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Introduction

As the new editors of *Best Integrated Writing*, we are excited and honored to revive an opportunity to showcase the best of student writing produced in courses at Wright State University. The student writings included in this edition exhibit a sampling of exemplary work produced across the disciplines—psychology, nursing, neuroscience, history, biomedicine, Earth and environmental sciences, and biology.

In reviewing these stellar student works, we are reminded of a central theme present in all the writings: humanity and the questions surrounding it. What does it mean to be human? What are the challenges and responsibilities of being human? How has the concept of humanity evolved over the years, especially in our post-Covid world? Also, of course, the perennial existential question: what does the future hold?

Looking at the relationship of humans and the environment, Kristin Johnson purports that the benefits of humans seeing themselves as part of the environment, rather than as separate entities, leads to better health for both. Jacob Pensky examines how desalination provides water security for the world’s population. Elissa Wakim explores how the connection between gut microbiota and neurodegenerative disease may reveal a potential reduction in the onset of Alzheimer's Disease; meanwhile, Elijah Bird reviews the research on the potential of tranexamic acid to treat a brain bleed. Focusing on the role of the selective serotonin reuptake inhibitor (SSRI) escitalopram, Olivia Mace connects that medication to the better management of anxiety. Examining the role of healthcare systems in the accessibility and quality of mental health treatment, Andrea Cessna uncovers possible nursing interventions and improvement. Providing a comprehensive review of the research on polyamorous relationships, Kacey O’Harra sheds light on recommendations for practices and future research. Finally, in a culture continually fascinated with the rise and fall of Napoleon Bonaparte, Clayton Cardinal argues that ambition was the determining factor in Bonaparte’s life, decisions, and ultimately his downfall.

Martin Luther King Jr. famously remarked, “an individual has not started living until he can rise above the narrow confines of his individualistic concerns to the broader concerns of all humanity.” Each of these student authors investigates integral questions in their work, exemplifying drive to continue their explorations of and strive for the betterment of humanity as they pursue careers in medicine, pharmacy, teaching, neuroscience research and nursing. We look forward to seeing the contributions of these students as they apply the same critical thinking, problem solving, and research skills to their future endeavors that they have demonstrated in their work within this edition.

--Kristie and Tracy
Acknowledgements

After a six-year hiatus, Best Integrated Writing resumes publication thanks to a multitude of individuals. We, as editors, are grateful for the contributions of all. The revival of the journal was the brainchild of Jane Wildermuth, who was then Head of Special Collections and Archives and has since taken on the role of interim university librarian. Jane’s initiative brought this journal to life again. Her colleague in Special Collections and Archives Alexis Whitney has been instrumental in the publication of the journal in CORE Scholar.

We wish to thank Alpana Sharma, Chair of the School of Humanities and Cultural Studies, who originally came to us with the idea of editing the journal, for her continued and steadfast support. Gary Schmidt, Dean of the College of Liberal Arts, has championed our efforts to expand the journal, giving more Wright State students an opportunity to showcase their work.

Finally, but perhaps most importantly, this journal could not exist without the dedication and attentiveness of faculty, as well as the hard work of student writers inspiring the nominations. We thank them both for their hard work and excellence in our academic community.
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ELIJAH BIRD

Nominated by: Dr. Yvonne Vadeboncoeur

Elijah Byrd graduated from Wright State University in 2023 with a BA in biological sciences. His focus is on emergency medicine. He recently moved to Columbus to pursue work at MedFlight.

Author notes:
My mom suffered a hemorrhagic stroke at the age of 52. Watching her struggle with such a life-changing event is what motivated me to study stroke and the cutting edge science behind its cure. As one of the leading causes of death and disability around the world, stroke is a problem that demands to be addressed. Although current treatment options have come a long way in recent years, there is still so much more to be discovered.

Faculty note:
Elijah reviewed the scientific literature on the efficacy of using tranexamic acid to treat a brain bleed, a deadly condition that requires rapid intervention to save the patient’s life. Tranexamic acid is widely used to treat excessive bleeding in many circumstances, but not for brain bleeds. The use of tranexamic acid is complicated by the difficulty in determining whether stroke symptoms are caused by a brain bleed, where its administration would be helpful, or a blood clot, where the drug would be detrimental. Elijah’s interest in the topic is very personal, stemming from his recent experience with his mother’s stroke. He did a great job of critically reviewing the evidence from multiple studies, and he created accessible figures to communicate the potential of this treatment to a wide audience.
The Potential Role of TXA in Treating Brain Hemorrhage

Introduction

Stroke is a dangerous, time-sensitive condition that impacts millions of people every year, becoming fatal for hundreds of thousands, and permanently disabling for even more (Guo et al. 2021). Stroke is broadly categorized into two main types: ischemic and hemorrhagic. Hemorrhagic stroke causes active bleeding in the brain and is significantly more deadly than ischemic (Figure 1). Brain hemorrhage remains fatal and commonplace, even in areas with advanced healthcare systems. Many people suffering from this serious medical emergency will die either as a direct result of destruction of their brain tissue or from one of the many complications that can arise during the long and complex treatment period following diagnosis. Even after the danger has passed, these patients will continue to struggle to lead normal lives, as stroke remains one of the leading causes of disability around the world (Liu et al. 2021).

In recent years, the quality of care for ischemic stroke patients has made great advancements. Tissue-type plasminogen activator (tPA) is a fast acting, easy to use, and relatively inexpensive drug that has proven clinically effective at curing brain ischemia (Gravanis, Tsirka 2008). tPA, colloquially known as a clot buster, works by quickly dissolving blockages during an ischemic stroke. However, due to the fundamental difference in pathology between ischemic and hemorrhagic strokes, tPA has no effect on and is contraindicated for those with intracerebral hemorrhage. This has left hemorrhagic stroke care lagging far behind the treatment options for ischemia (Sprigg et al. 2018). Until a similarly effective and efficient drug is found for treating brain hemorrhage, those suffering from it will continue to struggle against a disease that is extremely difficult to manage and cure. Tranexamic acid (TXA) has been proposed as a potential solution to this problem.

TXA is an intriguing option because much like its ischemic stroke counterpart, TXA is cheap, readily available, has quick response time, and consists of nothing more than a simple injection. Where it differs from tPA though is in its mechanism of action. TXA is essentially the opposite of tPA; it helps prevent clot breakdown, which is why it may be helpful for stroke patients whose illness is caused by active bleeding.

Early, promising evidence supporting tranexamic acid in this new role came from the CRASH-3 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage, third iteration) trial. This study, performed from 2012-2019, examined thousands of patients experiencing intracerebral bleeding and monitored the effects of TXA relative to a placebo. The authors of the CRASH-3 trial have championed the use of TXA for ICH after they found it significantly reduced chance of death in patients with brain hemorrhage. Several subsequent clinical trials attempting to produce similar results have instead found conflicting data, raising questions about TXA’s effectiveness and safety.

This review will examine the pathology of stroke and the function of TXA, and why the drug could be a sorely needed cure for one of the world’s most destructive diseases. I will address the differences between ischemic and hemorrhagic strokes and why a novel approach is needed to treat cerebrovascular accidents, despite the widespread effectiveness of drugs like tPA. I will break down the structure, mechanism, effects, and side effects of TXA. I will analyze critically various
studies and trials that have assessed the effectiveness of TXA on stroke patients. Lastly, the review will explore the strengths and shortcomings of TXA and make suggestions on where future research could continue to look for answers.

**Types of Strokes**

While hemorrhagic and ischemic strokes are similar in their effects on the human body, there are differences in their cause, progression, and overall impact on patient outcome. A stroke can be defined as any unintended interruption of normal blood flow or perfusion to the brain (Gravanis, Tsirka 2008). Ischemic stroke is caused by a blocked blood vessel in the brain, usually from a clot or plaque buildup. This blockage deprives brain tissue of fresh, oxygenated blood (Figure 2A). If left untreated, this ischemia will rapidly progress to infarction, or tissue death (Sekerdag et al. 2018). Hemorrhagic stroke is similar to ischemic stroke in that the brain is starved of oxygenated blood. In hemorrhagic stroke, however, this starvation is caused by a leak in the circulatory system. Typically, the result of a ruptured aneurysm or weakened arterial wall, leaks result in blood spilling out into the surrounding intracranial space (Figure 2B). As with any external bleeding, this leak in the system prevents oxygen exchange in the tissue. Named for the hemorrhage that occurs in the brain from a ruptured blood vessel, this type of stroke will also lead to infarction, as well as additional problems.

“Time is brain” is a saying used in emergency medicine to succinctly convey the seriousness of cerebral infarction. Irreparable brain damage begins immediately upon loss of perfusion, with millions of neurons, billions of synapses, and miles of nerve fiber destroyed every minute. For every hour that passes while oxygen is prevented from reaching its destination in the brain, 3.6 years are shaved off the patient’s life in terms of brain function (Saver 2006). Assuming they survive, stroke patients will often fight lifelong physical and mental disability, in addition to things like depression, social reclusiveness, loss of independence, and increased risk for developing additional future strokes. Due to the common occurrence and terrible outcomes of stroke, early recognition of its onset by family, friends, and bystanders is crucial to survival.

Stroke can be recognized by several hallmark signs and symptoms. Those associated with ischemic stroke are very similar in outward appearance to those associated with hemorrhagic stroke. These signs include hemiparesis, or motor weakness and lack of sensation in either the left or right side of the body. Hemiplegia, or total paralysis of one side of the body, is also common. These conditions may manifest themselves as an uneven smile, a lazy eye, a limp, or an arm that won’t move while the other works fine. Prolonged lack of oxygen in the brain can result in convulsions, posturing, loss of control over bodily functions, and eventually full loss of consciousness and responsiveness. Symptoms range from headaches to phantom sounds, smells, and sensations. Patients may report dizziness, nausea, and lightheadedness.

Due to the time sensitive nature of stroke and the current lack of simple treatment, early recognition and diagnosis are crucial components of modern stroke care. Together, recognition of these signs constitutes the Cincinnati Prehospital Stoke Scale. Often referred to simply as FAST or ‘Face, Arm, Speech, Time’ (Zohrevandi, et al. 2015), this scale focuses on the highly noticeable detriments to facial expressions, arm coordination, and coherent speech. The FAST scale applies to both ischemic and hemorrhagic strokes, as their externally visible signs are very similar, especially in
the early stages and when viewed by non-medical layperson. Even medical professionals have
difficulty differentiating between the ischemic and hemorrhagic varieties without the aid of advanced
imaging techniques, like CT or MRI scans (Figure 2). This can become problematic when treatment
specific to one type of stroke is needed.

Such scanning equipment is unavailable to first responders and may even be absent at
smaller hospitals, particularly rural ones. This poses a serious challenge to the use of some
medications for both hemorrhagic and ischemic stroke patients. Their treatment often revolves
around either the destruction or formation of clots to either enable or restrict blood flow, depending
on what is causing the stroke. Because of this, TXA may not be approved for stroke use on
ambulances, urgent care clinics, and at small emergency departments that lack imaging capabilities.
This could seriously limit the potential effectiveness of the drug, considering providers in these
settings are often the first to encounter the patient. Multiple trials studying TXA for stroke use
concede that early administration of the drug is key to its efficacy (CRASH-3 trial collaborators

In the absence of robust medical cures, preventative care and management of risk factors
have become important ways to combat the impact of stroke. Some of the most common reasons
for stroke are sustained elevated blood pressure, diabetes, smoking, obesity, high cholesterol, and
heart conditions such as congestive heart failure. Stress levels, alcohol and illicit drug usage, oral
contraceptives, and genetic predisposition are additional contributors. Stroke can also be a side
effect of other dangerous conditions. Traumatic brain injury (TBI) is one of the leading causes of
hemorrhagic stroke (CRASH-3 trial collaborators 2019). Bleeding in the brain caused by TBI
sustained in common occurrences like car accidents or contact sports can quickly progress to a life-
threatening situation.

In an attempt to manage risk factors, prescription of anticoagulants may also indirectly
contribute to the danger of hemorrhagic stroke. They’re often prescribed to people who are at risk
of having a heart attack or stroke (Polymeris et al. 2023). Ironically, anticoagulants, while decreasing
risk of ischemic stroke, can actually increase the risk of having a hemorrhagic one. These drugs,
only referred to as blood thinners, are commonly used by geriatric patients—a demographic that is
particularly susceptible to experiencing falls. Falls are a leading cause of head trauma in these
patients, and head trauma is a leading cause of hemorrhagic stroke.

Hemorrhagic stroke, often called intracerebral hemorrhage (ICH), is particularly dangerous
and imparts a much higher mortality rate on patients than ischemic stroke. ICH accounts for only
about 20% of all strokes, yet disproportionately represents stroke related death, being responsible
for 40-50% of the mortality of strokes (Sprigg et al. 2018). The increased lethality of this stroke
variety is because blood is spilling out through the ruptured artery. Beyond simply preventing
oxygen from reaching parts of the brain, ICH has additional devastating consequences. Because the
brain is encapsulated within the skull, there is very limited space for it to expand due to swelling,
inflammation, and bleeding. Much like a bruise on your arm swells outwards as blood pools beneath
the surface of the skin, a hematoma in the brain also swells with blood. The difference here is that
instead of pushing outwards against soft skin, the brain cannot push past the skull. The pressure
exerted by the blood pushes back against the brain, resulting in additional cell damage.
As more and more smaller blood vessels are constricted, secondary ischemic effects occur (Figure 2B). Hematoma expansion (HE) refers to additional movement of the bruised portion deeper into the brain (Liu et al. 2021). This is visible by comparing two or more CT scans taken over a period of time. Monitoring the shift of this expansion is critical to determining how aggressively to treat the stroke. Hematoma expansion is often used as a marker of poor prognosis due to the seriousness of the impending side effects. Around 25% of patients with hemorrhagic stroke will develop HE (Sprigg et al. 2018).

Intracranial pressure is a severe complication of hemorrhagic stroke. At the same time, parts of the brain unaffected by the pressure are still being deprived of oxygen because the blood is flowing out of the vessel at the bleed site before it can reach its destination. (Liu et al. 2021, Polymeris et al. 2023). The other part of the higher mortality rate for hemorrhagic stroke comes from secondary complications. These are conditions that occur as the result of a side effect from some treatment for the initial stroke. For example, medically induced comas for stroke recovery can also lead to deep vein thrombosis. This occurs when blood clots form in the legs due to a lack of circulation. These clots can cause a range of problems on their own but can be especially dangerous if the clot breaks off from its original site and travels to the lungs, heart, or brain. Thus, deep vein thrombosis can be a cause of additional strokes. Lastly, brain herniation represents the most severe and bleak outcome for ICH patients. This is when pressure inside the skull is so great that it pushes the brain down into the large hole at the base of the skull where the spinal cord connects.

Though hemorrhagic and ischemic strokes differ in their cause, both produce the same devastating result: death of brain tissue. Their similar outward presentation leads to a tricky situation for medical providers, who must quickly discern which one they are dealing with to formulate an effective treatment plan. The dangers of misdiagnosing one type of stroke as another are great, as treatment depends greatly on which type the patient presents with. In the past few decades, care for ischemic stroke has improved with the use of clot dissolving medicines like tPA. Despite this, there is no such widely accepted and approved treatment for hemorrhagic stroke victims (Sprigg et al. 2018). The main treatments for ICH are blood pressure monitoring, advanced imaging, and surgery if indicated.

If the patient does not respond well to medication, monitoring, and rest, then surgery is needed. A technique at the forefront of hemorrhagic stroke care is coil embolization, where a catheter is inserted and guided to the hemorrhage site to block blood flow. This option, though effective, is costly, invasive, and carries risk of complication (Medical Advisory Secretariat 2006). Considering the monetary expense and risk involved in such procedures, researchers have been searching for a cost-effective non-invasive alternative to surgery. Similar to how tPA has revolutionized ischemic stroke care, many have looked to tranexamic acid as a potential cure for hemorrhagic stroke patients.

**Tranexamic Acid**

Tranexamic acid is what’s known as an antifibrinolytic medication. Fibrin is a protein found in human blood that is responsible for clot formation. Plasmin is the enzyme that causes degradation of fibrin and thus a reduction in the capability of the blood to form clots. Antifibrinolytics are drugs
that prevent the degradation of fibrin in the blood, thus indirectly boosting clotting. Antifibrinolytics are different from clot promoters in that they prevent degradation of clots already formed, as opposed to actively increasing the number of clots or increasing the likelihood of a clot forming (Chapin, Hajjar 2015).

TXA is a synthetic chemical that mimics the structure and function of the amino acid lysine. It blocks the lysine receptors needed to activate plasminogen, preventing the conversion of plasminogen to plasmin (Law, et al. 2021). This lowers the amount of plasmin in the blood and thus reduces the breakdown of blood clots. By allowing clots to form, TXA is able to reduce blood loss from open wounds. It is this mechanism that researchers hope to exploit to achieve a similar effect at stopping the internal bleeding found in some types of strokes. However, because of its effects on the conversion of plasminogen to plasmin, TXA may have competing effects with the ischemic stroke medication tPA. Naturally present in the body as a plasminogen activator, tPA is given in concentrated doses to dissolve ischemic blood clots. Lysine analogues like TXA can prevent the breakdown of clots even in the presence of clot-busting medicines like tPA (Krishnamurti, et al. 1994). This could have serious consequences in cases of stroke misdiagnosis, e.g., if an ischemic stroke patient is mistakenly given TXA, subsequent doses of tPA would have reduced effectiveness.

TXA has a decades long history of use in the medical field for prevention of bleeding from different sources. Listed on the World Health Organization’s list of essential medications, it’s used to stop bleeding when conventional approaches like direct pressure, bandaging, tourniquets, stitches, and whole blood transfusion cannot be used or are simply insufficient. Examples of such situations are excessive nosebleeds, post-partum hemorrhage, and endometriosis (WOMAN trial collaborators 2017). TXA is also commonly used in conjunction with conventional blood loss control methods in multi-systems trauma patients. Patients at risk of exsanguinating levels of hemorrhage, e.g., those with grievous wounds from gunshots, stab wounds, high speed motor vehicle accidents, and falls from significant heights, do well when treated with TXA alongside transfusion and surgical intervention (Roberts et al). Two major studies in the early 2010’s were pivotal in cementing TXA’s role in trauma care after reporting significant reductions in mortality for patients who received the drug.

The MATTERS (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study) of 2012 compared the outcome of trauma patients who received TXA and blood transfusion to those who received only transfusion with no TXA. The TXA cohort saw reduced mortality when compared to the non-TXA cohort. TXA was also more beneficial in severely injured patients who needed 10 or more units of blood transfused (Figure 3). The MATTERS recommended TXA be integrated into trauma protocols, particularly in cases of extreme blood loss (Morrison et al. 2012).

One year later, the CRASH-2 (precursor to the aforementioned CRASH-3) produced similar evidence for TXA’s success in preventing hemorrhage. CRASH-2 looked at the effect TXA had on patient mortality and likelihood of blood vessel occlusion. Over 20,000 eligible patients were randomly assigned either TXA or a placebo and then evaluated for changes in condition. Significantly reduced all-cause mortality was seen in the TXA group when compared to the placebo (p=0.0035). There was no major difference in incidence of occlusive events between the two groups (Roberts et al. 2013).
In addition to proven effectiveness, another positive factor for TXA use is that side effects are typically mild (Colomina et al.). Most adverse, unintended effects are limited to acute abdominal discomfort, e.g., nausea, vomiting, diarrhea, and cramping. Rarely, more serious complications can arise, for example seizures. In the worst-case scenarios, TXA has been linked to detrimental clotting. This is especially concerning for patients with a history of, or increased risk of, developing ischemic stroke (Liu, et al. 2021). This contrasts with CRASH-3 findings, which reported that detrimental clotting effects were just as likely to occur in TXA groups as placebo groups. No negative side effects or safety concerns are known when using TXA to treat post-partum bleeding (WOMAN trial collaborators 2017.)

