painter all at once. A second group had mixed the orders of paintings. Both groups were then administered distractor tasks to perform. When tested for the paintings later, the mixed group performed significantly better at identifying painters (Kornell & Bjork, 2008). Another study followed up with a similar setup. This time, the two groups were tested with no mixed order, but the spacing of time between each painter and painting pair was changed. This resulted in no significant difference in performance. In the same study, another setup included mixed orders, which were shown either simultaneously or spaced with time. Again, the two groups performed equally well and also out-performed the previous two groups (Kang & Pashler, 2011). Based on these findings, it appears the spacing effect was not responsible for improving in associations. Rather, interleaving is responsible for improving the ability to differentiate and associate pieces of information.

Not only does interleaving improve associations and differentiations, it has been shown to improve test performance in a practical setting. For example, in the following study (Rohrer & Taylor, 2007), interleaving improved math scores for students practicing math problems. Spacing was not controlled for (students were not doing multiple math problems at the same time), which resembles a more practical classroom setting. The students were split into three groups. One group learned and practiced math through mixed topics (interleaving). Another group practiced through blocked review, practicing one concept at a time. A third group also used a blocked review but included overlearning, meaning they completed multiple problems testing a single concept at a given time. Referred to as the masser group, they solved twice as many problems as the original block group. The interleaving group overall did the same amount of problems as the masser group but spread at intervals the same size as the original block review. When tested, the masser group performed only slightly better than the original block group. However, the interleaving group performed significantly better than both groups. This suggests that additional practice is only useful for learning if spaced and mixed.

Studies on the neurological basis of interleaving are novel. In one study, (Lin et al., 2011) participants were required to perform serial (ordering) tasks, requiring some but minimal upper body motion. In order to do so, participants must learn a specific sequence. One group learned through block training, and another through interleaving. The participants were studied under fMRI blood-oxygen-level-dependent signals (BOLD) and excitability in the primary motor cortex (M1) through transcranial magnetic stimulation. During retention (learning phase), BOLD in prefrontal and sensorimotor regions and M1 excitability were higher in the interleaving group. Initially, the interleaving group performed tasks with slower

reaction time than the block training. However, after 5 days, the interleaving group experienced faster reaction times. M1 excitability was still higher, but BOLD in prefrontal regions were weaker compared to the block training group. These results suggest that interleaving produces higher activity in parts of the brain for learning, as seen by BOLD. Over time, the brain incorporates the information. This makes retrieval more efficient, requiring less activity in brain regions as seen by decreased BOLD. M1 excitability shows higher activation of relevant brain regions in completing tasks. It is plausible other areas of the brain are also easily excitable when activated through interleaving.

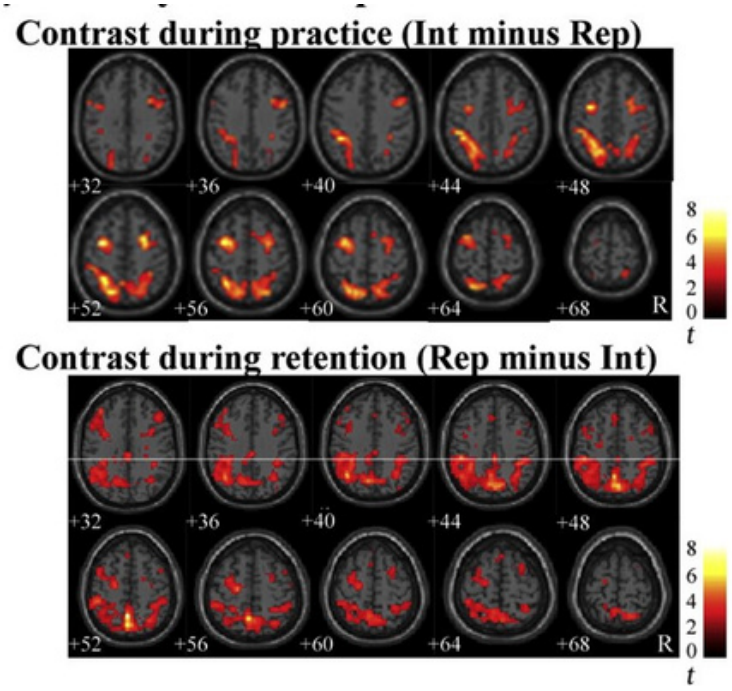

Figure 3. Increased blood flow was higher during practice in individuals with interleaving (top image, bottom row). During the retention phase, interleaving showed less blood flow activity compared to the control (bottom image, bottom row). Presumed that interleaving is more efficient, requiring less effort during retention (Lin et al. 2011).

