Brain Matters

The Undergraduate Neuroscience Society at University of Illinois, Urbana-Champaign

Volume 3

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Chief-Editor

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

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Brain Matters Staff

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

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Writer

My name is Dominick Ramirez, I am currently a sophomore looking to major in psychology. RSOs I'm involved in are Blood Club, Illini Classics Club, and Illini World Taekwondo. I'm interested in neuroscience because I want to learn more about the physiology behind mental disorders.

Writer

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Writer

Juan Bautista: Political Science Major; Molecular Cellular Biology Minor, Senior. Extracurricular organizations besides Brain Matters at UNS, include professional development chair at Minorities in Health Sciences and founder of Bandside UIUC a platform for student rock bands. Neuroscience is probably the only real thing there is from a metaphysical perspective so why not study it. Brain matters and UNS provide a great commons area for discussion on neurological topics.

The Use of Virtual Reality to Treat Anxiety-Related Disorders

Rajvi Javeri

Virtual Reality (VR) is defined as the computer-generated simulation of a three-dimensional image or environment that the user interacts with in seemingly real and physical ways - using special electronic equipment - such as a helmet with a screen inside or gloves fitted with sensors (Oxford Dictionary). When using VR, people's senses - including vision, hearing, touch, and even smell - are stimulated. The head-mounted display system with binocular screens, stereo sound, and movement-tracking follows the user's head movements and alters the virtual environment based on these movements. A scent machine that uses compressed air diffuses scented substances, making the experience even more life-like (Strickland).

For an individual to obtain the proper experience of VR, there must be an element of interaction involved. Interactivity depends on three main factors: speed, range, and mapping. Speed depends on how quickly the computer identifies the user's actions and reflects them for the user to perceive. Range refers to the number of possible outcomes resulting from any particular user action. Mapping is how well the system provides natural results in response to a user's actions (Strickland). In virtual reality, the user has the freedom to navigate themselves through the environment as they please. However, these environments tend to include some other forms of interaction to provide a more exciting experience for the user.

Other than its recreational uses, one of the most significant uses for virtual reality technology is in the treatment of anxiety- related disorders. Current treatments for such disorders include cognitive behavioral therapy (which is a type of exposure treatment) and visualization and systematic desensitization. These treatment methods, however, take longer amounts of time in order to have some effect, and they are mainly used to treat phobias and not depressive disorders (McLeod).

Research in evaluating the use of Virtual Reality to treat anxiety disorders began in the 90s. In the later years, virtual reality exposure (VRE) applications were broadened and applied to the treatment of cognitive, emotional and even physical disorders. In a meta-analysis of 13 studies, VRE treatment was compared with in vivo treatments for social anxiety disorders and agoraphobia.

The results were such that the magnitude of effect with VRE was greater in the control groups ($d=1.1$, $P<0.5$) and lower with the use of in vivo methods ($d=3.5$, $P<0.5$). With VR, the therapist can apply exposure and mediate the stimuli to increase or decrease intensity depending on the patient that is being treated. For example, in treating patients who are afraid of heights or flying on airplanes, the therapist could use VR treatment to be able to manipulate aspects- such as turbulence, take-off and landing, as well as repeated exposure- all during the course of one consultation visit (Rothbaum). VR also facilitates the evoking of memories that may be difficult for the patient to relive by forming associations between those mental images and sensory cues (Rothbaum). Lastly, it is noteworthy that in a world where technology has taken over most aspects of life, VRE would be more attractive for the current generation. According to PMX Agency, the current generation, or the "Gen Z," consumers are going to become the single largest group of consumers in the technology market. According to studies conducted by the International Data Corporation, 8.1 million virtual reality headsets were shipped to consumers around the world in 2016, and this estimate is projected to rise to 60 million by 2021 (Harrison).

Virtual reality therapy has been most effective in its use for exposure therapies as in the case of Post-Traumatic Stress Disorder (PTSD) and Phobias. Post-Traumatic Stress Disorder is a mental health condition that is triggered by either experiencing or witnessing a terrifying event. Such events could include a war, a terror attack or even a traumatic accident. The symptoms of PTSD do not usually occur until a month after the traumatic event.