The key indication for the use of TXA is hemorrhage that is unable to be controlled by the body’s natural clot formation (Morrison, et al. 2012). It’s most often used in cases of severe trauma but also for cases of excessive nosebleeds and menorrhagia. TXA was shown to reduce mortality in patients with post-partum hemorrhage (WOMAN trial collaborators 2017). It may be used during surgery to reduce blood loss from incisions as well. Though TXA is not currently FDA approved to treat intracerebral hemorrhage, some evidence shows that it may be effective at reducing stroke death (CRASH-3 collaborators 2019). This, however, is the subject of ongoing debate.

Like most medications, there exist some instances in which administration would be inappropriate. Such situations are known as contraindications, and they preclude the use of a particular drug or procedure. Contraindications for TXA are patient history of ischemia, including prior ischemic stroke, heart attack, deep vein thrombosis, or pulmonary embolism (Liu, et al. 2021). These conditions could worsen or recur under the use of TXA, due to its nature regarding clots. In addition to known history of ischemic stroke, it is imperative that medical providers are able to confidently rule out ischemia from being the primary cause of the patient’s current condition. Should TXA be given to a patient experiencing an ischemic stroke, there is little chance any benefit may occur, and it could exacerbate the stroke symptoms (Liu et al. 2021).

**TXA as a Treatment for Stroke**

Given its current uses, its indications, contraindications, and side effects, is TXA a viable option for hemorrhagic stroke patients? Could it exist as a middle ground between passive monitoring and risky, expensive surgical procedures? Those are the questions that the researchers behind recent trials are aiming to answer. Bolstered by the past success of TXA for treating traumatic bleeding and motivated by a lack of medicines for treating ICH, some have been keen to sing its praises. However, there are many in the medical community who remain skeptical. Even if proven effective, there are still pros and cons to weigh.

Following the decades of use for other conditions, several recent studies have attempted to prove TXA can also be used to stop internal bleeding within the brain. The CRASH-3 trial was a large, randomized controlled trial conducted at multiple hospitals around the world. It enrolled 12,737 ICH patients and randomly assigned them either TXA or placebo. The patients were evaluated using the Glasgow Coma Scale (GCS), which assesses neurological function. Patients that exhibited moderate brain damage were found to have reduced risk of death when given TXA vs those with moderate to severe injuries (p=0.007) (Figure 4). There was a correlation between the elapsed time until TXA administration and patient outcome. The faster the drug was administered,
the more likely it was to prevent patient death (CRASH-3 collaborators). This is consistent with the results of non-stroke related studies, e.g., the WOMAN trial found that early administration significantly improved outcome when given for post-partum blood loss.

Citing the CRASH-3, several subsequent studies have contributed to the ongoing discussion regarding TXA use for hemorrhagic stroke. TRAIGE (Tranexamic acid for acute intracerebral haemorrhage growth based on imaging assessment) was a randomized and placebo-controlled study that evaluated TXA use specifically in patients with hematoma expansion (HE). In the study, 696 patients were evaluated and randomly assigned either TXA or placebo. TRAIGE found that TXA did not reduce brain hemorrhage in any subgroup. It did not significantly reduce HE in stroke patients either (p=0.89) (Figure 5). The authors of this paper noted that by virtue of their focus on patients with hematoma expansion, TXA may show reduced efficacy given the severity of the condition. Recall that measurable HE is an indicator of poor patient outcome (Liu et al. 2021).

The TICH-2 (Tranexamic Acid to Improve functional status in adults with spontaneous intracerebral hemorrhage) was another randomized, placebo-controlled trial, in which 1,161 hemorrhagic stroke patients were enrolled and randomly given TXA or a placebo. Relative to placebo, TXA had no impact on long-term outlook in ICH patients (p=0.11); however, TXA did reduce hematoma expansion and did not contribute to detrimental clotting (Sprigg et al. 2018). Following the TICH-2 trial, the TICH-NOAC, a randomized controlled trial in Switzerland, aimed to explore the effect of TXA on stroke patients who were also taking a non-vitamin K oral anticoagulant (NOAC). These anticoagulants are commonly prescribed to people with risk factors for ischemic stroke. The TICH-NOAC trial found only a 7% reduction in HE for patients given TXA over the placebo, which was statistically insignificant (Figure 6). Likewise, TXA did not reduce all-cause mortality by the 90-day mark (Polymeris, et al. 2023).

A meta-analysis of 25 different papers, including the CRASH-2 and 3, TRAIGE, and TICH-2 papers mentioned in this review, found that TXA use resulted in overall significant reduction in hematoma expansion (p=0.001) (Xiong et al. 2023). However, TXA did not reduce mortality, nor did it show any positive effect on patient disability. This meta-analysis includes results from studies that looked at hemorrhagic strokes caused by a traumatic brain injury in addition to those caused by spontaneous vessel rupture. It remains unclear whether TXA would behave differently depending on what initially caused the stroke.

In addition to the mounting evidence that appears to contradict the CRASH-3 authors’ claims that TXA reduces ICH related death, there are questions being raised regarding the nature of that claim itself. The authors did not mention in their conclusion that TXA was only shown to reduce death in a single subset of their patients (those with the mildest symptoms). Mansukhani et al. found discrepancies in time to treatment numbers reported by the authors in their 2020 review of the paper. Proponents of the CRASH-3 study point to its large sample size and randomized and placebo-controlled methods. Though many of the subsequent trials studying the use of TXA for hemorrhagic stroke patients have much smaller patient cohorts, they all utilized similarly robust methods.

TXA has been shown time and again to be a successful antifibrinolytic agent when used to control hemorrhage associated with trauma. It’s cheap, easy to use, and has mostly mild side effects
(Roberts et al. 2013). However, conflicting reports on its efficacy regarding intracerebral hemorrhage seem to be at odds with expected results (Shi et al. 2022). Despite its effectiveness at stopping blood loss in myriad situations, more research is needed to definitively say whether the drug can treat bleeding within the brain. Of the trials that showed positive results for TXA use, most were limited to patients with mild to moderate severity. All trials showed increased effectiveness the earlier TXA was administered, highlighting the importance of symptom recognition and CT/MRI scanning. In conclusion, TXA appears to be relatively safe and effective when given early to patients with confirmed hemorrhagic stroke, with diminishing returns according to level of brain damage. Further research on TXA should be conducted, as well as investigation into other antifibrinolytic drugs and different derivatives of Lysine. Additionally, other parts of the clotting process should be explored to see if brain hemorrhage can be treated without the use of antifibrinolytics.
References


Figure 1.

Concept diagram depicting the relationship between the types of strokes.
Comparison of CT scans for the two types of strokes. Contrast dye causes blood to appear white. Similarly, perfused tissue appears lighter in color than ischemic tissue.
TXA significantly improved survival of trauma patients at every follow-up interval (p=0.006) (Morrison et al. 2012).
Patients with mild to moderate brain damage (GCS > 8) benefited from tranexamic acid. TXA did not improve outcome in patients with GCS < 9). TXA did not increase the risk of unintended occlusive events (CRASH-3 trial collaborators 2019).
TXA did not significantly reduce hemorrhage in any subgroup (Liu et al. 2021)
TXA did not prevent or reduce hematoma expansion relative to the placebo (Polymeris et al. 2023)

Figure 6

adjusted median difference in volume change:
-0.33 ml (95% CI -3.80 to 3.14), p=0.85
Ambition Giveth and Ambition Taketh Away: The Life of Napoleon

CLAYTON CARDINAL

HIST 3000: Introduction to Historical Analysis, Fall 2023

Nominated by: Dr. Sean Pollock

Clayton Cardinal is a senior at Wright State University and is pursuing a BFA in Social Science Education. He would love to end up a history teacher at La Salle High School in Cincinnati where he has been a cross country and track and field coach for nine years.

Author notes:
Napoleon was, and still is, a larger-than-life figure known for his incredible ambition and drive. When I learned of his teenage years as a budding writer participating in writing competitions and how he derided ambition as a "disordered passion," it just stuck with me. I could not shake how much that contrasted with the ambition he used to forge an empire.

Faculty notes:
In this ambitious essay, Clayton Cardinal cogently argues that ambition helps explain both the rise and fall of a man who gave his name to an entire age: Napoleon. Having himself at an early age derided ambition, Napoleon soon came to self-consciously embody it, comparing himself favorably to, as Cardinal shows, “an Olympic athlete,” “a shooting star,” and “the envoy of the Grand Nation,” France. Napoleon’s desire to create what he called an “empire of the world,” however, ultimately led to his ruin. Throughout the essay, Cardinal demonstrates strong command of the sources, which are interpreted with sophistication and nuance and seamlessly incorporated into the prose. Thanks to its clarity and concision, the writing is a pleasure to read.
Napoleon was a man defined by ambition. In his early life, before he joined the military, he derided ambition as “a violent and unthinking delirium.” Once he joined the military, however, he used his military brilliance and ambition to quickly rise through the ranks during the wars of the French Revolution, thrusting himself to the spotlight in the process. Napoleon took advantage of this situation to seize power, first establishing the consulate, then declaring himself emperor. However, ambition began to lead Napoleon astray after a naval defeat to the British at Trafalgar in 1805. In an attempt to starve Britain of resources, Napoleon established the Continental System and rapidly expanded French influence across the continent to enforce the System. This overextension reached a climax with Napoleon’s ill-fated invasion of Russia, which led to his eventual defeat a couple years later. Napoleon refused to accept this defeat and returned from exile only a year later to try again, but this attempt was short-lived and lasted a mere hundred days. This relentless ambition may have driven Napoleon to greatness, but it ultimately drove him to ruin.

The story of Napoleon began in 1769 on the 15th of August on the island of Corsica, just one year after the French conquered the island. Though he did attend a French military school from 1778-1785, this setting was “not a happy one,” according to Steven Englund in his biography of Napoleon. Englund would go on to claim that “young Bonaparte … reacted with revulsion to his new surroundings” due to the school’s focus on “the ways of the court.” David A. Bell, in his biography of Napoleon, notes that due to the circumstances of the time, “a literary vocation made more sense” than a military one, given Napoleon’s heritage as a Corsican making it nearly impossible to have a distinguished military career. As such, Napoleon’s early life was characterized by his skill as a writer. Bell turns to Napoleon himself on this matter, whom he quotes to have said of his teenage life, “I lived like a bear … always alone in my small room with my books … my only friends!” Bell would go on to quote how Napoleon introduced himself to Enlightenment thinker Raynal, “I am not yet eighteen, but I am already a writer.”

In 1791, Napoleon remained true to his conviction of being a writer and entered a writing contest. Though he did not win, his views on ambition were especially notable. “Ambition, like all disordered passions,” he wrote, “is a violent and unthinking delirium. … Like a fire fed by a pitiless wind, it only burns out after having consumed everything in its path.” Given the career Napoleon would go on to have, this quote is fascinating and something to keep in mind as the story of Napoleon unfolds.

His budding literary career, however, was not given the chance to flourish. The French Revolution significantly altered the potential trajectory of a military career. In this post-Revolution world, Napoleon’s Corsican heritage no longer held him back from having a distinguished military career. Napoleon put down the pen and took up a position as an artillery officer. By 1793, he took command of the artillery during the siege of Toulon, and his prowess on the battlefield saw him promoted to the rank of brigadier general.

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3 Englund, 21-22.
4 Bell, 16.
5 Bell, 16.
6 Bell, 17.
7 As quoted in Bell, 17.
In late 1795, Napoleon was given the task of defending the Convention from the Vendemiarie Uprising. A member of the uprising, a man named Jean-Charles-Dominique Lacretelle, later wrote on Napoleon’s victory over the royalist rebellion, saying, “The Republic thought it had triumphed that day, but only under the protection of a warrior who would soon destroy it.” While Lacretelle’s commentary has the benefit of hindsight, Jean-Barthelemy Le Couteulx de Canteleu’s recollection of his first meeting with Napoleon does not, and yet it was a similarly eerie prediction of the future, this time through a recalled quote from Napoleon, “In France we have silver, cannon, barrels of flour. … That is what is needed against anarchy; but today the government can obtain neither silver, nor flour, nor cannon.” Both accounts here set the stage for what is to come: Napoleon’s campaigns in Italy and Egypt and his rise to power over not just the military but the entirety of France.

Napoleon’s campaigns in Italy are considered “an exemplar of generalship” in the modern era. However, Napoleon felt the need to further sell his success via a newspaper he published regarding his success in Italy. To put it simply, Napoleon did not think lightly of himself. He described himself as “an Olympic athlete,” “a shooting star,” and “the envoy of the Grand Nation.” Perhaps more notable, however, was his claim regarding his “noble and virtuous ambition.” This newspaper was published in 1797, only six years after Napoleon himself derided ambition. Yet now, as he achieved military glory, it seemed such a negative view of ambition no longer suits him.

Napoleon’s high opinion of himself joined him when he left Italy for Egypt. After he easily defeated the reigning Mamelukes in 1798, Napoleon issued a bold proclamation to the Egyptian people. “I respect God, his Prophet, and the Koran more than the Mamelukes.” He went on to claim that it was the Mamelukes who destroyed Egypt’s historical grandeur and that it was through French intervention that Egyptian grandeur would be restored. This proved to be a false promise, as Napoleon was unable to properly administrate the Egyptian people and fled before a revolt could gather enough strength to defeat him. Yet despite this setback, perhaps because of the propaganda efforts from his Italian campaign, he returned to France to a hero’s welcome.

It only took a month from his return before Napoleon led a coup to seize power for himself. To encourage an apathetic French people tired of coups, Pierre-Jean-Georges Cabanis justified this coup by claiming, “republic and liberty will no longer be empty words; a new era is beginning.” Then to discredit his co-conspirators and seize power for himself, Napoleon described their plans for government as “monstrous, composed of completely unreasonable, incompatible ideas.” Napoleon’s argument carried the day, and his plans for government were installed in December of 1799. This established the Consulate and named Napoleon the First Consul. Perhaps learning from his mistakes in Egypt, Napoleon sought to consolidate and legitimize his power.

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8 Jean-Charles-Dominique Lacretelle, “Account of the 1795 Vendemiarie Uprising.” 1875, in Rafe Blaufarb, Napoleon: Symbol for an Age: A Brief History with Documents (Boston: Bedford/St. Martin’s, 2008), 35.
9 Jean-Barthelemy Le Couteulx de Canteleu, “Bonaparte in Barras’s Salon,” 1875, in Blaufarb, 37.
10 Blaufarb, 37.
11 Napoleon Bonaparte, “Historical, Political, and Military Notes on the Army of Italy,” October 1797, in Blaufarb, 38.
12 Napoleon, “Army of Italy,” in Blaufarb, 38.
13 Napoleon Bonaparte, “Proclamation to the Egyptians,” 1798, in Blaufarb, 44.
Napoleon’s first step in this process was reconciliation with the Pope and the Catholic Church. In his letter to Cardinal Martiniana, Pope Pius VII expressed how eager he was to see France returned to Catholicism, writing “[w]e thus embrace happily the propitious occasion presented to us.”16 After successful negotiations, Napoleon and the Pope signed a treaty that made Catholicism the dominant religion in France.

Napoleon’s second step in this process was reconciling with the emigres, many of them the former nobility of France, who had fled or been displaced by the French Revolution. These attempts were a massive success, as reported by the prefect of the Vaucluse in 1805: “[w]hen they left their homes, they were fleeing anarchy … Can one imagine that they would not be totally devoted to the astonishing man whose first acts of government [tended] to destroy the enemy who had driven them out?”17 These steps at consolidation allowed Napoleon to properly administrate France and his immediate conquests.

Napoleon used this successful consolidation to declare himself Consul-for-Life in 1802, which in turn, allowed him to set up a hereditary government in 1804 and then declare himself Emperor a month later. This act, however, created a new problem. Napoleon had married his wife, Josephine, back in 1796, yet they had had no children together. Without an heir, Napoleon’s new dynasty was in jeopardy. After several more years with Josephine, Napoleon eventually decided to divorce her in 1809 to “[seek] a new, younger spouse whose grandeur would complement his own.”18 According to Napoleon, “Three reigning families could give France an empress; the Russian, Austrian, and Saxon.”19 Ultimately deciding on Marie Louise of Austria in 1810, this marriage gave him the heir he so desperately sought and brought legitimacy to his new dynasty among his European peers.

With his imperial ambitions unlocked, Napoleon set his sights on Britain. Unfortunately for Napoleon, his attempts to invade Britain were met with failure, as the British defeated his navy at Trafalgar in 1805. This defeat would ultimately mark the beginning of the end, as Napoleon’s quest to defeat Britain and realize his ambitions eventually drove him to ruin.

Napoleon turned from Britain to central Europe. In order to wage these massive wars, Napoleon was able to integrate a significantly larger percentage of the population than had previously been seen in Europe. Carl von Clausewitz, a Prussian veteran of the Napoleonic Wars, reflected in his posthumous book *On War* on Napoleon’s innovations to the waging of war, “The people became a participant in the war; instead of governments and armies as heretofore, the full weight of the nation was thrown into the balance.”20 With this massive increase in resources, Napoleon was able to consistently crush his opposition on land.

Within a year of Trafalgar, Napoleon had defeated the Austrians and Russians at Austerlitz, forcing the Austrians to surrender; he had created the Confederation of the Rhine, dissolving the Holy Roman Empire, and he had defeated the Prussians at Jena and Auerstadt. By the end of 1807, he had forced Prussia and Russia to surrender, had created the Grand Duchy of Warsaw and the

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18 Blaufarb, 112.
Kingdom of Westphalia, and sent troops in to pacify Spain. Furthermore, he used this rapid military success to establish what he called the Continental System. This System was a blockade that blocked all trade from continental Europe to Britain in an effort to starve Britain of resources, so it would be forced to capitulate to Napoleon.

For this System to work, Napoleon needed to be able to enforce it. To enforce it, Napoleon needed to have control over continental Europe, either directly or through alliances. Napoleon certainly believed this rapid expansion would work. “The first sovereign who … will embrace in good faith the cause of nations,” he wrote, “will find himself at the head of all Europe and will be able to attempt anything.”21 He also expressed this thought with a more specific example in a letter he wrote to his brother Jerome, king of Westphalia, in 1807, “What people would want to return to arbitrary Prussian government once it had tasted the benefits of a wise and liberal administration?”22 As it turned out, the answer to Napoleon’s question was yes, those people would like to throw off their new French government, especially the Spanish. By 1808, the seeds of rebellion were growing in Spain. As the Supreme Governmental Junta explained to Spanish bishops, “[t]he French broke treaties and violated the laws of hospitality … If presented well and often, these facts … should convince [Spaniards] that the only alternative is victory or death.”23 The Supreme Governmental Junta was successful in its goal. It inspired a conflict lasting six years that eventually drove the French out of Spain, and while other nations and provinces may have appeared to stay loyal, as time would prove, it would only take one domino to fall for Napoleon’s overextension elsewhere to take effect. That domino would be his doomed invasion of Russia in 1812.