The incorporation of ideas and information into long term memory is incredibly important. To effectively use one's memory, one must also be able to retrieve information and use it. Much of that brain power relies on working memory, which is closely tied to short term memory. Additionally, any new pieces of information must first go through the short term memory before it can be stored in the long term memory.

The working memory allows the brain to act on or even modify information. For example, the brain can imagine breaking a chair without one actually breaking the chair in real life. Short-term memory cannot incorporate an infinite amount of information at the same time, however. In a very famous historical paper, George Miller estimates the limit to be 7±2 pieces of information (Miller 1956). However, the limit is actually not definite. Some pieces of information, known as chunks, contain multiple pieces of information together as one group. The chunk does not yet have a rigorous definition in the scientific community, but it is thought to be a group of information that the brain handles as one entity. In other words, a single chunk will consist of many pieces of information while taking less space in working memory. However, chunks do not completely bypass Miller's estimate. Further studies have shown the capacity of the brain to handle up to 4±1 chunks (Crowan, 2010), which is clearly less than Miller's original estimate. Because chunks themselves contain more information, each chunk takes up more space in working memory than a single item.

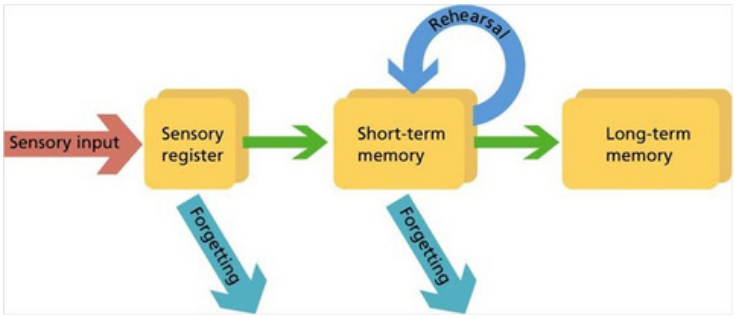

Figure 4. Basic schematic of encoding and retaining memory (Esteve 2016)

In a recent study conducted, participants were required to memorize a sequence of numbers. Depending on how many numbers were contained in each chunk, the maximum chunks the brain can handle varied. When chunks were only one number each, the limit was about 7. When chunks became very long, around 5 numbers each, the brain could only handle about 3-4 chunks (Mathy & Feldman, 2012). This corroborates the idea that the brain has a capacity for working memory, even when chunking. Despite this, chunking still helps carry more information in working memory than individual pieces of information alone.

The ability to use chunking effectively improves memory usage and memory consolidation dramatically. For example, studies conducted show that chess players rely on chunking entire movesets in a given board, like helping players remember where individual pieces are on a board, given only a few seconds to see the board (Linhares & Brum, 2007). It is also shown that pattern recognition in games like chess correlates with skill (Linhares & Brum, 2007).

Some neurological insights into chunking have corroborated with previous studies on its efficacy. For example, in one study (Bor et al., 2003), participants were required to memorize spatial patterns. One group had a disruption in learning at a random point in time. Another had a disruption specifically in between two different sets of information, establishing meaningful chunks in the participants' memory. The second group performed much better, and in fMRI brain scans, their prefrontal cortex was also lit up more (Bor et al., 2003). Chunking produces higher activity in brain regions important for processing information, chunking and improving short term memory. Ultimately, with chunking, higher activity allows for better consolidation of information.

While most memory and learning techniques were developed recently, there are some ancient techniques still used today, like the method of loci. Also known as the "memory palace," people would imagine putting pieces of information in each "room" of a building they are familiar with. Retrieval of memory simply requires finding the right "room." The technique was first used by ancient Greeks to memorize speeches, and now it is used in memory competitions, allowing people to effectively memorize large chunks of information (Dresler et al., 2017). Additionally, the memory

technique is just as effective when using locations in virtual reality as in with real locations (Legge et al., 2012). The memory technique is uniquely a mental construct, but it provides tangible improvements for information consolidation.