However, in some cases the symptoms can even surface years after the event. These symptoms typically include intrusive memories of the stressful event accompanied by upsetting dreams or nightmares, negative changes in mood, and changes in physical and emotional reactions, like being startled easily and always being on guard for danger (Mayo Foundation

for Medical Education and Research)

The major brain regions that are affected by traumatic stress include the amygdala, hippocampus and the prefrontal cortex. Findings from animal studies have concluded that PTSD leads to a decrease in hippocampal and anterior cingulate cortex volumes due to the change in the brain's "circuits," accompanied with an increase in the amygdala's response.

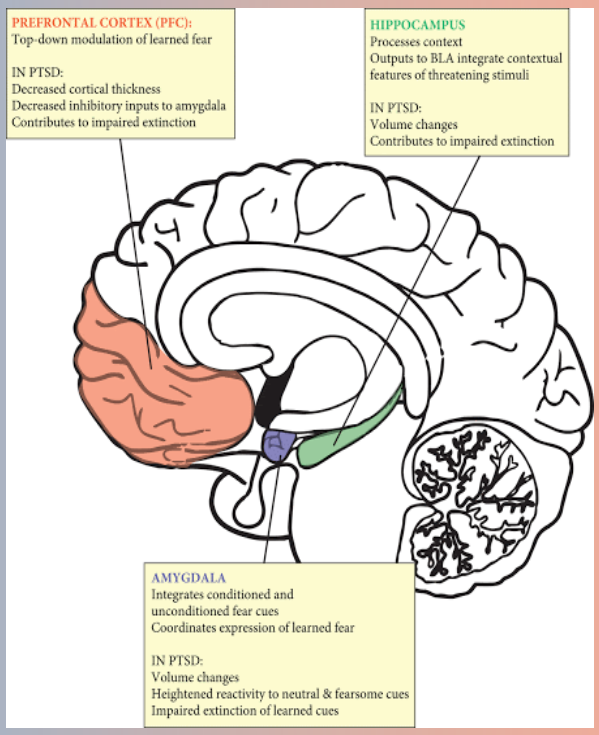

Fig 1. Diagram depicting the regions of the brain affected by PTSD

There is also a spike in norepinephrine and cortisol response to stressors. The hippocampal volume in Vietnam Veterans was studied using Magnetic Resonance Imaging, and it was found that they had 8% smaller right hippocampal volume relative to controls matched for a healthy brain (Brenmer).

To test the reliability of VR therapy, the department of psychiatry at the Emory School of Medicine in Atlanta, Georgia conducted a test on a participant- a 50-year-old Caucasian who served as a helicopter pilot in the Vietnam war. "He met the DSM-IV criteria for current PTSD, and current major depressive disorder, and past alcohol abuse" (Rothbaum 265).

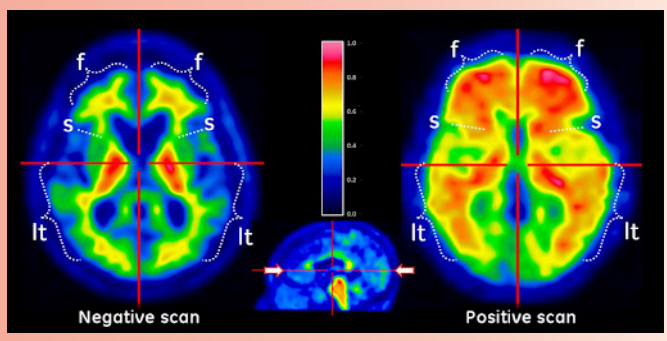

Fig 2. Comparison of a healthy brain (L) with a brain affected by PTSD (R) to depict the difference in brain volume of certain brain structures

During the VR exposure treatment, the patient was equipped with a head mounted display containing two mini-television screens and earphones over each ear. The set up was connected to a computer whose graphics and audio were consistent with the orientation of the patient's head and were computed in real time as the patient explored the surrounding environment. The therapist could communicate with the patient via a microphone attached to the headset. The treatment was delivered in 14, 90-minute sessions and the sessions increased in intensity as the weeks progressed. The participant could feel vibrations similar to those felt while seated in a helicopter through the VR set up. He was also shown virtual environments, such as those of a jungle clearing and was exposed to audio effects comprising noises that one would typically hear on the battlefield. In the later sessions, the participant's most traumatic memories were triggered and prompted by the therapist. To do this, the therapist would ask the patient to recount those traumatic memories repeatedly in past tense until his anxiety decreased due to a process known as habituation.