Napoleon’s invasion of Russia marked the height of his imperial ambition and overextension. The empire was already stretched thin, and discontent was rising, as evidenced by Spain’s rebellion. Invading Russia, even had he emerged victorious instead of being defeated, would have ultimately yielded the same result. When Napoleon first took over as First Consul of France, he made moves to consolidate and legitimize his power. His rapid expansion across Europe, however, was propped up by the establishment of puppet kingdoms ruled by his siblings. Napoleon’s defeat in Russia only accelerated those people throwing off their puppet governments to reestablish their own sovereignty. This can be seen in the Proclamation of Kalisch from the Prussian monarchy to the German populace. In this proclamation, the Prussians took advantage of rising German nationalism to encourage them to overthrow the occupying French government. “The Confederation of the Rhine … can be tolerated no longer because it is the result of foreign pressure and tool of foreign influence.”24

Napoleon’s rule did not survive his disastrous invasion of Russia, an invasion where fewer than 100,000 of the original estimated 650,000-man army made it back home, and he was sent off to exile upon his defeat. This exile did not last, and Napoleon returned for one last attempt at seizing power. In a conversation he had with political writer Benjamin Constant, Napoleon stated, “I wanted the empire of the world, and to take it, I needed boundless power.”25 This last attempt did not last more than one hundred days, and after his defeat at Waterloo in 1815, Napoleon was exiled

24 “Proclamation of Kalisch,” March 1813, in Blaufarb, 189.
25 Emmanuel-Auguste de las Casas, “Account of a Conversation between Benjamin Constant and Napoleon,” 1815, in Blaufarb, 192.
a second time, this time for good. During this second exile, Napoleon reflected on his life and his ambition. “Finally, my ambition? Ah, doubtless I had much, but of perhaps the grandest and most elevated sort ever!”26 Perhaps Napoleon should have taken his own advice before his ambition “consumed everything in its path.”

Napoleon’s ambition drove him to succeed in Italy and take control of France as First Consul. He successfully consolidated his power and was able to properly administrate France. However, due to his inability to invade Britain, he sought to defeat them by alternate means. He established a Continental System that would block all trade from continental Europe to Britain. To make this Continental System work, Napoleon rapidly expanded the influence of the French Empire, bringing Spain, Austria, Germany, and Prussia to heel. This overextension first showed cracks via revolts in Spain and then completely shattered after his disastrous invasion of Russia. Napoleon’s ambitious overextension directly led to his own downfall, as he was defeated and banished not once, but twice. Ambition gave Napoleon the means to take the power he so desperately sought, and ambition drove him to throw it all away.

26 Emmanuel-Auguste de las Casas, “Napoleon on Napoleon,” in Blaufarb, 213.
Bibliography


Exploring the Systems-Related Factors Influencing Depression and Anxiety in the Private Healthcare System: A Nursing Student’s Perspective

ANDREA CESSNA, RN

NUR 4880: Critical Reasoning in Complex Health Care Systems, Spring 2023

Nominated by: Dr. Rosemary Eustace

Andrea Cessna is a recent graduate from Wright State’s BSN program and is currently pursuing her MBA at SNHU. She received her associate degree in nursing and business at Clark State Community College.

Andrea notes:

The mental health population has been an underserved population for a long time in health care. I was drawn to the idea of researching how the systems issues of health care contribute to effective, accessible, and quality care related to mental health treatment. I found it interesting to see how many different systems made quality mental health treatment difficult to find for many patients. With more attention being brought to the importance of mental health treatment, I am hopeful that effective quality care will be easily accessible soon.

Dr Eustace notes:

This paper presents a student’s critical synthesis of the literature and excellent grasp of the application of the World Health Organization Health Systems Building Blocks Framework to identify strengths, and improvement opportunities for nursing interventions in mental health care. The student’s writing demonstrates an awareness of factors that impact complex health systems in nursing practice which is an important competency in system-based practice.
Exploring the Systems-Related Factors Influencing Depression and Anxiety in the Private Healthcare System: A Nursing Student’s Perspective

Introduction

In this literature review, I intend to assess health financing, health workforce, and leadership and governance influencing depression and anxiety in the private healthcare system. I believe that we have come far with improving the quality, effectiveness, and accessibility of healthcare treatment related to mental health conditions. However, we are still far from where we should be.

The most prevalent mental health conditions include depression and anxiety (Kandasamy & Campbell, 2019). These can be seen individually but are commonly seen as co-occurring. These conditions are often found in the adolescent and adult populations and can have detrimental effects on a person’s activities for daily living. Symptoms of depression include feeling sad or anxious, feeling irritable, not wanting to do normal daily activities, having difficulty falling or staying asleep, eating more or less than normal, feeling guilty or worthless, and thinking about harming yourself (CDC, 2022). Symptoms of anxiety include excessive and intense worry that is usually frequent throughout the day and persistent in nature. Intense fear or worry can become very high leading into a panic attack. These worries and fears will last for long periods of time and are often not proportional to real danger and often lead to a person avoiding people or places that they feel could bring on these feelings and/or panic attacks (Mayo, 2018). Both conditions can become debilitating, making it difficult or even impossible to maintain normal daily functions, including maintaining relationships, and even daily work. In the United States, the leading cause of disability was depression, affecting 17.3 million adults. Additionally, over 6 million adults are diagnosed with general anxiety disorder. However, only 43.2% of this population is getting care (Facts & Statistics, n.d.). Since the recent COVID-19 pandemic, the combined total of adults who experience depression and/or anxiety symptoms rose from 11% (pre-pandemic) to 33% (post-pandemic) (Weiner, 2022).

Depression and anxiety can be treated or managed with the right combination of therapy, complementary alternative therapies, and medication (Kandasamy & Campbell, 2019). Often symptoms can become significantly lessened or even completely eradicated with the proper treatment. In some situations, with therapy and complementary alternative therapies, medication is not needed. On the other hand, when left untreated, a person can develop worsening symptoms that continue to progress. Over time, this would increase the risk of developing more severe mental health conditions that include bipolar disorder or personality disorders (Kandasamy & Campbell, 2019).

There are many who do not get the care they need for several reasons. One reason includes medical coverage. In 1996, there was a Mental Health Parity Act (MHPA) that prevented large group health plans from setting financial limits on mental health benefits that are less than that of medical/surgical benefit limits (MHPAEA, n.d.). In 2008, this was expanded upon to include substance use disorder (SUD). Then in 2010, this law was amended to include individual health insurance coverage as well (MHPAEA, n.d.). An example of this would be when the insurance provider allows office visits to be covered at a $15 co-pay for a primary care provider without limits on how many visits are allowed per year; then the insurance company must also allow the member to be seen for counseling services for the same or less of a co-pay without limits on how many visits they are allowed per year. The insurance company cannot charge a co-pay for inpatient admissions related to behavioral health or substance use disorder if they do not impose the same co-pay on
medical inpatient admissions. Another example of a violation includes prior authorization for medical inpatient admissions routinely for 7 days but only approving mental health or substance use disorder inpatient admissions routinely for 1 day. While we can see that laws have been passed to hold the insurance coverage companies accountable to cover the mental health needs of the population, who was holding the insurance companies accountable? Typically, the insurance companies would be required to show proof that they are holding to the parity laws by submitting necessary documents and data for review by an auditing team. However, these audits were either not being done, or when a parity violation was found, no or minimal penalty was implemented on the managed care organization (insurance companies). Without real penalties, one could not expect the managed care organizations to change their behaviors. So, in 2021, when 10 states implemented corrective actions against 30 health plans for parity violations resulting in $31 million in fines (Davies, 2021), managed care organizations took notice. This was an unprecedented move to enforce the parity laws. The legal and compliance departments of many managed care organizations reacted by getting all their departments educated on parity laws but most importantly the utilization review department. The utilization review nurses were taught how to spot potential parity violations and how to report those to assist the managed care organizations with catching potential violations and preventing not only severe penalties and fines but also to prevent damage to their reputation.

With this movement made to hold the managed care organizations accountable, more services are now covered by many insurance companies that were once not covered, and/ or those services are more affordable. Additionally, a person’s mental health coverage should be similar or better than that of their medical coverage. Better medical coverage to support mental health treatment is a step in the right direction but is meaningless if there are in adequate providers available to deliver the care that is needed.

When looking at the statistics of the percentage of adults who experience symptoms of depression and anxiety pre-pandemic versus the statistics of those post-pandemic (11% compared to 33%), are there enough resources to support those who need treatment? The answer is simply no. The percentage of those afflicted with mental health conditions has tripled in a short period of time, and there are not enough medical professionals available to meet the needs of the population. It is expected that within a few years we could see a shortage of “between 14,280 and 31,109 psychiatrists” (Weiner, 2022). There are several potential causes for shortages, including the increased population, increased need for mental health treatment, especially since the pandemic, the majority of (more than 60%) psychiatrists being 55 years of age or older, and only having a limited capacity to train new psychiatrists (Weiner, 2022). With these shortages, the areas that feel the greatest impact are rural areas. There are reports that it could take months to get in for an appointment, and now patients are seeing much longer wait times when they show for their appointments. In addition to these shortages, there is a shortage of nurses. There are many factors contributing to the nurse shortage, including an aging workforce (greater than 50% of the registered nurses are over the age of 50), high turnover, and not enough faculty available to train nurses (Staff, 2022). With nursing shortages and a growing population, there is a greater patient to nurse ratio, which leads to burnout, further contributing to the problem.

With these known issues of access to care, there are some professionals who are starting to look to other avenues to address the needs of the many. With the accessibility of technology today, there has been an increase in the availability of telehealth and mobile health options that offer some form of cognitive behavioral therapy (CBT) (Weiner, 2022). But with the increase in the use of technology and the increase in the need for programs to assist with a greater capacity to train medical professionals, where does the money come from?
March 2022 Health and Human Services announced that there was going to be an increase in the funding to community behavioral health clinics across the nation (SAMHAS, 2022). The goal is to make care more readily accessible to patients without the long waits. These grants will help to implement the programs and/or support, improving the programs that are already established for mental health clinics. The government also approved increased funding to promote increased residency training programs to help combat the Physician shortage (Weiner, 2022). There are also major increases in scholarships and loan repayments offered to nurses (among other medical practitioners) that were signed into law in 2021 in an effort to build up our healthcare workforce.

As nurses, we need to be aware of the barriers that a person may experience to getting care as well as the gaps in care. We have the ability to provide education and resources to the patient that they may not be aware of. We can also approach a patient with a more holistic approach offering education about available telehealth and mobile applications but also being aware that financing and medical coverage could be a barrier to care. That being said, many times insurance companies have their own case managers that will assist in finding care that a member needs that would not only be in the network but close to the member. They also have access to additional resources that help to holistically treat their members free of charge.

**Method/Approach:**

I have found that there were very few articles reporting on the financial gap related to mental health healthcare. After searching several different ways to find articles to give insight into the gaps financially, I was able to locate an article that was informative. The article titled, “Understanding and Addressing the Treatment Gap in Mental Healthcare: Economic Perspectives and Evidence from China,” written by Qin and Hsieh, does discuss gaps found in the leadership and government building block as well as the health financing building block related to mental health treatment. This article found that many will not receive treatment for their mental health issues for one of two reasons. The cost is too high and/or the benefit is too low (Qin & Hsieh, 2020). According to this article, the World Health Organization reports that many governments only allocate on average approximately 3% of their healthcare budget to the treatment of mental health conditions, which means those who seek treatment will have high out of pocket expenses. They also found that partially due to the low funding available to the mental health healthcare sector, the technology is not available for use as it is for the physical health sector of healthcare (Qin & Hsieh, 2020). This means that the development of new treatments, including new prescription drugs, is not advancing as it is in the physical health sector or healthcare.

Another article titled, “Utilizing telehealth to enhance nursing care and reduce burnout,” written by Lindgren, discusses some gaps in the health workforce. This study also addresses the high turnover rate and the shortage of appropriately trained staff to deliver the care needed. In this article, recommendations were made to support that incorporating telehealth can increase the accessibility to healthcare (Lindgren, 2023). Another study stated the use of telehealth can increase accessibility as well as medication adherence (Talarico, 2021). This article found that patients were more likely to adhere to their medication regimen, keep follow up appointments, and feel satisfied with their consultations. While adherence was not where we want it to be, it was still showing an improvement. I think this shows that telehealth is not the answer alone. It would need to be in addition to regularly scheduled appointments.

Originally, it was very difficult to find articles that I felt covered the gaps in healthcare and the complex health condition that I was researching. I was able to find approximately ten sources.
After reviewing all the sources found, I was able to narrow down the original ten to three articles for this paper.

**Discussion**

There are many systems related challenges, barriers, and stressors influencing the process of care in managing and controlling depression and anxiety. However, I am focusing on the system issues of health finance, health workforce, and leadership and governance for depression and anxiety.

The health finance system block has challenges related to funding. Decreased funding leads to decreased ability to dedicate new technology for developing new treatments and new medications, as well as getting current best practice education out to providers. Decreased funding can also lead to higher costs for treatment (Qin & Hsieh, 2020).

The health workforce systems block has barriers that include a lack of available qualified nurses and other medical professionals able to deliver care. With a smaller workforce this leads to limited accessibility to care (Lindgren, 2023). Patients will have to wait longer to get in to see a medical professional (Qin & Hsieh, 2020).

The leadership and governance systems block has barriers as well. With the average government allocating an average of 3% of their health budget to the mental health sector, this also leads to an increase in the cost for the patient (Qin & Hsieh, 2020). Although with the passing of the Mental Health Parity Act in 1996 and the strict fines that could be imposed on those who violate it, we are seeing some improvement in the policies surrounding mental health healthcare in the United States (Davies, 2021).

The actions the nurse can take to prevent the stressors in the health care system at the primary level or prevention would include providing education to the patient about proper self-care, including taking the time to exercise, eating well, taking medication as prescribed, and getting enough sleep. This should include not smoking, drinking alcohol, doing drugs, or drinking caffeinated drinks if you are prone to anxiety (Talarico, 2021). The nurse can also include education about programs available to the patient. The nurse can also advocate for better policies and funding for the mental health sector.

The actions the nurse can take to prevent the stressors in the health care system at the secondary level of prevention would include medication education and the importance of adhering to the treatment plan provided by the medical professional, ensuring that the patient is aware of all the appointment options available including “in person” or telehealth options (Talarico, 2021) and ensuring the patient is aware of crisis interventions that are available if the need arises. The nurse can also work with the community and leaders to be sure that what funding is made available is used in the most efficient ways, making care more accessible to the mental health sector.

The actions the nurse can take to prevent the stressors in the health care system at the tertiary level of prevention would include organizing support groups or assisting in directing patients to support groups. The nurse can also direct patient rehabilitation programs that are available specifically for the treatment of mental health issues including depression and anxiety. Many of these rehabilitation programs offer several hours of therapy daily and work to develop goals and coping skills that can assist the patient long term. These programs also provide the patient with a crisis plan that can assist the patient with steps to follow if they feel they are entering into a crisis. These treatment programs are referred to as residential, partial hospitalization, or intensive outpatient.
program, and some are offered virtually or as a hybrid program utilizing telehealth (Lindgren, 2023). As a nurse with a heavy behavioral health background, I have seen many of these programs offered through different facilities that are effective for treating patients, offering long-term recovery.

Some of the limitations I experienced with gathering the evidence was the limited number of peer-reviewed articles related to depression and anxiety from the private healthcare sector. The evidence that I was able to find was, in one case, geared toward care offered in China versus what would have been more ideal, care in the United States. I was not able to find sources that included information that I was looking for. I had changed my approach to this paper several times because of the limited articles before deciding to write about these three health systems blocks.

Once I found a few articles that covered my topic, I was able to start applying some of the knowledge I have gained from working in the field as well as working for a managed care organization to help strengthen the way I searched for articles as well as add information and resources. I was able to transfer a lot of the evidence found in the articles “Utilizing telehealth to enhance nursing care and reduce burnout” written by Lindgren and “Understanding and Addressing the Treatment Gap in Mental Healthcare: Economic Perspectives and Evidence from China” written by Qin and Hsieh, as much of the evidence was more generalized. I was then able to apply this to the health systems building blocks I was researching to give evidence for the gaps.

**Conclusion**

If left untreated, depression and anxiety can lead to more complicated mental health conditions as well as physical health conditions. However, there are many gaps in the mental health healthcare including the areas of health finance, health workforce, and leadership and governance. Additional funding is needed to support increasing the accessibility and affordability of receiving appropriate healthcare for mental health conditions like depression and anxiety. It is also clear that the government needs to allocate more funding for the mental health healthcare sector. With additional funding dedicated to this sector, we will hopefully see new prescription drug treatments that will be more effective in treating these conditions and with fewer side effects. Additional funding could also lead to closing the knowledge gap from older treatment practices and instead bring education to providers about newer, more effective, and best practice treatment options. We also need to see more available options for telehealth healthcare and mobile applications available to deliver cognitive behavioral therapy. Focusing on having more telehealth availability would mean that our limited number of trained nurses can deliver care to more patients in a safe and effective way, as well as reaching patients well outside of their typical boundaries for delivering care. Telehealth visits combined with regularly scheduled “in person” appointments could lead to more accessible health care with an increase in the patient’s treatment plan adherence, which would lead to overall better mental health.
References


## Appendix

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Reintegrating Humanity and Nature in Education and Workplaces

KRISTIN JOHNSON

PSY 4650: Mind and Environment Capstone, Fall 2022

Nominated by: Dr. Ion Juvina

Kristin Johnson is a recent Wright State University alum (2023) with their bachelor’s degree in psychology and a minor in Computer Science.

Author notes:
The separation of “human” and “nature” has become more apparent over time, but examining the effects that reintegration of humans and nature has on people makes a strong case for seeing ourselves as part of the environment (rather than separate entities). I think that we’re better off when we acknowledge and incorporate how our surroundings affect us and how we affect them in turn, leading to better health both for humans and the environment. This likely must happen at multiple impactful points (school, work) for there to be real, lasting, and positive change.

Faculty notes:
The Mind and Environment Capstone seminar focuses on the circular and mutually transformational interactions between mind and environment, as well as how these interactions affect both environmental and human sustainability. This exemplary essay demonstrates that the student examined the topic in depth, fully understood the course content, conducted a thorough literature review, was receptive to faculty feedback, and produced writing that is both informative and inspiring.
Reintegrating Humanity and Nature in Education and Workplaces

Abstract

There has been an observable disconnection between humans and natural environment in select Western cultures over the past 100 years. Reintegration of humanity and nature can be achieved through shifting to a sustainability-focused model of education and the teaching of reflection about natural experiences to children to equip them for sustainable living. Biophilic designs can continue to encourage this shift because the effects are immediately good for both physical and mental health. Green ergonomics can also encourage this reintegration by reducing the friction between the user and the technology in ways that encourage sustainable practices with ease. By combining these ideas, there may be a path forward with nature back in our everyday lives, which could improve the chances of sustainability practices becoming more prevalent.

Keywords: green ergonomics, biophilic design, sustainable education, reflection, nature
Reintegrating Humanity and Nature in Education and Workplaces

Over the last century, industrialization has resulted in efficiency for profit purposes as a goal under our current economic systems. This has led to a disconnect between people and nature, and the effects are not necessarily good for us. People are drawn to nature, and as the authors of the book *Psychology for Sustainability* said, “We love nature because we ourselves are nature” (Scott et al., 2021). This positive effect of nature is reflected in several studies, such as the mental health benefits nature provides therapy clients and the reduction in stress and depression from LEED (Leadership in Energy and Environmental Design) buildings, which facilitate workspaces that, for instance, have better indoor air quality and daylight (Greenleaf, Bryant, & Pollock, 2014; Singh et al, 2010). Reintegrating ourselves with nature will likely have multitudes of benefits for us, both in the short term (such as better health and an overall increase in happiness) and the long term (sustainable living conditions in the future). This paper suggests two areas that this reintegration may be facilitated: a shift to sustainably-minded education and a focus on biophilic workspaces and green ergonomics to reintroduce nature to our everyday lives and as encouragement to reflect on nature and coexist with it.

Literature Review

Nature Disconnection

Connection to nature and images of nature have been dwindling over the last century, signaling a disconnect between humanity and nature as technology advanced rapidly over the past 100 years. This disconnect has been observed in English literature, musical lyrics, and movie storylines starting around the 1950s (Kesebir & Kesebir, 2017). This examination of artistic output over the last 100 years found that mentions of nature in a sampling of English literature works started declining significantly after the 1950s. This trend was not observed for references to human-made structures or objects, which saw a slight increase over time. When song lyrics and film storylines were examined, the same trend was observed, with fewer mentions of nature-associated words appearing after the 1950s. This trend may indicate a disconnection that is furthering over time, as the works we create as human beings are reflective of who we are, how we see the world, and our role in nature. Because we are now more frequently surrounded by man-made structures, they may take up more of the representation in our works of art.