Using the method of loci effectively requires practice and training (Legge et al., 2012). To test for the effectiveness of the memory palace, a study was conducted on older subjects to practice memorizing a list of words. The subjects were trained in the method of loci during the study. The adults who were asked to utilize the memory palace technique performed significantly better at remembering words compared to the control (Gross et al., 2014). On pieces of paper, those who used the method of loci remembered words in the correct order, and even left spaces in between for words they forgot (Gross et al., 2014).

Neurological correlates also indicate the effectiveness of the method of loci. For example, in a neurological study conducted on memory athletes and control participants, those who utilized the method of loci performed significantly better than other strategies, like active or passive learning, even up to at least 4 months later (Dresler et al., 2017). In an fMRI scan done on the participants during memory consolidation and retrieval, those who trained with memory of loci had heightened activity between visual lobes, temporal lobes, and default mode networks (Dresler et al., 2017). It is believed that the method of loci promotes increased connectivity between different parts of the brain, promoting memory consolidation.

Evidence-based research in effective memory techniques is relatively new. While some methods were well-known since ancient times, most have only been uncovered recently. Neurological studies on the effects of memory techniques are currently ongoing but already substantiate the techniques. Despite the significantly improved performances from these techniques, many participants in these studies believed traditional studying strategies were more effective. As researchers begin to understand more of these memory techniques, it is crucial that people learn to understand the importance of these techniques as well. Learning new material can require effort, but there are always strategies to make learning and memorizing easier and more efficient.

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Why Do We Procrastinate?

Apil Mahat

Abstract

Procrastination is defined as the voluntary postponement of important tasks while being aware of the negative consequences. This phenomenon is found to be very common in undergraduate students with over 70% claiming to be frequent procrastinators. The origin of procrastination can vary from person to person, however in general this behavior is the result of many biological and psychological factors. Thankfully, through specific training methods we can adjust our behavior and increase our behavior.

Procrastination is to put off something intentionally and habitually. In most contexts people procrastinate on work tasks, school tasks, home chores or any other work that people find difficult/ inconvenient. Procrastination has a negative connotation as it implies that someone is too lazy to complete a task and they deliberately push away from doing the task in favor of something less important. Procrastination affects the majority of the global adult population to some degree with the main demographic being college students and young adults. According to an article titled “The Nature of Procrastination”, approximately 80-90 percent of college students procrastinate regularly with 50 percent admitting that habitual procrastination negatively impacts their academics. (Steel, 2007). Habitual procrastination in students can not only lead to poor academic performance but can lead to many mental and physical problems such as self-induced stress, low self-esteem, weight gain any many other negative side effects caused by the loss of time due to procrastination. Because of its harmful nature, it would make sense for students to avoid this behavior; however, there are many inherent biological and psychological factors that leave some students to be more or less likely to procrastinate (Klassen et. al., 2008).

A college student deliberately not doing their homework or studying in favor of hanging out with friends for a single night is not very problematic. The issue that many students have is a consistent inability to do tasks in a timely and organized manner, leading to assignments and other work to be done last minute and result in lower quality. This may be attributed to many things such as social media, social events, decreasing attention span, etc. all of which are due to short term distractions and can be easily remedied (Klassen et. al., 2008). However, there are also other phenomena such as the procrastination paradox that can cause habitual procrastination (Whitbourne, 2012). Susan Whitbourne, a PhD professor of psychological and brain sciences at the University of Massachusetts Amherst explains the phenomena in her article “The Paradox of Procrastination”. The overall concept of the paper is that when faced with a daunting task such as studying for a difficult exam, students will be dismayed from studying because of the high difficulty. Because they don’t want to study, they are likely to procrastinate, the procrastination leads to last minute exam preparation and thus a poor exam grade. Because of the poor grades, students will believe that they are unable to do well in their class which then makes studying for the next exam even harder and thus leads to chronic procrastination. This constant cycle can result in more than just wasted time, overtime poor academic performance and lack of confidence and motivation can lead to decline in mental health because of self-induced stress. High stress levels can then make many other aspects of a student’s life more difficult. For example, high stress can lead to many physical complications such as heart disease, obesity and other unwanted physical effects on students (Witbourne, 2012).