The therapist simultaneously viewed the virtual environments with which the patient was interacting and would comment appropriately while maintaining the exposure until the participant's anxiety habituated. Results from pre-treatment to post-treatment are positive (Rothbaum).

After the treatment, the values indicating arousal and depression, among others, appeared significantly lower, indicating a decrease in clinical severity.

The scales used to measure the results included: The Clinician Administered PTSD Scale (CAPS), The Impact of Events Scale (IES), and the Beck Depression Inventory (BDI). The patient's CAPS total score was 64 (severe) before treatment, which dropped to 42 (Moderate) after treatment, indicating a decrease in clinical severity. The patient's pre-treatment IES score was 33 (1 standard deviation (SD) above the average of all Veterans suffering from PTSD in his group) which decreased to 18, indicating a 2 SD move following therapy. His 6-month follow up indicated a total IES score of 0 which denoted a complete absence of intrusive symptoms related to the traumatic incident. Lastly, his BDI score dropped from a 37 to a 30 which was still in the severe depression range. However, his 6-month follow up score of 21 fell into the moderate depression range (Rothbaum).

Another effective use of Virtual Reality therapy is in the treatment of phobias. A phobia is an extreme and irrational fear or aversion to something, which may or may not have a grounding in reality. These phobias interfere with the day-to-day functioning of an individual and are often paired with anxiety. Symptoms include panic attacks, elevated heart rate, trembling and feeling out of control or powerless (Open Path Psychotherapy Collective). One of the most common phobias is the fear of flying. About 10-40% of the population has a fear of flying, and the anxiety produced by flying is so intense that it can impede an individual's daily functioning and can even influence the kind of job they settle for (Price).

People who have the disorder usually ingest some form of alcohol or sedative in order to deal with the fear.

Exposure therapy is the most common method used in the treatment of phobias. It involves exposing a patient to the stimulus that he/she fears, so that they can habituate to it. Habituation is the diminishing of a psychological or emotional response to a frequently repeated stimulus (Oxford Dictionary).

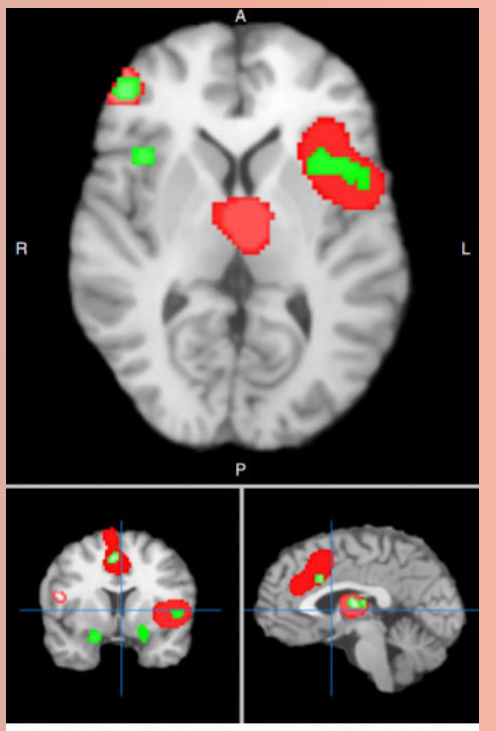

Fig 3. (green) regions activated in response to a phobic stimuli

Repeated exposure to the stimulus in a controlled manner for prolonged periods of time can help the patient cope with the phobia. Virtual Reality is itself a type of exposure therapy and this makes it an effective tool in combating phobias. In this type of therapy, patients learn how to identify the thoughts that are causing this anxiety and then learn how to overcome and replace these thoughts with more helpful ones (Winerman).

A study was conducted by Price et al. to treat the fear of flying in a 42-year-old female who met the criteria for a situational type phobia according to the DSM-IV criteria. During the first half of the treatment, the female sat for seven sessions of anxiety management techniques which included: breathing relaxation, biotherapy, thought-stopping, cognitive restructuring and preparation for stressors*.

After six weeks, the second part of the treatment was initiated in which there were six sessions of VRE administered. Each session lasted 30-45 minutes and exposed the patient to the simulation of taking off and landing along with various variables such as turbulence and adverse weather conditions. After this time period, the outcome of the therapy was evaluated with a self-report questionnaire and subjective unit of discomfort (SUDS) ratings. It was noticed that the patient experienced a decline in self-reported anxiety and could complete an actual flight with very little anxiety which indicates that the treatment was successful (Price).