Sustainable Education

The current system of education has goals that aim for perpetuating the current systems of continuous economic growth that are exacerbating issues such as the climate crisis. In his book “Hope Is An Imperative,” David Orr explains that there is a disconnection between students and understanding broad systems, since education has become highly specialized and technical (Orr, 2011). According to Orr (2011):

Students of all ages will need the kind of education and skills appropriate to building a society with fewer cars but more bicycles and trains, fewer large power plants but more windmills and solar collectors, fewer supermarkets and more farmers’ markets, fewer large corporations and more small businesses, less time for leisure but more good work to do, and less public funding but more public spirit (pg. 70).
Education needs an overhaul from the current system to a more ecologically focused and sustainable experience. Hill and Brown (2014) highlight several key ideas regarding transformative education as an imperative step towards sustainability. They quote Sterling (2001), saying “most mainstream education sustains unsustainability,” referencing the fact that the current systems of education in place in the Western world are implemented in such a way that children are educated for participation in and facilitation of an unsustainable system. They suggest using sustainability as a guiding framework for education, place-responsiveness (highlighting the importance of place both local and within systems, particularly in an outdoors context), and stress the importance of connection. One example of the way these goals can be achieved is through transformative outdoor experiences tied into education. Fostering a sense of connection to nature and to the local environment are both expressed as essential steps by many educators interviewed in the paper. A sense of connection to place and learning about one’s place in the systems around them, particularly in the context of nature and the environment, can lead to deeper, more reflective attitudes and behaviors that contribute positively to sustainability. Orr, referencing Shepard’s 1982 book, *Nature and Madness*, notes that Shepherd called for an education system that “required rethinking the conduct of childhood and the need to connect the psyche with the Earth in the earliest years. Contact with earth, soil, wildlife, trees, and animals, he thought, is the substrate that orients adult thought and behavior to life” (as cited in Orr, 2011, pp 86-87).

Because what we are exposed to shapes how we view the world, reintroduction to nature could be a way to combat this downward trend of human-nature disconnectedness and may allow us to reintege ourselves back into the idea of “being one with nature.” As Hill and Brown (2014) noted, outdoor experiences alone aren’t always enough to contribute to a pro-environmental mindset. Hoyem (2020) found that reflection on the relationship between nature and humanity was more likely to result in pro-environmental behavior after an outdoors experience than simply having the experience alone. In a series of interviews with Norwegian outdoor enthusiasts, varying levels of reflection about their experiences with nature were observed, ranging from reverential and reflective of both outdoor experiences and nature connectedness to only focusing on the outdoor experiences themselves, with little additional reflection on nature independently from these experiences. Most of the respondents expressed difficulty in adequately describing their relationship with nature and some even struggled to understand the questions regarding their relationship with nature and ecological concerns, despite being recruited while actively participating in outdoor activities (in this case, hiking). The study noted that these outdoors experiences alone most likely don’t contribute to environmental awareness, but that reflectiveness on those experiences does. The respondents who showed reflective tendencies or expressed that they had reflected on their relationship with nature were also the only respondents who had considered their part in environmentally friendly actions (such as waste reduction) and were actively attempting to participate in environmentally friendly actions, while the other respondents who had not reflected on their relationship to nature had few or no opinions on the matter. This makes a strong case not only for increased outdoor education and experiences, but also for tools for people in these educational systems to learn how to reflect on their experiences and their relationship with nature. This could, in turn, lead to an increase in environmental awareness and desire to perform environmentally friendly actions, especially when paired with an increase in sustainability education.

**Biophilic Design and Green Ergonomics**

Further along in the life cycle of the average American person is the necessity for income, usually through employment. One common type of job may involve the use of an office space, often...
taking place in large concrete buildings among other large concrete buildings in areas known as “business parks.” In recent years, there has been a push for design changes to these locations to reflect a more nature-oriented environment. This change of design environment is known as biophilic design. Biophilic design is described as “our innate human desire for spaces that more closely resemble natural outdoor environments due to its evolutionary benefits,” (Wilson, 2013; Aristizabal et al., 2021). The study by Aristizabal et al., 2021 found that a multisensory approach of audio and visual biophilic design interventions in a simulated office space reduced stress levels. The cognitive performance of the participants was significantly better in any of the biophilic conditions (including indoor plants, sounds of wind blowing, and combinations of both) than in the control condition, with their working memory and response inhibition both improving. These findings are likely related to those in the study conducted by Yin (2019), except this study used virtual reality experiences in addition to physical ones in order to assess biophilic design on people. It was found that even small amounts of exposure to biophilic design elements, such as trees and a sunny window, resulted in participants having lower blood pressure readings than when they were not exposed to them. The cognitive benefits mirror that of the Aristizabal et al., 2021 study as well, with participants having improved short-term memory in the biophilic conditions.

**Green Ergonomics**

Ergonomics, or human factors, is a field in psychology that is concentrated on the health, safety, and productivity of people when they use things like machines, tools, or technology (Proctor, 2018). More broadly, human factors and ergonomics focuses on how humans interact with their environments and how to make those interactions safe and helpful. Nature can be seen as part of a human’s environment, so focusing on sustainably encouraging safety and health is a closely connected idea. Green ergonomics is a concept where the field of ergonomics is viewed from the point of the human-nature connection because of the impact both healthy and unhealthy environments can have on people (Thatcher, 2012). The relationship of humanity and the natural environment, like nature, is described as “bi-directional,” since we influence our surroundings and our surroundings influence us simultaneously, for better or worse (Thatcher, 2012). Green ergonomics includes concepts such as focusing on designs that require the use of less resources, such as considering the ergonomic differences of driving a solar-powered car versus a fossil-fuel powered vehicle (Hilliard & Jamieson, 2008). Ensuring that the information provided to the driver is relevant and causes less cognitive stress will make the driving experience safe and more effective, encouraging the use of a more sustainable product, thereby impacting both the people using the technology and the environment. Green ergonomics is also concerned with well-being of individuals in settings like office spaces, as previously described regarding biophilic design. However, arguably the most important aspect of green ergonomics is the focus of encouraging pro-environmental behaviors by making those behaviors easier and safer to engage in. Green ergonomics could potentially act as a point that facilitates larger, more systemic changes, such as through providing more information about how products were developed and made, so more informed eco-friendly choices can be made by the people using them (Thatcher, 2012). Training is another way that green ergonomics can potentially have an impact; by training people on more eco-efficient ways to do things that affect the environment, people will be better informed and able to employ more sustainable strategies.

Humanity-centered design is an area where green ergonomics can be integrated. Humanity-centered design is a method of design that focuses on the broader scope of the ecosystems in which humanity exists, which includes areas such as the environment of the earth and other living
creatures, while striving to consider root causes and the community it serves using a systems-thinking viewpoint (Norman, 2023). Green ergonomics could be utilized in design choices in order to solve root causes of sustainability issues, rather than treating symptoms of the issues. Change at a large scale requires many participants, and by using green ergonomics to make it easier to implement those changes (whether it is by, for example, providing more information or changing the way a resource is used), those changes are more likely to become permanent.

**Discussion**

The growing disconnect between humans and nature since the 1950s does not have to continue the same path. The integration of nature back into both our minds and our spaces, from the way we think about ourselves in the context of nature to the tools we use allowing easier pro-environmental behaviors, is a viable way forward into a more sustainable way of living. By starting sustainable education earlier, like early childhood education, the knowledge of the impact of ourselves on nature and nature on ourselves can be encouraged and emphasized so that sustainable actions and attitudes do not seem like radical shifts later in life. Achieving this by encouraging outdoor activities and reflective exercises encouraging students to connect how those activities made them feel to the systems of nature in a larger context could be one avenue for this educational shift. By focusing on education, the people who will shape the systems (both physical and conceptual) in the future can be equipped with the information needed to make sure that those systems are sustainable both for themselves and for humanity in future generations.

Similarly, introducing more biophilic design choices and more exposure to nature in the day-to-day lives of employees would likely make this transition from the formal education years to adulthood easier and more likely to continue the sustainability attitudes and actions that were fostered earlier on. Even without considering biophilic design as part of this cycle, biophilic design has positive effects for the people that are in those environments both physically and emotionally. It would likely benefit the people in these places of employment to be surrounded by the sights and sounds of nature, instead of current arrangements featuring little outdoor influence. Future research could address other workplaces outside of the office, such as in settings in the service industry where fast-paced stressful events that occur regularly can be observed.

Green ergonomics has the best chance for bi-directional impact between humanity and nature. By making the relationship between people and the environment better by reducing the friction of engaging in sustainable behaviors, these behaviors are more likely to be adopted and practiced, such as in the example of the solar-powered car. Reducing the cognitive strain by displaying the pertinent information to the operator rather than the traditional information a fossil-fuel-powered car provides is potentially going to allow operators an easier time utilizing these technologies. Assisting with removing the barriers to sustainable actions from a technical perspective, while making sure people are kept safe and content, could go a long way in normalizing them, which could in turn lead to more pro-environmental actions being taken as they become more mainstream to participate in. Research in the future could continue to observe what current methods we have of reaching goals and the impact those methods have on the environment, the issues people run into when trying to adopt new and sustainable ways of doing things, and assessing if there are ways to reduce the friction between the people using the technology and the technology itself to encourage the further use of sustainable technologies.
Conclusion

While there has been an observable disconnect between humanity and nature in some Western societies over the past century, this does not have to be an irreversible trend. Focusing on shifting current education to a sustainably motivated one, encouraging regular outdoor experiences with nature, and giving people the tools to reflect on their feelings about those experiences could go a long way in starting to shift the role of sustainability from an afterthought into the forefront. Modifying the day-to-day lives of adults to include more nature with greener office spaces that bring nature indoors and mimic outdoors could continue this mindset shift, as well as have positive physical and mental effects on the employees in those spaces. By starting with education, normalizing outdoor experiences, encouraging the reflectiveness to evaluate the meaning of those experiences, and continuing with nature permeating our spaces post formal education, we can begin to reconnect with nature and thus, ourselves.


Balancing the Mind: The Role of Selective Serotonin Reuptake Inhibitors in Managing Anxiety

OLIVIA MACE

NEU 4030: Senior Capstone - Neuroscience Review Article

Nominated by: Christopher Wyatt

Olivia Mace is an aspiring pharmacist currently enrolled in Wright State University’s Physiology and Neuroscience Bachelor's program with a Psychology minor. Simultaneously employed in an Upstate New York pharmacy, Olivia combines academic knowledge with practical experience in medication dispensing. Olivia aims to leverage her unique perspective from both academics and the pharmacy setting to address challenges in the field and contribute to improving patient outcomes.

Author note:
Driven by the goal of becoming a pharmacist, I sought to delve into the pharmacological aspects of mental health. As a NCAA Division 1 student-athlete, I personally grappled with the prevalent anxiety associated with performance demands. Motivated by this experience, I aimed to explore escitalopram, which is designed to alleviate anxiety and comprehend its mechanisms. This exploration stems from a desire to contribute to the understanding and improvement of mental well-being, particularly for individuals navigating the challenges of anxiety in high-pressure environments.

Faculty note:
Olivia’s senior capstone review article focuses on the role of the selective serotonin reuptake inhibitor (SSRI) escitalopram in the management of anxiety. SSRIs have been successfully used to treat depression for decades, with fluoxetine (Prozac) being introduced to the US market in 1987. Recently it has been found that the SSRI escitalopram has efficacy in treating anxiety as well as depression. Olivia’s review is detailed and timely. Unmanaged anxiety and depression are common among students and this review will be of interest to students, parents and the university population in general.
Balancing the Mind: The Role of Selective Serotonin Reuptake Inhibitors in Managing Anxiety

Introduction

The management of mental health is critically dependent on the interplay between neurochemistry, genetics, and psychological well-being. Selective serotonin reuptake inhibitors (SSRIs) have emerged as a crucial class of medications in the treatment of anxiety disorders, such as generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). Some notable medications within the SSRI classification include paroxetine, sertraline, and escitalopram. Over the years, SSRIs have gained widespread acceptance due to their efficiency and favorable side effect profiles, setting them apart from traditional treatments like tricyclic antidepressants and benzodiazepines (den Boer et al. 1987). However, SSRIs remain a relatively recent addition to anxiety prescriptions, leaving room for ongoing research.

SSRIs modulate serotonin, a mood regulating neurotransmitter within the central nervous system (CNS), and its respective receptor to ease anxiety. SSRIs can regulate the serotonin network through serotonin receptor activity within the context of anxiety and restore balance to an overly sensitive or unresponsive system. To understand this modulation, the neural pathways associated with the fear response, the genetic factors influencing individual responses to SSRIs, the addition of therapies to increase the prescription's efficacy, and the potential effects of prenatal exposure to these medications on child development must be considered. Thus, present-day intersections of pharmacology, genetics, and psychology are crucial for mental health treatment.

This review examines escitalopram, also known by its generic name, Lexapro.

Escitalopram represents the S-enantiomer of citalopram, a widely recognized SSRI (Benezah et al. 2023). This specific isomer is known for its antidepressant efficacy and is often prescribed as a dual-purpose medication, serving both as an antidepressant and an anxiolytic. Escitalopram made its debut in 2002, and as such, questions regarding its mechanisms of action and potential effects, mainly when used during pregnancy, remain areas of ongoing research and exploration (Benezah et al. 2023). All in all, escitalopram promises to be both enlightening and clinically relevant to combatting anxious feelings within its patients.

Unveiling the Mechanism of SSRIs in Easing Anxiety

SSRIs elevate extracellular serotonin levels in the nucleus accumbens by inhibiting the reuptake of presynaptic serotonin, consequently alleviating certain emotional states (Benezah et al. 2023; Hicks et al. 2015). In essence, SSRIs enhance postsynaptic receptor binding by prolonging the presence of serotonin in the synaptic cleft through reuptake inhibition. However, autoreceptors located on serotonin-regulating presynaptic neurons influence this process as well. It is clear that serotonin, or as it is otherwise known, 5-hydroxytryptamine (5-HT) plays a pivotal role within the CNS. There are two major subcategories of 5-HT receptors, 5-HT1 and 5-HT2, with further subdivisions like 5-HT1a-d receptors within 5-HT1. Alterations in 5-HT metabolism, mainly related to 5-HT1 receptors, have been associated with various psychiatric disorders, including anxiety and suicidal thoughts (Kahn et al. 1988). Thus, enhancing 5-HT receptor...
sensitivity is considered a strategy to augment 5-HT function to counterbalance an insufficiently responsive normosensitive receptor system and reduce anxiety. However, it's important to state that research indicates that the sensitivity of these receptors may vary depending on the type of anxiety, with some being hyposensitive and others hypersensitive.

To elucidate receptor activity associated with anxiety, examining specific autoreceptors within the 5-HT receptor system is essential. Notably, the 5-HT\textsubscript{1A} receptors located on the cell body and 5-HT\textsubscript{1D} receptors on the axon play a pivotal role in regulating serotonin levels, offering critical insights into whether these receptors exhibit hyposensitivity or hypersensitivity. The quantity of serotonin released profoundly influences the overall serotonin availability within the synaptic cleft. The assessment of serotonin levels occurs through the measurement of 5-hydroxyindole-acetic acid (5-HIAA), a 5-HT metabolite present in cerebrospinal fluid (CSF) (Kahn et al. 1988). This methodology enables researchers to employ agonists while evaluating 5-HT receptor sensitivity, examining its hormonal and behavioral ramifications (Kahn et al. 1988).

Studies have shown that individuals suffering from anxiety and impulsivity often exhibit lower levels of 5-HT due to heightened threat responsiveness (Kahn et al. 1988). Among the 5-HT receptors, researchers focus on 5-HT\textsubscript{1A}, a vital component of the fear pathway influencing anxiety. Activation of the 5-HT\textsubscript{1A} receptor inhibits raphe firing, contributing to anxiety modulation (Trulson and Arasteh 1985). Furthermore, 5-HT\textsubscript{1D} appears to be the predominant subtype of 5-HT\textsubscript{1} binding sites for serotonin (Heuring and Peroutka 1987). Elevating the net serotonin levels in the synaptic cleft can normalize postsynaptic receptor function in cases of hyposensitivity, thereby attenuating anxiety by inhibiting the fear pathway.

**Fear Pathway's Crucial Role in Anxiety: Unveiling the Connection**

The fear pathway is primarily shaped by serotonergic projections originating from the median and dorsal raphe nuclei (MRN and DRN), often implicated in serotonin dysfunction cases. These nuclei wield considerable influence over the regulation of fear and anxiety, as they interface with neurotransmitter systems responsible for the processing and expressing of these complex emotions (Kahn et al. 1988). Notably, the fear pathway manifests in crucial regions such as the dorsal periaqueductal grey (PAG), the median hypothalamus, and the amygdala. The amygdala is central to the fear pathway, often related to its headquarters. The amygdala is a brain region associated with emotional processing, and reducing its reactivity is seen as a positive change, suggesting alleviated anxiety-related responses. Expressly, the central nucleus of the amygdala assumes a pivotal position in orchestrating the fear response, primarily through its extensive projections into the PAG and the hypothalamus (de Olmos 1990). In the basolateral nucleus of the amygdala, excitatory information is received, particularly in response to panic-inducing or anxiety-provoking sensory stimuli (Amaral et al. 1992). These pathways are predominantly glutamatergic, with modulation by serotonergic input. Notably, the amygdala receives serotonergic information from the raphe nuclei, suggesting the mediation of SSRI anxiolytic effects in this region. The elevation of serotonin levels in the amygdala resulting from SSRIs inhibits cortical and thalamic inputs to the amygdala, thereby preventing its activation in response to stress-inducing stimuli, effectively interrupting the initiation of the fear pathway. When the central nucleus of the amygdala becomes activated, it sets in motion a complex network of pathways collectively referred to as the fear pathway. As the hub of fear-related processing, the central nucleus dispatches sensory signals related to fear to various destinations. These destinations
include the PAG, noradrenergic cells within the locus coeruleus (LC), the hypothalamic-pituitary-adrenal (HPA) axis via numerous efferent connections with the paraventricular nucleus (PVN), the parabrachial nucleus (PBN), and the dorsal motor nucleus of the vagus (DMNV). The PBN and DMNV activation results in a cardiorespiratory response to the stimuli. Figure 1 illustrates the amygdala’s pathways to the PAG, dorsal raphe nucleus (DRN), PVN, and LC.

**Figure 1** Serotonergic pathways’ activity between the amygdala, periaqueductal grey, hypothalamic-pituitary-adrenal axis, and locus coeruleus.

The PAG represents a critical output pathway originating from the central nucleus of the amygdala, playing a pivotal role in eliciting panic or anxiety responses. The PAG orchestrates the coordinated movements necessary for defensive and escape reactions to these stimuli. This connection between the amygdala and the PAG is excitatory, facilitating the generation of such responses. Conversely, when the DRN transmits action potentials along its efferent pathways to the PAG, it exerts an inhibitory influence, dampening panic and PAG responses. SSRIs enhance this inhibitory effect on the PAG, attenuating anxious and panic reactions to various stimuli.

The LC maintains a reciprocal relationship with the DRN, where the DRN can either stimulate or inhibit it. Excitation of the DRN results from noradrenergic innervation, while inhibition stems from serotonergic projections. This serotonergic inhibition assumes particular significance given that the LC exerts direct and indirect influence over the amygdala and the PAG. The LC influences these structures via excitatory pathways, amplifying the stress response. When introduced, SSRIs inhibit LC firing, thereby diminishing excitatory responses in the amygdala. Consequently, reduced excitatory input alleviates anxiety and panic responses.
While this provides a fundamental understanding of how SSRIs operate, it is important to note that the pharmacokinetic characteristics governing the enhancement of serotonergic activity can vary across different medications within the SSRI class. These variations are attributable to genetic diversity and differences in drug-related phenotypes, which will be elaborated upon in subsequent discussions (Hicks et al. 2015).