Because of the very negative effects that procrastination has on students it would make sense to avoid it all costs. Initially it would seem that the cause for procrastination would be completely psychological, with behavioral factors like motivation and self-regulation being the only explanation (Harris, 2019). However, there are physical predispositions in the brain that cause some students to be more likely to procrastinate than others (Jaffe, 2013). The biggest physical culprit for chronic procrastination is the interaction between the limbic system and prefrontal cortex in our brain. The limbic system and prefrontal cortex are two regions of our brain assigned to regulate completely opposite functions. The limbic system is the part of our brain associated with emotion and other more primitive functions such as eating, pleasure/reward system, reproducing and controlling of chemicals such as dopamine and serotonin. The prefrontal cortex is associated with controlling more intelligent functions such as reasoning and logic. In the context of procrastination, the limbic system leans toward seeking short term pleasure and the prefrontal cortex is more rational and leans toward getting tasks done early to reduce stress. Because all students are unique it is possible for some students to have a stronger acting prefrontal cortex that allows them to better act off rational decisions and make them less likely to habitually procrastinate. On the opposite side there are also students that have a stronger limbic system making their emotional/ thrill seeking side stronger than their rational decision-making side, thus leading to students that are more likely to procrastinate regardless of psychological aspects such as willpower or motivation.

Although there are physical predispositions that make some students more susceptible to procrastinating, the main reasons behind procrastination are psychological. Some factors that affect how well a student performs are self-regulation and self-esteem. A study done by Robert M. Klassen in the journal “Contemporary Ducational Psychology,” Klassen takes many psychological factors

such as self-regulation, academic self-efficacy and self-esteem and surveys students to see if factors that affect procrastination rates also affect GPA (Klassen, 2008). In the experiments 261 students were surveyed to rate how well they were able to self-regulate, their self-esteem, their academic self-efficacy (the definition of self-efficacy being one's belief in themselves to succeed), and how often they procrastinate on a numeric scale.

The values that the students gave were then compared to the student's GPA. The results of this experiment show that when students that were unable to self-regulate their time, they struggled with procrastination and had lower GPA's than students that identified as having good self-regulation of time. The demographics that had the most trouble with procrastination and had the lowest academic performance were those that lacked self-esteem and self-efficacy (Klassen, 2008) . This shows that in some students procrastination has less to do with time management and laziness but more to do with their lack of self confidence in the ability to do a difficult task, making them less likely to want to do it and thus increasing their procrastination rates and decreasing their academic performance.

Now that we know procrastination is due to more than just laziness and distractions, we can begin to add more strategies for how to prevent procrastination (Chrishildrew, 2015). The first common strategy is to remove all potential distractions such as phones or friends from your workspace. Other strategies include properly managing time and creating a self-rewarding system to incentivize yourself to complete tasks. Although these tips help with the self-regulation previously mentioned, they don't address the self-esteem or self-efficacy that cause habitual procrastination. Syeda Batool, a researcher from Govt. College University in Lahore, also conducted research highlighting the correlation between self-esteem and educational performance. In her research paper "Academic Procrastination as a product of low self-esteem: A mediational role of academic self-efficacy" she comes to a similar conclusion, saying that "Procrastination serves as an ego protecting mechanism, which is used as a defensive device by people with low self-esteem."(Batool, et. al., 2017). From her research she also concludes that self-esteem and self-efficacy are positively correlated, and self-efficacy is the strongest predictor of procrastination. She suggests that increased self-esteem will result in a decrease of procrastination habits.

This means that the most effective way to reduce procrastination habits is to participate in academic activities that boost one's self-esteem. This now raises the question of what effective strategies that improve one's self-esteem and confidence in academic ability. Michelle Harris, author of "The Link Between Self-Esteem and Social Relationships: A Meta-Analysis of Longitudinal Studies" says "The meta-analytic finding that social relationships have a prospective effect on self-esteem provides support for central theories in the field of self-esteem, such as sociometer theory, reflected appraisals theory, and attachment theory." As outlined in the introduction, all of these theories highlight the key role of positive social relationships, social support, and social acceptance in shaping the development of self-esteem in all phases of the human life span."(Harris, 2019).". In this quote Harris talks about her experiment comparing self-esteem with social relationships, the important part being that she concludes positive social experiences are an important part in developing one's self-esteem. For a student these social interactions would be are going to office hours, seeking study groups, and opening up to friends about academic stress. These strategies at face value may not seem to prevent procrastination, but talking to others and hearing about their difficulties and getting reassurance from others can help make stressful classes seem less daunting and easier to work on, these strategies are all effective in helping students study whilst also developing their social relationships, which further develop their self-esteem, lowering procrastination and increasing academic success and a false sense of hopelessness that lead students to avoid doing certain tasks and spiraling into a chronic problem of ones perception of what they are capable of doing rather than just being too lazy to study.

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