Research conducted at the University of California on the neural activity of rodents provides promising results relating to Virtual Reality Therapy. Experiments are being conducted on them in VR settings, wherein their brain signals from the

*The anxiety reducing techniques employed in the first half of this study were to prepare the participant for the flight. The techniques were not a control of any sort.

hippocampus are being recorded.

Being associated with memory and spatial mapping, the neurons in the hippocampus have a GPS-like system, which helps them navigate their way through space. The purpose of this study was to find out whether VR could simulate the same type of brain mapping as in the hippocampus. Interestingly, they found out that 60% of the neurons in the hippocampus stopped firing during the experiment. This is possible because VR is immersive, and this immersion can lead to changes in the way the brain processes stimuli. It has been speculated that VR's ability to "shut down" the hippocampus could have rewired the brain and that the various pathways in the brain can be formed and reinforced through repetition (Guillette, Verizon). These findings indicate that the long-term use of VR on the brain can be an effective cure for phobias. As mentioned before, VRT is a type of exposure therapy. Exposure Therapy can change the fear circuit- which involves the amygdala and the prefrontal cortex- after treatment. During habituation, the bilateral anterior medial temporal lobe and the amygdala show a decline in regional cerebral blood flow on repeated exposure to the feared stimuli. This results in a decrease in subjective anxiety ratings and a drop in the patient's heart rate during stressful conditions (Landowska). In this manner, VR proves to be effective against phobias.

While analyzing the benefits of Virtual Reality Therapy, it is equally important to keep in mind the drawbacks associated with it. The first major drawback is that VR interfaces have not been designed to be used as medical equipment yet. This means that the major challenge associated with VR therapy is the sterilizing of the equipment for its use on multiple patients. VR equipment has not yet been modified to accommodate people with disabilities and special needs, which limits the extent of its use. This can pose problems because a large number of war veterans- who need the treatment most- will not be able to reap its benefits. Additionally, cost is another hindrance in the use of VR therapy in a number of medical facilities. Although equipment cost has reduced significantly in the previous years, schools and health centers are afraid to purchase equipment in the absence of subsidies.

The cost of the equipment also limits the availability of the treatment, leading back to the issue that it will fail to satisfy the needs of most people (Burdea).

With the invention of technology, science has opened several opportunities that are proving to be necessary for the betterment of humanity. These opportunities are providing a better chance for us to adapt, and therefore we shouldn't forgo them. When it comes to Virtual Reality Therapy, its uses now encompass the treatment of anxiety-related disorders such as PTSD and phobias. According to the meta- analysis, when compared to other exposure therapies such as systematic desensitization, VR therapy appears to have a greater magnitude of effect. VR, when used to treat veterans of the Vietnam war showed a significant reduction in the patient's symptoms of depression and anxiety. The immersive quality of VR therapy allows it to be used for the treatment of phobias too. It achieves this by rewiring the brain's circuitry – such as the fear circuit- involving the amygdala and the prefrontal cortex. It also stimulates habituation, causing reduction in the cerebral blood flow in the amygdala and the bilateral anterior medial temporal lobe. Further research and development in the use of Virtual reality equipment in treatment, if encouraged, can prove to be immensely beneficial and can improve the standard of living for people who have experienced many hardships, helping them come close to leading a normal life.

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Progression in Understanding Combat Induced Mental Disorders

Dominick Ramirez

Many names have been created to describe the combination of symptoms that soldiers face after returning from combat. Until recent advancements in science, there has not been much consensus as to the cause and proper treatment of disorders that had medical symptoms but had no visible injuries to cause them. During World War I, the large amount of manpower involved in the conflict, along with the corresponding large numbers of soldiers that became afflicted, made these disorders unignorable for governments and the medical community. During this time, there was a disagreement within the medical community as to whether the symptoms were caused by physical injuries to the brain or were psychological. The term shell-shock was coined by Psychologist Charles Samulel Myers in 1915 to describe the disorder but had no concrete definition.