**Genetic Factors Influencing SSRI Response**

SSRIs metabolism or pharmacokinetic parameter values fluctuate with a person's genotype, specifically CYP2D6 and CYP2C19. These genotypes are essential in noting when using an SSRI due to its effect on drug safety and efficacy (Hicks et al. 2015). For example, serious side effects of SSRIs, including arrhythmias from QT prolongation, the medical term for an extended interval between the heart contracting and relaxing, are more common in individuals prescribed an SSRI with CYP2C19 poor metabolizers. This side effect is one example of how the CYP2D6 and CYP2C19 polymorphisms can alter SSRI biotransformation. Both genes are highly polymorphic, and their allele frequencies tend to be similar between populations.

Escitalopram is a pharmacologically active S-enantiomer of citalopram. Citalopram has a racemic mixture of R- and S-enantiomers, which allows for similar pharmacological effects. Both these SSRIs are catalyzed by CYP2C19. Variations in this genotype affect drug exposure because CYP2C19 is a major metabolic pathway. Due to this effect, SSRI pharmacokinetic parameters or treatment outcomes depend on genotype variability, and seeing fifty percent failure of initial SSRI therapy is acceptable (Hicks et al. 2015). These variations in genotypes affect the serotonin transporter, 5-HT, and the serotonin receptors that contribute to the SSRI response and have a part in the dictation of side effects (Gvozdic et al. 2012).

**CYP2C19 and Its Influence on Escitalopram’s SSRI Response**

The level of metabolism determines the various phenotypes of CYP2C19. When an individual has two increased function alleles or one normal function allele with one increased function allele, the phenotype is an ultrarapid metabolizer. Some examples of the CYP2C19 diplotype for this phenotype include *17/*17 and *1/*17. People classified as CYP2C19 ultrarapid metabolizers exhibit notably reduced drug exposure compared to extensive metabolizers, potentially elevating the risk of treatment failure (Huezo-Diaz et al. 2012). The homozygous *17/*17 genotype has an increased metabolic capacity and could benefit from various therapies than *1/*17 heterozygotes (Rudberg et al. 2014). The allele CYP2C19*17 is known for increasing metabolic capacity due to its variant in the gene's promoter region, causing enhanced transcription (Sim et al. 2006). The increased metabolism and lower plasma concentrations will increase this SSRI failure for this ultrarapid metabolizer. Instead of changing the dosing amounts, the recommendation is to consider an alternative drug that CYP2C19 will not primarily metabolize. An extensive metabolizer has two normal functioning alleles like *1/*1. This metabolizer allows for normal metabolism; around thirty to fifty percent of patients have this type of genotype (Hicks et al. 2015). This type of phenotype allows for initiating SSRI dosage to be at the recommended level.

CYP2C19 intermediate metabolizers have a more reduced metabolism compared to the
extensive category. These patients can start escitalopram at the initial dosage. This group of intermediate metabolizers represents the second majority of patients, as eighteen to forty-five percent have this genotype (Hicks et al. 2015). These patients carry one normal functioning allele or one increased function allele with a non-functioning allele. This group's allelic combinations include *1/*2, *1/*3, and *2/*17. *1 represents a normal functioning allele with *2 and *3 representing non-functioning alleles. *17, as seen in the ultrarapid metabolizer, has increased function. The intermediate phenotype could have an elevated plasma concentration (Stingl et al. 2013). This increase in plasma concentration means the acceptance of utilizing the starting dosage. However, elevated dosages with weaker metabolisms, such as in an intermediate phenotype, could increase the chance of an adverse drug reaction (Noehr-Jensen et al. 2009). Due to this increased risk, an alternative SSRI like sertraline or paroxetine should be used with weaker metabolizers, since these drugs are not assimilated primarily by CYP2C19.

The lowest metabolizer is known as the poor metabolizer. This metabolizer is seen in two to fifteen percent of patients (Hicks et al. 2015). These individuals do not have any functioning alleles, such as *2/*2, *2/*3, or *3/*3. Similar to the intermediate metabolizers, these patients have an increased plasma concentration, and increased dosing will cause adverse drug reactions. If there is a necessity for escitalopram, administering half of the initial dosage should eliminate the risk of QT prolongation (Stingl et al., 2013; Funk and Bostwick, 2013). Side effects are also more prone to occur in poor metabolizers than normal metabolizers, which warrants this reduction in dosage.

Thus, prescribers and patients understanding these genotype-phenotype variations and their effects on escitalopram is vital for the patient's safety. Jeopardy of this safety with wrongly prescribed dosages causes adverse effects. These unfavorable effects can range from CNS effects, gastrointestinal dysfunction, and arrhythmia from QT prolongation (Hicks et al. 2015). Not to mention, escitalopram can cause more depressive or suicidal thoughts in patients if it is not adequate for that individual (Hicks et al. 2015).

The Impact of Prenatal Escitalopram Exposure on Child Development

Exposure to escitalopram and other SSRI drugs while in the womb can also accentuate anxious behavior in the behavioral, emotional, and social development of the child (Rutter et al. 2006). The onset of these effects occurs as early as preschool-aged children or children at age five. This impact on children is still emerging, and a complete understanding of how antidepressants during pregnancy affect children is yet to be known. Escitalopram alleviates anxiety and depression; researchers monitored mothers using escitalopram either before and/or during pregnancy for their drug usage. Children of these mothers were then categorized by when their mother used escitalopram throughout their pregnancy. These categories include early (weeks 0-16), mid (weeks 17-28), or late (>week 29) (Lupattelli et al. 2018). These children were then compared to children who did not have exposure to escitalopram while in the womb. These children are affected by SSRI exposure due to the drug's ability to cross the placenta and the blood-brain barrier (Gaspar et al. 2003). This crossing of the placenta interferes with fetal brain maturity by inhibiting serotonin signaling (Heikkine et al. 2002). Thus, children prenatally exposed to SSRIs are more prone to internalizing and depressive-anxious behaviors at age five. Children exposed to SSRIs prenatally did not express these behaviors. Unfortunately, this trend continues into early adolescence, and children exposed to SSRIs during prenatal development exhibited a twenty-five percent higher risk of being
diagnosed with any psychiatric disorder and an eighty-four percent elevated risk of receiving a depression diagnosis, in comparison to children born to mothers who ceased SSRIs before pregnancy (Malm et al. 2016). Therefore, this development of depressive-anxious behaviors in early childhood is related to later-life psychiatric diagnoses and poor social adjustment.

However, the timing of when mothers use escitalopram affects the severity of anxious/depressive behaviors in children. In the analysis conducted when the children reached the age of five years, the offspring of mothers who had used SSRIs in the late stages of pregnancy exhibited a significantly elevated risk of displaying anxious or depressed behaviors in comparison to unexposed children (Lupattelli et al. 2018). No relationship between other aspects of child development and escitalopram exposure appeared, and this pattern did not become apparent after exposure to SSRIs in mid-pregnancy (Lupattelli et al. 2018). The study assessed various behavioral, emotional, and social outcomes at different times, with evaluations conducted at approximately 1.6, 3.1, 5.1, and 6.5 years of age. One of the evaluations includes the Child Behavior Checklist (CBCL). It involves a questionnaire completed by parents or caregivers to evaluate various aspects of a child's behavior and emotional well-being. Significantly, as the children grew older, there was a 0.06 standardized effect increase in the CBCL scores related to anxious/depressed behaviors among those exposed to SSRIs in late gestation compared to their unexposed peers (Lupattelli et al. 2018).

Furthermore, the study identified no interaction between prenatal SSRI exposure at different stages of gestation and children's emotional and social traits. It is essential to note that there was no apparent connection between the mothers who ceased SSRI use during pregnancy and the CBCL outcomes of their children (Lupattelli et al. 2018). Thus, mothers using escitalopram during pregnancy can cause a greater predisposition for their children to experience anxious and depressive behaviors. Anxiety Relief with SSRIs and SNRIs

Clinical, demographic, and genetic factors will influence responses to antidepressants like SSRIs. However, there still are efficacy differences between the various prescriptions. Comparing SSRI drugs to Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) is typical due to a vast number of similarities. SNRIs treat conditions such as depression, anxiety, and certain chronic pain disorders. SNRIs manipulate serotonin and norepinephrine levels, which regulate the body's mood, emotions, and certain bodily functions. These levels increase due to the binding and blocking of reuptake transporters. People who experience these conditions have lower levels of these neurotransmitters, so SNRIs cause an increase in serotonin and norepinephrine, which restores the balance and improves the overall well-being of patients.

Between SSRI and SNRI, the efficacy of both is relatively similar, with neither proving superior to the other. Since they combat different neurotransmitters, their effect will vary for different people. However, both SSRIs and SNRIs are effective in treating anxiety, obsessive-compulsive, or stress-related disorders, accounting for clinical and methodological differences, as the medications had a higher efficacy than a placebo (Gosmann et al., 2021). Cross-medication comparisons also showed that escitalopram had the highest efficacy. The size ranges for effectiveness were 1.06 for citalopram and 2.75 for escitalopram (Gosmann et al., 2021). These results determine that escitalopram proves to have the most significant difference in combating the various conditions. Escitalopram is more selective for the reuptake of serotonin than other SSRIs due to those drugs having a lower affinity (Li et al., 2017). This selectivity
allows escitalopram to be more effective and safer in treating major depressive disorder (MDD) and other conditions (Li et al., 2017).

In another experiment, researchers assessed the efficacy of SSRI drugs using various clinical measures over 24 weeks. To eliminate subjectivity, researchers unified participants' baseline conditions in measurement through the Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Anxiety Rating Scale (HAM-A29). These assessments were repeated at weeks 1, 2, 4, 8, 12, 16, 20, and 24 to track changes in depression and anxiety symptoms (Jiang, 2017). The Clinical Global Impression (CGI) and Hamilton Depression Rating Scale-17 (HAM-D-17) were also used at all visits except week 20. The primary efficacy measure was the remission rate, defined as having MADRS scores ≤10 and HAM-A29 scores ≤7 at week 24. Additional efficacy assessments included the response rate, defined as a ≥50% reduction in MADRS scores from baseline, and changes in MADRS, HAM-D-17, HAM-A29, CGI-severity (CGI-S), and CGI-improvement (CGI-I) scores. Quality of life was assessed using the Short Form-12 (SF-12), physical component summary (PCS), and mental component summary (MCS) scores at baseline, as well as at weeks 8 and 24. Safety measures included evaluating treatment-emergent adverse events (TEAEs), monitoring concomitant medications, and checking vital signs like blood pressure and heart rate at each visit. Researchers recorded the participants' weight at baseline and weeks 8 and 24. Additionally, physical examination findings, electroencephalogram data, and clinical laboratory analyses were conducted at baseline, week 24, and in cases of early discontinuation from the study to assess safety and overall health. With these assessments, researchers could signify the efficacy of escitalopram.

Throughout the 24-week treatment period, the administration of escitalopram exhibited notable success in promoting remission among patients, with substantial enhancements in the alleviation of depression and anxiety symptoms (Jiang, 2017). Moreover, the overall quality of life for these individuals showed significant improvement. Interestingly, the initial levels of anxiety experienced by the patients did not appear to significantly impact the effectiveness of the treatment, as it yielded positive outcomes across various subgroups. In essence, the findings from this study suggest that escitalopram proved to be a highly effective and generally well-tolerated option for the long-term management of MDD when coupled with anxiety. These results underscore the potential benefits of this therapeutic approach in addressing the complex and often intertwined challenges presented by MDD and co-occurring anxiety, offering hope and improved well-being to affected individuals (Jiang, 2017).

These results are consistent throughout the research literature, with other principal findings of escitalopram demonstrating greater efficacy than other SSRIs and SNRIs. MADRS mainly assessed these predominant findings.

Unraveling the Superiority of Escitalopram Among SSRIs

There are multiple hypotheses as to why escitalopram shows superior efficacy than other SSRIs. One idea sprouts from the allosteric modulation of the serotonin transporter with escitalopram (Kennedy, 2006). This modulation indicates that escitalopram does not bind to the primary active site of the serotonin transporter but to the low-affinity allosteric site. The low-allosteric site influences how well other substances, like ligands, can bind to the primary site. This binding of escitalopram to the low-affinity allosteric site allowed for more binding of escitalopram to the primary site. This binding strengthened the inhibition of the reuptake of
serotonin by the serotonin transporter. The enhancement of binding and reuptake allows for higher levels of serotonin in the synapses that allow for the medication's effects of alleviating symptoms of depression and anxiety through its impact on mood regulation and symptom improvement (Kennedy, 2006). These interactions with the serotonin transporter are unique to escitalopram compared to other SSRIs and cause more significant binding to the primary site, which describes why it is more effective than other drugs (Kennedy, 2006).

Another alternative explanation to this hypothesis deals with SNRIs. SNRIs perform a dual reuptake inhibition of serotonin and norepinephrine that is associated with venlafaxine, which is a superior antidepressant when compared with most SSRIs. Even though it's generally believed that dual reuptake inhibitors like venlafaxine are more effective in treating depression, escitalopram can be as effective as venlafaxine (Kennedy, 2006). Escitalopram can decrease its dissociation rate from the serotonin transporter, potentially through the allosteric site mentioned earlier. As a result, it stays bound to the transporter for longer, leading to extended inhibition of serotonin reuptake and higher levels of extracellular serotonin in the synapse. While venlafaxine may be more potent than most SSRIs, escitalopram's specific mechanism of action, involving prolonged inhibition of serotonin reuptake and elevated extracellular serotonin levels, could explain why it is as effective as venlafaxine (Kennedy, 2006). Additionally, escitalopram maintains the advantage of being an SSRI, which is generally better tolerated by patients in terms of side effects.

**Enhancing Escitalopram's Efficacy through Complementary Therapeutic and Psychological Approaches**

Combining escitalopram and cognitive behavioral therapy proves to be even more beneficial for helping combat anxiety. A randomized, double-blind, pharmaco-fMRI trial demonstrated that the addition of escitalopram to Internet Cognitive Behavioral Therapy (ICBT) for social anxiety disorder (SAD) yields several positive outcomes (Gingnell, 2016). Firstly, it increased the number of responders, indicating that more individuals responded positively to the combined treatment. Secondly, it reduced anticipatory speech anxiety, which is a significant symptom of SAD, and suggests an improvement in this specific aspect. Lastly, the combination therapy with escitalopram appeared to attenuate amygdala reactivity, particularly in response to an emotional face-matching task. Remarkably, these effects were sustained over time, as validated by the data from a 15-month follow-up (Gingnell 2016). These findings align with clinical observations that SSRIs may enhance the effects of Cognitive Behavioral Therapy (CBT) and are consistent with neuroimaging trials that have indicated that the attenuation of amygdala reactivity may underlie the improvement of symptoms in individuals with anxiety disorders. In summary, this study suggests that combining escitalopram with ICBT offers a promising approach to enhance treatment outcomes for SAD, targeting both behavioral and neural aspects of the condition (Gingnell 2016).

**Conclusion**

In conclusion, the understanding of the mechanisms behind the efficacy of SSRIs, particularly escitalopram, in easing anxiety has grown significantly in recent years. SSRIs, including escitalopram, have emerged as powerful tools in the treatment of anxiety disorders,
offering comparable or even superior effectiveness to traditional treatments with more favorable side effect profiles. These medications primarily act by increasing the availability of serotonin, a neurotransmitter that plays a pivotal role in anxiety regulation.

Anxiety is intricately linked to the 5-HT serotonin receptor. With the use of escitalopram, 5-HT's dysfunction that causes anxiety can be combatted through reuptake inhibition of presynaptic serotonin, causing the postsynaptic receptor enhancement from the prolonged serotonin's presence in the synaptic cleft. Two major subcategories of 5-HT serotonin receptors in the CNS, 5-HT1 and 5-HT2, are associated with anxiety regulation. This anxiety modulation mechanism can occur through autoreceptor activity within the 5-HT1 receptor system, particularly the 5-HT1A and 5-HT1D receptors. SSRIs, including escitalopram, enhance the sensitivity of these receptors, which can counteract the excessive fear pathway activation associated with anxiety.

The fear pathway also plays a crucial role in anxiety regulation, and SSRIs, especially escitalopram, help inhibit this pathway. Serotonergic projections from the raphe nuclei primarily drive the fear pathway in the brain. SSRIs like escitalopram inhibit this pathway by elevating serotonin levels in the amygdala and reducing excitatory input, leading to a decrease in anxiety and panic responses.

Genetic factors, such as CYP2D6 and CYP2C19 polymorphisms, are crucial in determining an individual's response to escitalopram and other SSRIs. Understanding these genetic variations is essential for ensuring safety and efficacy in SSRI treatment. CYP2C19 influences escitalopram, and its effectiveness can vary depending on the patient's metabolic capacity. Poor metabolizers may experience adverse effects if given standard SSRI dosages. In contrast, ultrarapid metabolizers may need alternative medications. Escitalopram metabolized by CYP2C19 may require dose adjustments based on an individual's genotype. The genetic variability also impacts the risk of side effects and treatment efficacy. Future research can help patients respond better to escitalopram by refining genetic testing to determine an individual's CYP2C19 and CYP2D6 genotypes and their impact on escitalopram metabolism. This research can help tailor dosage recommendations and improve treatment outcomes.

Prenatal exposure to escitalopram can impact a child's behavioral, emotional, and social development, with children exposed to SSRIs in utero exhibiting an increased risk of anxious and depressive behaviors. The onset of prenatal exposure affecting child development occurs during early childhood and leads to an increased risk of psychiatric disorders later in life. The timing of exposure during pregnancy can affect the severity of these behaviors, with late-stage exposure showing the most pronounced effects on child development. Researchers should continue to investigate the long-term consequences of prenatal exposure to escitalopram, mainly focusing on its impact on child development and potential interventions to mitigate adverse effects.

When comparing SSRIs and SNRIs, the efficacy in treating anxiety is relatively similar, with escitalopram often showing superior results. Escitalopram's increased effectiveness is attributed to its unique allosteric modulation of the serotonin transporter, allowing for increased binding and inhibition of serotonin reuptake. The prolonged serotonin binding to its transporter results in elevated extracellular serotonin levels.
The combination of escitalopram with CBT has shown promise in the treatment of social anxiety disorder, with improved response rates, reduced anticipatory anxiety, and amygdala reactivity attenuation, suggesting a comprehensive approach for managing anxiety. A potential direction for future research would include the exploration of the synergistic effects of escitalopram with other therapies, such as different forms of psychotherapy, to determine the most effective treatment combinations for various anxiety disorders that can continue to grow and help further enhance escitalopram's efficacy and understanding.

In summary, the evolving understanding of the mechanisms of action of escitalopram and its unique characteristics has shed light on its effectiveness in alleviating anxiety. Escitalopram and other SSRIs play a significant role in easing anxiety by modulating serotonin levels and affecting various neural pathways and receptors in the brain. Additionally, genetic factors and combination therapies can further enhance their effectiveness in treating anxiety disorders. These insights offer valuable guidance for healthcare providers and individuals seeking effective treatment for anxiety disorders, with the potential for enhanced therapeutic outcomes through a combination of pharmacological and psychological approaches. Research on escitalopram should aim to improve treatment outcomes through combination therapies and personalized medicine and continue to explore prenatal exposure research.
References


Characterizing the Polyamorous Experience Through Research

KACEY O’HARRA

PSY 4540: Human Sexuality Capstone

Nominated by: Dr. Patricia Schiml

Kacey O’Harra is a research-oriented graduate of the WSU Behavioral Neuroscience concentration program, hoping to apply to Neuroscience PhD programs in the coming years to continue a career focused on researching the fine details of how the brain works. Kacey is also physically disabled and completed a minor in Disability Studies focusing on how various physical differences, mental and physical health conditions, and neuropsychological profiles interact with research both inside and outside of the medical field.

Author notes:
I became interested in this topic when a neuroendocrinology study examined in this capstone included data from polyamorous participants which challenged not only interpretation of the results, but also many assumptions within the existing rhetoric on human sexuality and interpersonal connection. The rapidly growing numbers of people both experimenting with and living long-term with relationships outside the normative standard, combined with the questions raised by the variance they introduce, show the importance of the work summarized here. This was a great opportunity to branch from my usual spheres of neuroscience and "back-end" psychology into more clinical and "front-end" psychology work.

Faculty notes:
Kacey’s paper, Characterizing the Polyamorous Experience Through Research, was a well-conceived and thorough review of the literature to date surrounding the nature of polyamorous relationships. Such non-traditional relationships are growing in number in our culture, and the paper not only describes their structures, motivating factors, and stability, but also addresses how they are changing our culture as they become increasingly accepted.
Characterizing the Polyamorous Experience Through Research

Abstract

Scientific study of polyamory and the individuals who practice it has seen a sharp increase in the last decade, revealing data and subjective experiences that support their capacity to be closely intimate and fulfilling, to bolster personal development, to provide a positive and stable family environment, and to mutually strengthen the bonds of each relationship involved. Understanding the unique experiences and challenges faced by polyamorous lovers is essential for cultural competence in relational research, clinical practice, institutional regulations, and moving toward greater social acceptance. Examined here are the associated stigmas and their impacts on polyamorous individuals, the motivations people have for becoming and remaining poly, the underlying values of the concept, the benefits these relationships can carry, prosocial behaviors that facilitate successful polyamory, the different ways multiple consensual relationships are arranged and interpreted, need fulfillment, the dynamics of poly families, and how jealousy and compersion interact within polyamorous contexts.

Keywords: consensual non-monogamy, marriage, parenting, counseling, healthcare, social work, relational maintenance
Characterizing the Polyamorous Experience Through Research

Polyamory represents a particularly defined form of consensual non-monogamy (CNM), the umbrella term for intimate relationship structures in which all parties involved are aware of each other and approving of extradyadic interaction. Other CNM relationship structures such as swinging and open relationships vary in their boundaries and negotiations, especially regarding sex versus love; however, polyamory, in keeping with the roots of the word, specifies emotionally intimate or loving relationships with more than one individual which may or may not include sexual intimacy (Grunt-Mejer & Chanska, 2020). Gaining a better understanding through study of the thoughts, feelings, behaviors, and experiences of polyamorous individuals and the processes behind the maintenance of multiple healthy and consensual emotionally intimate relationships is essential not only for professional competence in practices, such as therapy and social work with polyamorous clients, but also to broaden and correct bias in our understanding of relational issues and satisfaction, even as applied to monogamous couples (Balzarini et al., 2017).

Overview of Polyamory Research

Research and academic literature concerning multiple intimate partners primarily began with the sexual revolution characterizing the latter half of the 20th century (Duplassie & Fairbrother, 2016) and has steadily increased since (Meyer-Goodwin, 2021). However, many fail to differentiate polyamory from other markedly contrasted types of CNM such as swinging (Balzarini et al., 2018). Most do not measure or control for potentially critical variables such as the amount of time participants have been practicing non-monogamy (Flicker, Vaughan, & Meyers, 2021), and almost all theory and data analysis is based on dyadic relationships, which are notably not to be assumed in polyamorous culture (Boyd, 2017). Most studies rely on small convenience samples (Haupert et al., 2016), and much of the sampling and data collection is done online, greatly limiting its generalizability, as this tends to exclude those with less access to technology, less knowledge of or interest in online forums, and less permissive circumstances for openly identifying as polyamorous (Meyer-Goodwin, 2021).

More than one in five single Americans has engaged in some form of consensual non-monogamy, with about 5% acting on a CNM relationship at a given time (Haupert et al., 2017). Despite sample skewing in many non-monogamy studies thus far suggesting its prevalence in highly educated Caucasians (Morrison et al., 2013), this proportion tends to be the same across different ethnicities, education and income levels, geographic regions, and religious and political affiliations, but begins to vary with gender and sexual orientation (Haupert et al., 2017). CNM survey participants have consistently identified as non-heterosexual and as some form of genderqueer more often than their monogamous counterparts, partially explained by these respondents being more fluid over time and less likely to define their gender or sexuality in more polar or traditional terms (van Anders, Manley, & Diamond, 2015). An early study noted that many of the bisexual polyamorous women studied had no same-sex intimate experience or bisexual identity before becoming polyamorous, suggesting a greater openness of sexuality could mediate the correlation (Sheff, 2005). The inference that polyamorous or other non-monogamous individuals are mostly bisexual has little foundation, however, especially considering that only about 1-3% of the US population reports being bisexual, and CNM is not
as uncommon among heterosexual and predominantly homosexual people as this assumption necessitates, suggesting sampling bias in studies on non-monogamy is a more likely explanation for many of these quantitative differences. Some counteracting influences have also been hypothesized, such as a potential decline of non-monogamy among gay men following the AIDS crisis, or the concurrent rise of mononormative scripts in LGBTQ+ culture along with the rise of marriage equality (Haupert et al., 2017).

Most polyamorous respondents have up to three partners, and one committed partner at the time of being surveyed is most common (van Anders, Manley, & Diamond, 2015). Many studies, however, exclude participants without at least two concurrent partners at the time of the study (Balzarini et al., 2019b), which due to the fluidity and constantly evolving negotiations of polyamory (Kleese, 2018), may exclude poly individuals who don’t prefer to or aren’t able to find and maintain three or more committed partners at all times in order to retain an outside definition of non-monogamy, while single relationships come and go and evolve over time. Though polyamory is practiced, structured, and negotiated in very diverse ways, throughout many communities on average, multi-directional poly relationships involve three people at a given time, often with at least one married couple (Boyd, 2017), and the average polyamorous family appears to be a couple cohabitating with children and both with their own partners (Kleese, 2018).

Public & Professional Perceptions

Most of the general population, including many clinical professionals, believe that humans are naturally monogamous, often vaguely mentioning supportive evolutionary theories without explicitly discussing any in particular, and purport the moral correctness and necessity of the practice by its standardization in society and theorized biological roots. Many monogamous individuals feel that true love is based in sharing one’s entire life with a single partner, a sense of being uniquely chosen, and immense time and effort, which many feel are only possible with one exclusive partner (Grunt-Mejer & Chanska, 2020). In response to critiques on the universal superiority of monogamy, such as the prevalence of infidelity and divorce, or results across nearly 50 countries showing that most men and about half of women expect to have more than one partner within five years (van Anders, Manley, & Diamond, 2015), cheating is defended above CNM morally with the argument that there is at least an attempt at monogamy (Brown, 2020) and that issues in the relationship can be resolved if both partners take responsibility. Further dissatisfaction is usually attributed to choosing the wrong partner. Serial monogamy, describing the common situation of being in many separate and relatively short monogamous relationships one after another over time, is defended even by clinicians as having still greater security and self-certainty than in any non-monogamous relationship. The statements of professional experts in relationship therapy characteristically waver, seemingly without their awareness, between one concept of ideal love that comes naturally and easily with the right partner and one which is supposed to require constant work and sacrifice (Grunt-Mejer & Chanska, 2020).

Although most with experience in polyamory agree that social tolerance is improving, at least in Western culture where many of these studies are conducted (Boyd, 2017), the vast majority of reactions and perceptions from friends, family, coworkers, and the public are still
those of shock and disgust (Cardoso, Rosa, & da Silva, 2021). One of the most unanimously experienced reactions of misunderstanding involves sexual generalizations about people’s motivations for polyamory; most agree that people generally see the relationship structure as a fetish or kink (Boyd, 2017), and common comments from family and peers include that a polyamorist simply desires a threesome (Table, Sandoval, & Weger, 2017) or to cheat or sleep around without consequences (Cardoso, Pascoal, & Maiochi, 2021). Consensually non-monogamous people are universally viewed as more promiscuous and at higher risk for sexually transmitted infections (STIs), even by respondents who are CNM themselves, and only very marginally improving when polyamory as multiple loving relationships with or without sex is distinguished from other CNM such as swingers who frequently negotiate only on extradyadic sex and often maintain largely monogamous emotional boundaries (Balzarini et al., 2018).

Table, Sandoval, & Weger (2017) theorize that this sexualization of the intent of polyamory results from internalizing monogamy as the moral basis of intimate relations.

People outside the community define polyamory with examples that are often gendered, imbalanced, and functionally instrumental or manipulative rather than rooted in meaningful relationships, frequently using language surrounding what is “allowed” compared to the language stressing respect and consent used by polyamorous lovers (Cardoso, Pascoal, & Maiochi, 2021). Even when explicitly mentioned, it tends to go ignored in outside perceptions that all partners regardless of gender usually have their own additional relationships with other people (Cardoso, Rosa, & da Silva, 2021). Many find that their peers see a cohabitating or long-standing partner as the “real” partner, and any other relationships as flings or affairs, assumed meaningless by comparison and not based in true human connection (Brown, 2020). Polyamorous relationships are generally seen as incapable of the levels of passion, closeness, trust, satisfaction, or commitment that can be achieved by monogamy (Balzarini et al., 2021).

Polyamory is also dehumanized to an extent that outpaces homosexuality in the modern world based on the lack of emotion attributed to those engaging in each (Rodrigues et al., 2018). The average outsider views polyamorous-identifying people as intensely selfish, rejecting of self-control and responsibility, escaping of commitment, and unwilling to compromise their needs with those of their partners. This view persists in the majority of clinical professionals, who pathologize CNM without distinction from cheating secretly in an otherwise monogamous relationship, purporting influences of fear of abandonment, incapacity to form meaningful bonds, or a lack of understanding of healthy dependency (Grunt-Mejer & Chanska, 2020). Common theories from therapists without experience with polyamorous clients also include secretly unfulfilling marriages, personality disorders, especially antisocial personality disorder, or unresolved neuroticism (Duplassie & Fairbrother, 2018). At best, polyamory is construed by negative onlooking clinicians and public members as a sign of immaturity or a phase, seen as tolerable only in young adults; CNM is equated to “dating around” before “settling down” at a certain age (Brown, 2020), and friends and family often assume monogamy will prevail once a polyamorous person finds the “right” partner (Table, Sandoval, & Weger, 2017).

In professional work and university environments, polyamorous lovers guard the details of their personal lives carefully in order to maintain an image of being competent, trustworthy, and in control of themselves (Table, Sandoval, & Weger, 2017). Many feel once they are no longer assumed to be monogamous, they are seen and treated as unreliable, rebellious, or
mentally ill, and must continuously attempt to validate themselves at significant costs to mental effort and emotional energy (Brown, 2020). Stigma against high promiscuity is notorious for its social exclusion and disgusted reactions, seen during the HIV crisis with gay men and more modernly with African American women (Balzarini et al., 2018). There are social and even legal ramifications to being “outed” as polyamorous, much like the consequences of being openly homosexual, as outlined in queer theory (Meyer-Goodwin, 2021). Sexual double standards and monogamous coding in the law amplify the potential repercussions for women in alignment with feminist theory (Aguilar, 2013), and comments on media depictions of polyamorous relationships are heavily gendered, with “women” being one of the most common words used in negative comments (Cardoso, Rosa, & da Silva, 2021). While the dominant narrative of monogamy is well-established with nearly infinite guidance, validation, and support, and therefore does not generally require critical thinking about one’s individual beliefs about intimacy and relationships, the constant moral challenge from all of everyday society and the internalized mononormativity and poly negativity faced by polyamorous people has been found to negatively impact their relationship maintenance and satisfaction in ways polyamory itself has not been shown to (Duplassie & Fairbrother, 2018).

**True Motivations and Values**

Contrary to widely held public assumptions, controlled research on polyamorous relationships has not found them to be any less emotionally close, healthy, or trusting. Studies into polyamory specifically have even found fairly consistent results that these relationships tend to bring greater happiness, more frequent and enjoyable sex, better physical health, higher satisfaction (Duplassie & Fairbrother, 2018), greater intimacy, better need fulfillment, more secure attachment (Morrison et al., 2013), and even simultaneously higher eroticism and nurturance on average than monogamous couples, thanks to complementary influence from multiple relationships (Balzarini et al., 2019a). Polyamorous families feel they garner much more essential support for raising their children from multiple partners, rather than the children receiving less attention and affection (Arsenau, Landry & Darling, 2019). Although avoidant attachment is associated with more positive views on consensual non-monogamy, actual engagement in CNM is negatively associated; it has been proposed that this could be because avoidant motivations and behaviors are not likely to be well received in the polyamorous community with its foundations in open communication and trust (Duplassie & Fairbrother, 2018). Despite being perceived as at higher risk for STIs than monogamous dyads by people of every relationship orientation (Balzarini et al., 2018), polyamorous and other CNM partners are not just more likely to test for STIs at the generally recommended level but are also more likely to use condoms during sex with all sexual partners (Lehmiller, 2015). By contrast, rates of unprotected sex are high for monogamous infidelity reported in 20-40% of marriages and 70% of monogamous relationships, and partners often do not find out there has been any potential exposure outside the couple, greatly increasing the risk of unknowingly transmitting an STI (Meyer-Goodwin, 2021).

The values polyamory grounds itself in have been outlined in literature, not only the consent and honesty necessitated by the basic definition of the practice, but also integrity, rejection of possessiveness, and knowing oneself. Fluidity and acceptance of change are also critical to many experiences; the boundaries of relationships and how kinship is interpreted
evolve over time with life changes and ongoing negotiation (Kleese, 2018), such that polyamorous study participants tend to have more committed relationships that previously involved sex than those that currently involve sex, with many challenging the adequacy of “ex” or “ex-partner” as a label in interviews (Vilkin & Sprott, 2021). Poly participants of the Loving More nonprofit compared to the general population on average disagree more strongly that “it is better to have a bad marriage than no marriage at all,” are more likely to agree that personal freedom in marriage can be more important than companionship, to which most tend to disagree, and are more likely to disagree that “couples don’t take marriage seriously enough when divorce is easily available,” while the general population tends to agree (Fleckenstein, Bergstrand, & Cox, 2012). Mutually fulfilling polyamory can reportedly be facilitated with introspective and articulate communication of needs, getting comfortable with experiences outside mainstream culture (which could account for more queer individuals willing to participate in CNM research), finding partners with shared values and lifestyles, embracing sexuality, access to community resources, (Duplassie & Fairbrother, 2018), openness, sharing tasks, and having supportive networks (Rubinsky, 2019a).

There are many motivations that drive different people to be polyamorous, both initially and through ongoing benefits like those mentioned above. For many, with emotional intimacy and love as the staples of bonds defined as polyamorous, the mutual self-development through close relationships underlying Relational Cultural Theory (Meyer-Goodwin, 2021) is allowed more opportunity for growth through additional meaningful relationships unrestricted by the social expectations of monogamy (Mitchell, Bartholomew, & Cobb, 2014). Certain experiences appear to be common introductions to the concept of CNM, such as exposure to the CNM practices of others, discovering bisexuality or other major aspects of sexuality in adulthood, or unexpectedly experiencing romantic love for two people simultaneously (Duplassie & Fairbrother, 2018). Differences in sexual preferences between partners are also mentioned as an important motivation for consensually non-monogamous adults identifying with BDSM or kink, a population that overlaps substantially possibly due to shared values in consensual negotiation of relationship dynamics and preserving individual autonomy (Vilkin & Sprott, 2021). On the other hand, life becoming too busy or not having anywhere to go for privacy can motivate reducing relationships or not seeking out new partners (Duplassie & Fairbrother, 2018). Polyamorists stress that although uniquely beneficial to their personal development, continuous and intense emotional work is required at levels monogamy does not generally demand and can be more difficult to manage (Aguilar, 2013).

Relationship Structures

Relationship structures vary among polyamorists, with some identifying one relationship as primary and all others as secondary, some considering multiple partners as co-primary (Balzarini et al., 2019a), and some rejecting any implied hierarchy between their relationships (Balzarini et al., 2017), an interpretation enabled by the principle of polyamory that each partnership is valuable and entirely unique based on different intellectual, emotional, and lifestyle connections (Aguilar, 2013). For many polyamorous units, one or two partners are considered primary based on marriage, living together, or having children together (Arsenau, Landry, & Darling, 2019). In a 2017 survey, about 55% of participants identified either with co-primary or non-hierarchical configurations (Balzarini et al., 2019c). A number of the
relationships labeled as non-hierarchical can be interpreted as pseudo-primary based either on the length of the relationship compared to pseudo-secondaries, cohabitation, or a significantly greater amount of time around each other, similar to living together (Mitchell, Bartholomew, & Cobb, 2014). However, the effect size of differences between primary and secondary relationships is smaller between these pseudo-primary and pseudo-secondary partners (Balzarini et al., 2019c).

Many partnerships that can be considered primary or pseudo-primary are afforded certain privileges to a greater extent. These partnerships can pass more easily as monogamous relationships in a mononormative society, allowing for more public and family acceptance, and often eliminating a need for secrecy that persists in many cases with secondary relationships. Individuals are also able to invest more in their primary relationships with inherently limited resources such as money and children, although it should be noted that relationship investments accrue over time and will be higher by nature of most primary dyads; it is unknown how much this accounts for primary-secondary investment differences. Similarly, commitment levels differ on average between primary and secondary polyamorous pairs, but as relationship marginalization is a strong predictor of commitment, it could account for any amount of the variance between these types of relationships (Balzarini et al., 2017).

The average polyamorous primary partner relationship is rated with more satisfaction than the average monogamous relationship; however, satisfaction is not necessarily higher for secondary partnerships (Balzarini et al., 2021). There is some interaction regarding relational satisfaction. For example, greater satisfaction with a secondary partner is associated with greater commitment to both primary and secondary partners (Balzarini et al., 2017), and need fulfillment interactions between relationship types predict satisfaction in both (Mitchell, Bartholomew, & Cobb, 2014). Greater communication in primary dyads and the greater proportion of time spent on sex in secondary relationships appear to be mostly mediated by the much greater amount of time spent together, especially for cohabiting couples (Balzarini et al., 2017). Likely for the same reason, more nurturance and less eroticism is experienced with primary partners compared to secondary partners, with the combined effect of both exceeding the eroticism and nurturance experienced by the average monogamous couple (Balzarini et al., 2019a). Consensually non-monogamous lovers appraise their primary partnerships with both more personal importance and more confidence that their partners will not act against their consent (Mogilski et al., 2019).

**Jealousy and Compersion**

Compersion, a concept not exclusive to the context of intimate relationships but emerging as a term from the polyamorous community due to the salient relevance of the missing language, encompasses the affection and positive range of emotions that can be experienced secondhand in response to a partner’s extradyadic involvement (Meyer-Goodwin, 2021). Polyamorists compare the response of joy and love felt in their unique circumstances to that experienced by people regardless of relationship orientation around a loved one accomplishing something important to them or receiving recognition, although the polyamorous experience of compersion uniquely interlaces with intimacy in its positive reflection (Balzarini et al., 2021). Polyamorous lovers describe feeling reassured through their partner’s independent support network and its reciprocal support of their relationship, excited as though the joy is contagious, empowered by their...
partner’s ongoing free choice to be with them, more loving through seeing their partner give and receive love, and for a minority, even aroused by extradyadic sex (Flicker, Vaughan, & Meyers, 2021). Compersion is not experienced universally by polyamorists (Rubinsky, 2019b) and comes more easily to some than to others but can be facilitated by a learned release of insecurity, similar to how jealousy can be cognitively learned through past experience (Meyer-Goodwin et al., 2021).

Romantic compersion has been conceptualized in both social and scientific discourse as the opposite of jealousy, especially as it posits itself on the assumption that a relationship’s love is in abundance with no need for competition (Morrison et al., 2013). However, increasingly including consensually non-monogamous relationships in research has suggested that these experiences may not be opposing ends of a continuum (Flicker, Vaughan, & Meyers, 2021). Mogilski et al. (2019) even propose that romantic compersion in polyamory, especially among queer polyamorous individuals, could more closely reflect the comfort of provisioning resources to a highly valued partner. Concepts of jealousy can still be present in polyamorous relationships, even alongside high compersion, and the two can commonly be felt simultaneously as part of a more complex system of emotions and cognitions (Balzarini et al., 2021), although polyamorous people report jealousy from an extradyadic threat less often than jealousy from insufficient needs or other more general relationship insecurity (Rubinsky, 2019b). This difference is likely related to principles defining the ongoing practice of polyamory, which promote working to overcome jealous feelings through introspection, open communication, and negotiation (Balzarini et al., 2021). Jealousy behaviors of spying and controlling do, however, strengthen the negative impact of identity gaps on poly relationships (Rubinsky, 2019a).

Polyamorous lovers report more cognitive jealousy, or processing and appraisal, but less emotional jealousy, or affective reaction, than monogamous lovers in response to extradyadic involvement, most likely influenced by the common practice of communicating frequently and transparently about such involvement. This cognitive reappraisal could also explain the disappearance of typical gendered patterns in jealousy toward sexual versus emotional extradyadic involvement in polyamorous samples. A mirrored pattern appears in reactions of compersion; however, men are more likely than women to report feeling compersion over their partner falling in love, while women are more likely than men to report compersion in response to their companion’s sexual involvement (Mogilski et al., 2019). In support of this challenge to the scope of jealousy’s conceptualization and treatment in relationship research, Rubinsky (2019b) found that the expression of jealousy, rather than the experience, appears to be more impactful on couples; the communicative response to jealousy outweighed both the emotional and cognitive affect in explaining variation in relationship satisfaction. Insight such as this from understudied consensually non-monogamous samples is critical to relational therapy and research because the assumption of jealousy as an unavoidable and polarly negative experience surrounding actual (not just perceived) extra-pair involvement may have obscured a large part of our understanding of healthy reactions to such involvement (Balzarini et al., 2021).

Neat Fulfillment

In the past hundred years, Western culture has seen an increasing emphasis on love in partnership and marriage, translating to normalization of a greater and more exclusive reliance
on romantic partners for the fulfillment of various types of needs, not only for sexual and emotional intimacy, but also needs like companionship and intellectual stimulation. Overreliance on romantic partners in fulfilling needs to the point of relational problems has been cautioned by clinicians and research findings (Mitchell, Bartholomew, & Cobb, 2014). The polyamorous community contains narratives avoiding over-burdening individual relationships by sharing needs like tasks, emotional advice, sexual needs, coping mechanisms, (Rubinsky, 2019a), independent free time, and the above-mentioned companionship and intellectual stimulation (Mitchell, Bartholomew, & Cobb, 2014).

Additionally, polyamorists monitor the ongoing needs of their existing partners, and how the fulfillment of these may be impacted by the intense and exciting feelings of first connecting with a new partner, coined as new relationship energy or NRE (Rubinsky, 2019a). Greater fulfillment of needs from more relationships appears to be more relevant of an influence in the general decision to be polyamorous and unrelated to active commitment to different partners or the active motivation to seek additional partners. Contrary to common assumptions, need fulfillment appears to operate independently between an individual’s different concurrent relationships; polyamorous individuals do not appear to seek out partners to compensate for insufficiently met needs or to contrast how well different partners meet their needs (Mitchell, Bartholomew, & Cobb, 2014).

Polyamorous parents and families praise having more support for their needs and the needs of their children (Arsenau, Landry, & Darling, 2019), and may through more comprehensive fulfillment of their own needs and the associated mental outcomes, improve their ability to be a relaxed and positive presence around children. Additional partners involved with children also fulfill critical family roles of demonstrating healthy, supportive, and loving relationships, introspective awareness of one’s own needs, and in the case of poly men, healthy depictions of masculinity and male-male interactions that are mutually supportive instead of antagonistic (Kleese, 2018).

**Recommendations for Practice and Future Research**

Given the substantial data supporting the validity of polyamorous relationships and the closeness and satisfaction they attain to an equal or greater extent compared to the monogamous standard, human service practitioners should examine and attempt to confront their personal prejudices on how they regard CNM relationships and the clients that present them, allowing interactions to address the unique problems polyamorous clients and community members face, rather than their consensual non-monogamy as the problem itself (Duplassie & Fairbrother, 2018). Relational experts must avoid theorizing a universal concept of love and instead focus on the subjectivity of the emotions it encompasses and trust human experience. They should avoid attempting to pressure clients into monogamy as well as disbelieving or denying the validity of multiple intimate attachments (Grunt-Mejer & Chanska, 2020). Particular aspects or identities of sexuality should not be pathologized without causing significant distress or delegated as overtly personal and private, facilitating the erasure of dissent from heteronormative and mononormative culture (Cardoso, Rosa, & da Silva, 2021).
Workplaces and universities, given the data on polyamory in culture, should strive not to discriminate against different kinds of partnerships and families (Brown, 2020). Institutions should consider the inclusion of polyamorous arrangements with questions concerning insurance coverage, relationship statuses on medical information forms, hospital policies on the number of supporting parties during pregnancy and birth (Arsenau, Landry, & Darling, 2019), divorce, guardians registered with children’s schools, next-of-kin communication with doctors, assisted reproduction, immigration legislation, and other concerns (Boyd, 2017). Future research on polyamorous individuals should acknowledge co-primary and non-hierarchical poly arrangements, include participants and measures for non-dyadic relationships, distinguish between forms of consensual non-monogamy differing in their structure or general boundaries, control for additional variables such as the amount of time subjects have been practicing CNM, and attempt to profile typical variation in boundaries and negotiations.
References


Desalination as a Source of Freshwater

Jacob Pensky is a senior at Wright State University pursuing a B.S. in Earth and Environmental Sciences. After spending two years at Bowling Green State University, he transferred to Wright State in 2022. He expects to graduate in the spring of 2024.

Author notes:
Converting seawater to fresh, potable water through desalination is an exciting yet complex process. Drinkable seawater can bring water security around the globe, but desalination plants are expensive, inefficient, and environmentally hazardous. Like so many other climate-related crises, water security will come down to advancements in clean, sustainable energy that can make desalination plants clean and sustainable. Research on this topic was challenging, but learning about the mechanics and challenges of desalination was fascinating.

Faculty notes:
Jacob Pensky's article deals with technology we use to make saltwater drinkable. Drought-stricken coastal communities need desalination plants, especially as Earth's climate warms, but they are expensive and energy-intensive. This article describes ways to reduce the environmental and monetary costs.
Desalination as a Source of Freshwater

Freshwater is becoming more of a rare commodity every day, especially in areas experiencing rising sea levels and drought. Both of these stressors have significant effects in coastal areas. Sea level rise, in particular, can flood and contaminate underground aquifers, which are one of the most common sources of freshwater around the world. This means that regions in need of water may have to turn to Earth’s vast saltwater oceans, which is where desalination comes in. Desalination is the process in which salt is removed from seawater to produce freshwater that is fit for human consumption. Because of the sheer volume of saltwater on Earth, the scarcity of freshwater would not be a concern if clean and efficient desalination were achieved. Still, visions of transcontinental pipelines sending clean, potable seawater to every corner of the Earth will likely not be realized anytime in the near future. Desalination needs to be a reliable source of freshwater as rising sea levels are damaging underground aquifers in populous coastal areas, but it will not be until plants are run with clean, sustainable energy that allows for proper management of hazardous reject brine.

The brine left over from the desalination of salt water is a primary reason why it is not a reliable source of freshwater. Desalination “brine” refers to the salt that is left over after being removed from salt water. When salt is removed from water during desalination, it is often released back into the body of water that it came from, along with other harmful contaminants like chlorine, copper, and other heavy metals that are used during the filtration process. This brine has an extremely high salinity that can be almost twice as much as the body of water it is being deposited into (Ihsanullah et al., 2021). This poses a major threat to species that have become acclimated to a certain salinity level. Also, desalination plants need to heat the water to high temperatures for it to be properly filtered, especially in multi-stage flash and multi-effect distillation processes. Naturally, the reject brine from these plants has a much higher temperature than the surrounding water. Seagrasses are often the most vulnerable in high-salinity, high-temperature discharge areas, as the abnormally high salinity inhibits their ability to conduct photosynthesis (Sánchez-Lizaso et al., 2008). Because they are a primary producer, seagrasses have a significant effect on the surrounding ecosystem.

The reject brine from desalination is a difficult burden to shake, but there are techniques that, if further developed, can help mitigate the harmful environmental effects. One of these techniques is to recover the brine and recycle it for various other uses. For example, instead of releasing the brine back into the source, it can be released in areas where it can benefit the natural environment. Saltwater brine can be used to restore brackish wetland ecosystems (Rodríguez-DeLaNuez et al., 2012). For species that are adapted to saline environments, the addition of saltwater brine can provide nutrients that become limited during drought. This method is very useful because it allows the brine to be disposed of as-is without any extra treatment. However, finding areas that will benefit from the brine can be challenging, and if desalination becomes more prevalent as freshwater becomes scarcer, the amount of brine that needs to be managed will only increase. To make the brine easier to dispose of in different areas, its chemical composition can be altered. Specifically, harmful metals can be recovered to make the brine less hazardous (Bello et al., 2021). Metal recovery has gained tremendous popularity in recent years, primarily due to the economic benefits of recovering certain metals, with magnesium being one of the most abundant and valuable (Zhang et al., 2021). The technology for metal recovery is still relatively unreliable and expensive, but it presents a promising upside as a way to manage harmful brine from desalination plants.

In addition to environmentally hazardous byproducts, desalination plants are expensive and require a great deal of energy to function. Many plants still rely on fossil fuels like natural gas to
operate, which contributes to the climate change that is making freshwater so scarce. There are two main categories of desalination plants: membrane filtration and thermal distillation. The primary process in a membrane filtration plant is reverse osmosis, which essentially just pushes water through a membrane at high pressure to filter out impurities. Thermal distillation includes two different processes that share many similarities. These processes are multi-stage flash (MSF) and multi-effect distillation (MED). MED involves sending water through different stages, each at a decreasing temperature and pressure, to evaporate the freshwater. MSF also relies on evaporation, but it does so by flashing the water with high temperatures at each stage to evaporate small portions of the water each time. Membrane filtration processes are cheaper than thermal distillation processes, as the cost to construct a reverse osmosis plant that can process 50,000 cubic meters of water per day was estimated to be around 74 million USD in 2008, while an MSF plant of the same size was estimated to cost 149.5 million USD (Wittholz et al., 2008). Thermal distillation plants are more expensive because they require both electricity and thermal energy, while membrane filtration only requires electricity (Al-Karaghoulil et al., 2013). However, thermal distillation can have a higher capacity for freshwater production once built. If they could be reliably run with clean, sustainable energy sources like solar, wind, and even hydroelectric, thermal distillation plants could be the most cost-efficient method of obtaining fresh water. The great energy costs mean that if they are run on fossil fuels, the environmental harm caused by the carbon emissions will outweigh the benefits of desalinated water.

Desalination needs an abundant source of clean energy if it is going to be of use to humanity in the future. The construction and operation of plants depend on having a large amount of energy, as does managing their hazardous reject brine. Possible sources include solar, wind, and nuclear energy. However, hydroelectric energy could serve as the most viable option for clean, efficient desalination, though it remains quite unproven (Bundschuh et al., 2021). This is because desalination plants are going to be constructed in coastal areas where hydroelectric power plants can also thrive. This proximity allows the facilities to work hand in hand to provide energy to produce clean water. One of the few real-world applications pairing hydropower with desalination is in Eagle Mountain, California, where the two facilities work together to protect the quality of the groundwater in the area (Saulsbury, 2020). This partnership provides energy for both desalination and the management of reject brine around the plant.

Along with addressing the energy needs of desalination, the Eagle Mountain site is focused on improving groundwater quality, which is one of the main reasons why desalination will be such an important technology in coming years. Temperatures are rising worldwide. This means that sea levels are also rising due to the melting of ice sheets. As seawater rises onto land, it makes its way into the freshwater underground aquifers that are relied upon for drinking water in coastal areas. Naturally, this flooding damages the quality of the water in the aquifers. If sea levels continue to rise, the damage to aquifers will only worsen. Another source of freshwater will need to be found, and desalination will have to be that source.

The world needs clean drinking water, as natural sources of freshwater, like lakes, rivers, and underground aquifers, have been put in jeopardy by human-caused climate change. Desalination has a great deal of promise when it comes to dealing with this lack of water, but high energy costs and harmful reject brine hold it back from being a primary source of freshwater. The expansion of renewable energy sources like hydroelectric power could be the catalyst that allows desalination to thrive, but until then, desalination is still a work in progress.
References


The Impact of the Gut-brain Axis on Alzheimer’s Disease

ELISSA WAKIM

ANT 6030: Biomedical Review Article Independent Study

Nominated by: Dr. Christopher Wyatt

Elissa Wakim, a graduate student at Wright State University, is pursuing a Master's Degree in Immunology and Microbiology with the aim of becoming a doctor. Having completed her undergraduate studies in Physiology & Neuroscience with a minor in Psychology at the same institution, she demonstrates a strong academic foundation. Amidst the challenges posed by the COVID-19 pandemic, Elissa committed herself to obtaining licensure as a certified phlebotomist, actively participating in plasma procurement for immunocompromised patients. Elissa envisions herself as a compassionate and innovative physician, leveraging her diverse background to advance medical science and improve patient care.

Student note:
In pursuing my vision of becoming a doctor, I have found my passion lies in addressing the significant knowledge gaps impacting countless individuals worldwide, particularly within the realm of neuroscience and Alzheimer's Disease. Focused on mitigating the devastating effects of this illness, I have directed my research towards understanding and improving the gut microbiome as a means of reducing the onset of Alzheimer's Disease. This approach not only targets an underrepresented group of individuals who have not yet reached a concerning stage of the disease but also offers hope to those who may not have access to preventative treatments.

Faculty note:
Elissa’s review for the Graduate Biomedical Review Article class was one of the best I have ever seen. It focuses on the links between the gastrointestinal tract and the brain; the gut-brain axis and the development of Alzheimer's disease. As a student in the Microbiology and Immunology Masters Program Elissa was particularly interested in the gut microbiota and their connection to neurodegenerative disease. She tidily reviewed the literature and wrote a fascinating and compelling piece of work.
The Impact of the Gut-brain Axis on Alzheimer’s Disease

Introduction

Alzheimer’s disease is a global health crisis that affects millions of individuals and their families daily. We all have encountered this neurodegenerative disease one way or another, and it is expected to increase dramatically within the next couple of decades. Despite rigorous research efforts, the exact etiology of Alzheimer’s disease remains unconcluded, and effective treatments are limited. Within the last few years, there has been increasing evidence that the complex and bidirectional communication between the brain and the gut (Gut-brain axis) plays a crucial role in the pathogenesis of Alzheimer’s disease. The gut-brain axis consists of a very complex system of signaling pathways that involve the enteric nervous system, the central nervous system [CNS], and the gut microbiota. Modification of the gut microbiota composition (dysbiosis) can alter brain function, promoting the development/progression of Alzheimer’s disease. Imbalances in the gut microbiota lead to increased permeability in the gut, increased systemic inflammation, and increased production of neuroactive substances. As a result, neuroinflammation, accumulation of protein aggregates in the brain and synaptic dysfunction are observed. All of these are hallmark characteristics of Alzheimer’s disease.

Understanding the complex interplay between the gut microbiota and Alzheimer’s disease offers immense hope to new research of varying mechanisms with potential paths to better therapeutics. This research paper aims to further explore the multidimensional impact the gut-brain axis has on Alzheimer’s disease, understand the underlying mechanisms, and discuss possible therapeutic strategies capable of targeting this communication system.

Increased research would not only be of scientific interest but also of ethical interest, as it offers the possibility to improve the lives of millions of diagnosed patients and their loved ones.

Alzheimer’s Disease

Alzheimer's disease [AD] is a progressive neurodegenerative disorder that primarily affects cognitive functions and leads to memory loss, impaired reasoning, and a decline in overall cognitive abilities. It is a complex and multifactorial disorder that is characterized by the progressive degeneration of brain cells, particularly neurons. This degeneration results in a gradual loss of cognitive function, memory, and the ability to perform daily activities. It is known to be the most common cause of dementia, accounting for approximately 60-70% of all cases.

Alzheimer’s disease can be broadly classified into two main types: early-onset AD [EOAD] and late-onset AD [LOAD]. Early onset AD typically manifests before the age of 65 and is often associated with genetic mutations, while late-onset AD occurs after the age of 65 and is believed to have more complex etiology involving both genetic and environmental factors. Additionally, Alzheimer’s disease can be classified into sporadic familial forms, with the latter being linked to specific mutations in genes like APP, PSEN1, and PSEN2 (Alzheimer’s Association, 2021). These genes play an important role in producing the amyloid-beta plaques. Late-onset Alzheimer’s disease is mainly influenced by genetic and environmental factors.
Dr. Alois Alzheimer, a German psychiatrist and neurologist, was the first person to describe the disease in the year 1906. He documented a case of a patient named Auguste Deter, who exhibited severe memory loss, language problems, and changes in behavior. Upon her death, Dr. Alzheimer examined her brain and discovered abnormal protein deposits [known as amyloid plaques] and tangled bundles of fibers [neurofibrillary tangles], which are now recognized as hallmarks of the disease (Maurer et al., 1997). Since Dr. Alzheimer’s groundbreaking work, significant progress has been made in understanding the disease. Researchers have identified genetic risk factors, developed advanced imaging techniques, and uncovered intricate details of the underlying pathology. Despite these advances, many aspects of Alzheimer’s disease remain elusive, and effective treatments are still lacking.

The amyloid hypothesis is one of the leading theories regarding the pathophysiology of Alzheimer’s disease. It postulates that the accumulation of beta-amyloid protein fragments in the brain plays a key role in disease pathophysiology development (Selkoe & Hardy, 2016). The abnormal processing of the gene AAP [amyloid precursor protein] leads to the production of beta-amyloid peptides. These beta-amyloid fragments form plaques that disrupt neuronal communication and trigger inflammation, ultimately leading to cell death (Hardy & Higgins, 1992). The amyloid-beta 42 variant of the beta-amyloid peptides has neurotoxic effects instituted by differing mechanisms including synaptic dysfunction, calcium homeostasis disruption, and tau hyperphosphorylation induction, leading to the formation of neurofibrillary tangles (Heneka et al., 2015).

Another critical aspect of Alzheimer’s disease is the aggregation of tau protein into neurofibrillary tangles within neurons. Tau is a microtubule-associated protein that is mostly found in neurons. It plays an important role in stabilizing the microtubules which are involved in intracellular transport and structural integrity. In Alzheimer’s disease, these tau proteins hyperphosphorylate and undergo a conformational change. This causes them to detach from the microtubules and provoke them into neurofibrillary tangles that are insoluble. These tangles interfere with cellular function, causing neurons to malfunction and die (Ballatore et al., 2007; Iqbal et al., 2010). The exact relationship between beta-amyloid and tau pathology is an active area of research, but it is known that the spread of tau pathology through the brain contributes to the progression of cognitive decline in Alzheimer’s disease (Braak & Braak, 1991).

Oxidative stress is another key mechanism that has been implicated in the pathophysiology of AD. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species [ROS], also known as free radicals, and the ability of the body’s antioxidant defenses to neutralize them. In the context of Alzheimer’s disease, oxidative stress plays a significant role in disease progression through several mechanisms. One of which is the accumulation of amyloid-beta plaques in the brain promoting the generation of reactive oxygen species and diminishing the function of antioxidant enzymes (Butterfield & Halliwell, 2019). Tau proteins forming neurofibrillary tangles also exacerbate oxidative stress, leading to damaged cells, dysfunction, and cognitive decline as seen in Alzheimer’s disease patients (Wang et al., 2020).

Alzheimer’s is a global health crisis that affects millions of individuals worldwide. According to the World Health Organization (WHO), approximately 50 million people had dementia in 2020, and this number is projected to triple by 2050, largely due to population aging. The economic burden of AD is substantial, with costs related to healthcare, long-term care, and lost productivity totaling hundreds of billions of dollars annually in the United States alone. Families of individuals with Alzheimer’s disease also bear a significant financial and emotional burden. Social impacts,
alongside economic impacts, also play a big role in AD prevalence. These impacts mainly include the caregivers and healthcare system. AD profoundly affects not only those diagnosed but also their families and caregivers. Providing care for individuals with AD is emotionally and physically demanding, often resulting in caregiver burnout and strain on family relationships. Meanwhile, the increasing prevalence of AD poses challenges to healthcare systems worldwide. Facilities and resources dedicated to dementia care are often insufficient, leading to delays in diagnosis, limited access to specialized care, and a need for innovative approaches to managing the disease.

Even though AD research has come a long way since 1906, there are still many challenges to face including lack of effective treatments, early diagnosis, complexity of the disease, and ethical/societal issues. One of the most pressing challenges is the absence of disease-modifying treatments. While several medications can temporarily alleviate symptoms, none have been shown to halt or reverse the progression of the disease. Early diagnosis is crucial for effective intervention, yet identifying Alzheimer's disease in its early stages remains challenging. Biomarkers and advanced imaging techniques are being used to enhance early detection. AD is a very complex disorder with multiple contributing factors, making it difficult to develop targeted therapies. Researchers are exploring various approaches, including immunotherapy and gene therapy, to address the diverse mechanisms involved. Lastly, as research progresses, ethical concerns related to genetic testing, consent, and data privacy become more prominent. Striking a balance between advancing scientific knowledge and protecting individuals’ rights is an ongoing challenge.

Alzheimer's disease is a devastating condition that robs individuals of their cognitive abilities and places a heavy burden on society. Despite significant advancements in research, numerous challenges remain, including the absence of disease-modifying treatments, the complexity of the disease, and ethical concerns. Continued research and investments in AD are essential to improve the lives of those affected and eventually find a cure for this debilitating neurodegenerative disorder.

Recent studies have shed new light on the complex relationship between Alzheimer’s disease and the gut microbiota. A relatively recent study led by Cryan et al, 2019 drew attention to a bidirectional communication system that linked the central nervous system and the gut to the pathology of Alzheimer's disease. It has then been investigated that alterations to the large quantity of microbes located in the digestive tract [gut microbiome] influence the neuroinflammation, accumulation of amyloid-beta in the brain, and the oxidative stress seen in Alzheimer's disease patients. This relation allows researchers to explore the extent of influence one has on the other. This may open new avenues for research and therapeutics regarding this disease.

**Gut Microbiota/** Composition & Function

The human Gut shelters a dynamic and complex ecosystem of microorganisms commonly known as the gut microbiota. This system plays a pivotal part in human health and disease. The gut microbiota has trillions of microorganisms including fungi, bacteria, viruses, and archaea (Sender et al., 2016). The composition and diversity of gut microbiota can vary widely from person to person and can be influenced by various factors, including diet, genetics, age, and environmental exposures. Emerging research has highlighted the pivotal role of the gut microbiota in not only aiding in digestion but also in modulating the immune system, synthesizing essential nutrients, and influencing various aspects of human physiology, making it a subject of great interest in the fields of medicine, nutrition, and biology. Understanding and harnessing the power of the gut microbiota has the potential to revolutionize healthcare and enhance our knowledge of the intricate interplay between microbes and their human hosts.
The composition of the gut microbiota is a complicated and intricate ecosystem that is influenced by many different factors. Diet is one of the most potent determinants of the gut microbiota composition. A study by David et al. (2014) showed that shifts in people’s dietary patterns significantly changed the gut microbiota within a few days. These dietary shifts included the consumption of fiber-rich plant-based foods rather than high-fat, low-fiber diets. Fiber-rich diets promote the growth of beneficial bacteria such as Bifidobacterium and Lactobacillus, whereas high-fat diets are correlated to increasing the number of harmful bacteria like Firmicutes while decreasing Bacteroidetes. In addition to shifting dietary patterns, greater dietary diversity results in a richer and more resilient microbiota.

Apart from diet, host genetics play a crucial role in shaping the gut microbiota. A landmark twin study done by Goodrich et al. (2016) revealed that genetics can influence an abundance of specific bacterial taxa. While the overall structure of the microbiota is more influenced by environmental factors, certain genetic traits can predispose individuals to home-specific microbial communities. For instance, genetic variations in mucin production or immune system genes can affect the adhesion and interaction of microbes within the gut. These genetic factors, in conjunction with environmental influences, underline the personalized nature of the gut microbiota and its response to various external stimuli, contributing to the ongoing research efforts to better understand and manipulate this complex ecosystem for improved health outcomes.

**Figure 1**: Shows the influence of diet on gut microbiota and well-being: The gut microbiota plays a role in the breakdown of dietary components and in the control of the body's metabolic processes. The health and disease status, characterized by the balance between beneficial and harmful bacteria, is influenced by the production of various microbial metabolites, which in turn depends on the nutrients provided.
Because the gut microbiota is mainly located in the small and large intestines, it has a significant role in both digestion and metabolism. These two mechanisms participate in breaking down and using the dietary components acquired from our food. One main function of the gut microbiota is the fermentation of complex carbohydrates that escape digestion of the small intestine. This leads to the production of short-chain fatty acids, also known as SCFAs, like acetate, butyrate, and propionate which are taken up by the host and function as important energy sources. SCFAs have great effects on the overall health of the gut. For example, Butyrate has been associated with maintaining the integrity and function of the epithelial cells found in the colon. They do so by providing a source of nourishment to the cells which then contribute to the preservation of the barrier of the gut (Koh et al., 2016). Eubiotic microbiota provides health benefits, and dysbiotic microbiota causes harm [Figure 1]. Research has shown that adhering to a Mediterranean diet for instance is more favorable in terms of a healthy gut. This diet is rich in fruits, vegetables, whole grains, and olive oil. Mediterranean diets have been linked to lower levels of inflammatory markers like C-reactive protein and interleukin-6 (Garcia-Molina et al., 2015). Other healthy promoters include GABA, Vitamins, polyphenols, and indoles. Polyphenols are anti-inflammatory and contribute to immunomodulatory effects, thus reducing the risk of potential inflammation (Calder et al., 2011). Western diets, on the other hand, are high in saturated fats, sugars, and processed foods. All of which cause inflammation and lead to an impaired immune function (Ghanim et al., 2009). Disease promoters include amines, polyamines, H2S, and methyl phenols.

Another large process that the gut microbiota is involved in is the breakdown of indigestible plant polysaccharides and dietary fibers that are undigestible. Microbes localized in the colon carry many enzymes that can break down complex molecules into more simple forms, which are able to be absorbed and utilized by the host. The gut microbiota can convert lignans from our diet into enterolignans, which act as antioxidants and positively affect our health (Kuijsten et al., 2005). Together, these microbial activities involved in digestion increase the host’s ability to obtain nutrients and bioactive compounds from the diet. These factors highlight the importance of the gut microbiota in advancing nutrient utilization and maintenance.

The relationship between the gut microbiota and the immune system is complex and begins developing early on in life, continuing to grow throughout an individual’s lifespan. Being able to understand it allows us to better understand immune homeostasis. The gut is consistently being exposed to a large array of microbes, thus it’s crucial for the immune system to be able to differentiate between commensal (beneficial) and pathogenic (harmful) microorganisms. The gut microbiota aids in educating the immune system, helping its proper function and development. Studies examining germ-free animals showed that the absence of a microbiota leads to an abnormal immune system, like underdeveloped lymphoid tissues, and a compromised immune response (Smith et al., 2007).

An important mechanism that highlights the influence of the gut microbiota on immunity is the shaping of the immune cell composition in the gut-associated lymphoid tissue [GALT]. There is a large population of immune cells like B cells, T cells, and antigen-presenting cells in the gut. They are influenced by signals sent from the gut microbiota, which helps it maintain a balance between the anti-inflammatory and pro-inflammatory immune response. For instance, some gut microbiotas induce the production of regulatory T cells [Tregs]. These cells function to suppress excessive immune responses and prevent autoimmune reactions (Belkaid and Hand, 2014), which are important in preventing chronic inflammatory conditions. Commensal bacteria is able to induce the
production of anti-inflammatory cytokines, like interleukin-10 [IL-10], and weaken the proinflammatory production (Round and Mazmanian, 2009). This intricate balance of cytokines helps maintain the immune tolerance to gut microbiota and prevents unnecessary immune activation. In addition, the microbiota is also involved in producing antimicrobial peptides and immunoglobulin A [IgA]. These components are essential parts of the mucosal immune defense system (Belkaid and Harrison, 2017).

Researching the gut microbiome reveals a very complicated web of connections that goes beyond topics related to just digestion and metabolism. Microbes hold significant power of not only our physical health but also our mental health. The emerging field has allowed researchers to further study the interconnectedness, especially relating to our cognitive and emotional well-being. These functions are seen within the gut-brain axis. It highlights the influence the gastrointestinal system exerts on our emotional and mental states.

**Gut-Brain Axis**

The Gut-brain axis is a very intricate bidirectional system that links the central nervous system [CNS] with the gut. The central nervous system includes the brain and the spinal cord. This complex system has a large array of biochemical signaling pathways that are mediated by many components, including hormonal, neuronal, and immune mechanisms. Most relatively, the gut-brain axis permits constant information to be exchanged between the gut and the brain, which allows them to work together to regulate a host of physiological and psychological processes (Mayer, 2011).

The gut microbiota, consisting of trillions of microorganisms, plays an important role in this dialogue. These microorganisms interchange information with the gut lining, serving as the physical barrier between the gut components and the bloodstream, resulting in the production of signaling and metabolite molecules. Some of these substances can cross the gut lining, entering the bloodstream, and influencing our brain and behavior. Because of this, we would be able to see changes in our cognitive and emotional processes (Cryan et al., 2019). This interaction is fundamentally important not only in understanding digestive health but also in understanding neurological and psychiatric conditions, which continue to shed light on the implications, opening the door to a wide array of diseases and disorders.

Research has shown that signals originating from the gut can influence brain function and behavior. For example, microbial metabolites, like short-chain fatty acids and neurotransmitters, influence mood and cognition (Cryan & Dinan, 2012). Contrarily, the brain also can exert an intense influence on the gut, modulating secretion, motility, and permeability. This bidirectional interplay emphasizes the holistic nature of our health, where the brain and the gut are intricately linked together, and their actions result in alterations affecting our thoughts and behavior and leading to diseases, like Alzheimer’s disease.

The vagus nerve is a very significant component of the gut-brain axis (figure 2). It functions to mediate the bidirectional communication between the gut and the central nervous system. The vagus nerve is also labeled the tenth cranial nerve and is a major parasympathetic nerve that stimulates many organs in the body, one of which being the gastrointestinal tract. The nerve can relay sensory information from the gut to the brain using the afferent fibers. It provides feedback on the gut’s condition and signals, when in the presence of microbial metabolites, nutrients, and immune responses. The information is then sent to many different brain regions including the
nucleus of the solitary tract. This tract is responsible for regulating mood, appetite, and autonomic regulation. It can integrate the signals resulting in brain function alterations (Bonaz et al, 2016).

Figure 2 shows there are different paths of communication available between the brain and the gut microbiota, including the vagus nerve, the immune system, short-chain fatty acids, and tryptophan (the precursor of serotonin).
The gut-brain axis relies on a complex communication system of neurotransmitters and hormones that regulate the connection of the gut and the central nervous system. Serotonin (5-HT), for example, is a neurotransmitter that is primarily known for its role in regulating our mood. It is abundantly found in the gastrointestinal tract and plays a central role in the gut-brain signaling (figure 3). Enterochromaffin cells, found in the gut, release serotonin as a response to being stimulated and influence gut secretion, motility, and signaling to the brain (Mawe & Hoffman, 2013). In addition, the gut normally produces a multitude of neuropeptides and hormones such as leptin, ghrelin, and peptide YY, all of which modulate energy and appetite. Leptin is produced by adipose tissue and functions to relay information about energy storage to the brain. This aids in regulating feeding behavior and the amount of energy we can spend (Friedman & Halaas, 1998).

The gut microbiota can also affect the production and regulation of neuroactive molecules like gamma-aminobutyric acid [GABA] as well as brain-derived neurotrophic factor [BDNF]. Both molecules are also involved in mood and cognitive function (Cryan & Dinan, 2012).

**Figure 3:**

Figure 3 shows the bidirectional brain-gut interactions that are related to serotonin signaling. In green, the Enterochromaffin cells consist of more than 90% of the serotonin that is produced in the body. This serotonin is labeled as 5-HT, and its synthesis is regulated by SCFAs and secondary bile acid (2 Bas) that are made by spore-forming clostridiles, resulting in increased stimulation and levels of tryptophan (TPH1). Enteroendocrine cells (EECs) signal to the afferent nerve fibers via synapse-like connections.
As we expand our research of the complex mechanisms involved in the gut-brain axis, a clear intersection emerges between the gut microbiota and the shaping of its balance and communication within the axis. We have long established that the gut microbiota has influence beyond just gastrointestinal health and that it holds important implications for neurological wellbeing. This connection highlights the need to look deeper into the relationship between the health of our gut microbiota and our neurological state and condition. One condition of significant importance is Alzheimer's Disease. With the disease projected to increase dramatically within the next few decades, research is continuing to shed light on how dysbiosis of the gut microbiota may influence the pathogenesis and progression of Alzheimer's disease.

**Gut Microbiota Dysbiosis in Alzheimer's Disease**

Emerging research has focused on the complicated relationship between the gut microbiota and the pathogenesis of Alzheimer's Disease. There have been many studies linking gut dysbiosis to its pathogenicity. Dysbiosis, in our case, is the state of imbalance in the function and the composition of the gut. Studies have shown that modifications in the amount of specific microbial taxa, like Lactobacillus and Bifidobacterium (beneficial bacteria), increase proinflammatory microbes. These compositional alterations in the gut microbiota are associated with increased permeability of the gut epithelial barrier. This leads to the translocation of bacterial products like liposaccharides into the blood. The translocation activates systemic inflammation and can contribute to neuroinflammatory processes seen in the progression and development of Alzheimer’s disease (Cattaneo et al., 2017; Vogt et al., 2017).

Recent research suggests that the gut microbiota influences Alzheimer’s disease via the gut-brain axis as well. Dysbiosis is shown to lead to the production of neuroactive metabolites, such as short-chain fatty acids, which can control microglial activity in the brain, as well as promote neuroinflammation. As a result, these neuroinflammatory processes aggravate and lead to the accumulation of pathological protein aggregates (amyloid-beta and tau), which are commonly known to be hallmarks of Alzheimer’s disease.

The dysbiosis of the gut microbiota in Alzheimer’s disease patients is increasingly being recognized as a contributing factor of the pathogenesis of this disease. It is being highlighted in the understanding of the gut microbiome as a potential therapeutic avenue in the management of Alzheimer’s disease (Sampson et al., 2016; Vogt et al., 2017).

**Therapeutic Approaches Targeting the Gut-Brain Axis in Alzheimer's Disease**

Therapeutic approaches targeting the gut-brain axis in Alzheimer’s disease have gathered significant attention in the last few decades as a possible avenue of disease management. These approaches aim to regulate the gut microbiota activity as well as the composition to decrease neuroinflammation and its downstream effects on the pathology of Alzheimer’s disease.

One approach uses prebiotics and probiotics to regain the balance of the gut microbiota. Probiotics are live microorganisms that positively influence the composition of the gut microbiota, while prebiotics are non-digestible compounds associated with the promotion of beneficial gut bacteria growth. Research has shown that live microorganisms play a central role in stimulating a healthy gut microbiota and enhancing overall health. Multiple studies have focused on the
advantages of probiotics in maintaining and restoring the gut microbiota such as that conducted by Goodoory et al. in 2023. This study, published in the Journal of Gastroenterology, showed that administering a specific probiotic strain led to significant enhancement in the symptoms of irritable bowel syndrome, such as abdominal pain and bloating. The Journal of Clinical Gastroenterology also published an important study that focused on probiotic use in patients with antibiotic-associated diarrhea. The research showed that there is certain probiotic supplementation which can reduce the risk of developing antibiotic-associated diarrhea. This supports the claim that probiotics serve as preventative measures against disturbance in the gut microbiota. Another study published in the Journal of Psychiatric Research investigated the potential connection between the use of probiotics with mood enhancement. It suggested that implementing probiotics in one’s diet may play a major role in modulating the gut-brain axis and positively influencing the mental well-being of patients. One main point that all the research highlighted was that the effectiveness of probiotics is strain-specific, which means that not all probiotic supplements will produce the same results.

Fecal microbiota transplantation [FMT] is a method that is more direct. It is a procedure that manually transplants beneficial gut bacteria from a donor stool to a patient with a damaged microbiota composition (Xu et al., 2021). Research has shown that fecal microbiota transplantations obtained from a healthy donor led to improvements in cognition and a decline in neuroinflammation (Tian et al., 2019).

Dietary interventions and nutrition have also been studied as possible therapeutic approaches to targeting the gut-brain axis in Alzheimer’s disease. Research has shown that diets rich in polyphenols, omega-3 fatty acids, and fiber have been shown to promote the growth of beneficial gut bacteria as well as reducing inflammation of the gut and brain (Bordalo et al., 2019). These dietary modifications enhance the function of our gut barrier and can decrease the translocation of proinflammatory molecules found in the bloodstream. Such approaches highlight the many strategies that can be placed to address the interplay between the gut microbiota and Alzheimer's disease. This potentially can lead to the development of new therapies in the fight against this neurodegenerative disease (Swanson et al., 2020).

**Conclusion**

In conclusion, this paper has highlighted the important role of the gut-brain axis in Alzheimer’s disease and focused on its profound involvement in understanding the pathogenesis and possible therapeutic interventions for this tragic neurodegenerative disorder. Current research, as exemplified by studies such as those studies by Cryan and Dinan (2019) and Meyer (2011), has shown the complex bidirectional communication between the central nervous system and the gut, highlighting the major influence the gut microbiota has on the development and the progression of Alzheimer’s disease. Dysbiosis of the gut microbiota, as discussed in studies by Goodrich et al. (2016) and Vernochi et al. (2020), is seen when there is an imbalance of microorganisms, which leads to altered microbial composition and function. Effects of this imbalance that contribute to the neuroinflammatory processes that underlie Alzheimer’s disease include an increase in systemic inflammation, gut permeability, and translocation of neuroinflammatory molecules (Belkaid et al., 2014 & Heneka et al., 2015). Many therapeutic approaches, supported by research such as that by Wang et al. (2020) and Ghanim et al. (2009), are available to target the gut-brain axis including prebiotics, probiotics, diet changes, and fecal microbiota transplantation.
Recognizing the gut-brain axis as an important player in Alzheimer’s disease allows multiple paths of research to emerge and therapeutic developments to evolve. New prospects and holistic approaches may come forth as researchers continue to better understand this complex disease. The ability to harness the microbiota’s influence on Alzheimer’s disease opens doors to a new perspective in battling this disease. While research has been ongoing and lengthy, there is still so much to discover and explore in this field with a high possibility in ultimately strengthening our ability to delay or even prevent the progression of it. This research would be able to bring so much hope to people suffering from the disease and to their families as well.
References


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