Presently, the term post-traumatic stress disorder (PTSD) has been developed to describe the mental condition that develops in response to experiencing or witnessing an event that has the potential to cause death or great bodily harm. Unlike shell-shock, PTSD is a more generalized term, applied to events such as natural disasters, sexual assault, war, and automobile accidents as opposed to exclusively experiences in war. During a traumatic event, the brain causes the body to enter a state of self-preservation during which the sympathetic nervous system. This is the division of the nervous system responsible for regulating involuntary body functions such as sweat secretion and reflex adjustments of the cardiovascular system. In a stressful or dangerous situation, it releases large quantities of epinephrine from the adrenal gland, which causes an increase in heart rate, the widening of skeletal muscle blood vessels, and other effects which prepare the body to either fight, flee or freeze. PTSD occurs when the transition from this state to a responsive state brought about by the parasympathetic nervous system fails to happen.

The symptoms of PTSD fall within the realm of intrusive memories, avoidance of reminders of the traumatic event, adverse changes in thinking and mood, and changes in physical and emotional reactions. In a military context, PTSD is often seen as the leading cause of mental ailments, and thus, these injuries are described as solely psychiatric. However, some research suggests that this is not always the case. Besides PTSD, another affliction, blast-induced traumatic brain injury (bTBI), is another prevalent injury among troops. While these conditions often exist simultaneously and have similar symptoms, bTBI is a form of traumatic brain injury which is currently not very well understood and, therefore, more difficult to detect and treat. A common assumption in past years was that explosive blasts had similar effects to sports concussions and traffic accidents; however, recent studies have shown that there are physical differences in the brain that develop after experiencing a survivable blast (Denes V Agoston, MD and Alaa Kamnaks 2015).

In one case, scientists found that brains of deceased veterans that survived explosions and lived for years afterward had a unique honeycomb pattern of axonopathy or damage to nerve cells called axons, which are different damage patterns from other types of head injuries. These lesions were found in multiple areas of the brain, including the frontal lobe, which contains the parts responsible for personality expression and the execution of voluntary muscle movement. These findings could explain why the survivors went on to develop behavioral symptoms similar to those of athletes with concussions. (Ryu, J., Horkayne-Szakaly, I., Xu, L. et al. 2014). In another study that examined the brains of veterans post-mortem, dustlike scarring was found along the borders between grey matter and interconnecting white matter. This is different from the brain scarring caused by concussions in that it did not have a staining appearance on the tissue it affected. When compared to samples of people who had experienced ordinary concussions or had drug addictions (which have the potential to cause visible brain damage), it was found that the dust pattern was unique to bast survivors. (Sharon Baughman Shively, MD, Iren Horkayne-Szakaly, MD, Robert V Jones, MD, et al. 2016) These and similar studies provide a foundation for further study in trying to understand the different types of mental injuries sustained in war as not much is currently understood as to how exactly blasts cause

war were completely psychological; however, these advances have confirmed the existence of causes that, while previously suggested, were unable to be proven due to technological limitations.

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Symptoms and Possible Causes Cures for Parkinsons Disease

Michael McHenry

Parkinson's disease is the world's second most common neurodegenerative disorder, afflicting nearly 10 million people worldwide.1 While it is a fairly common disease, its exact causes are unknown and there is no known cure. Since the early 1800s, Parkinson's disease has befuddled scientists. But now, cutting edge research has led scientists to believe that the solution to the Parkinson's puzzle may lie within our intestines. Before delving into its interesting connection to the gut, one must first understand the basic symptoms of Parkinson's Disease (PD). Usually, Parkinson's disease most often affects individuals over the age of 60, but in some cases, symptoms can be seen in patients before they turn 50.1 The main symptoms associated with Parkinson's disease are uncontrollable shaking, slowed movements, impaired coordination, and body stiffness. These symptoms make life for those with the disease difficult, especially as they get older. The primary cause of those symptoms is the depletion of the brain's dopaminergic neurons.1 Dopaminergic neurons are responsible for releasing dopamine, a neurotransmitter that functions to facilitate communication between the substantia nigra and the basal ganglia. This interaction helps a human fine-tune his/her movement by helping the brain determine the energy cost of a particular movement.8 Without dopamine-producing neurons, this interaction becomes impossible and results in the previously listed symptoms of the disease.

Currently, the most common treatments for Parkinson's are drugs that raise dopamine levels within the patient's brain. The most common of those drugs is Levodopa, a precursor molecule to dopamine. Levodopa is converted by the CNS into dopamine, thereby making up for the lack of dopamine produced by dopaminergic neurons. Other therapies include drugs that mimic dopamine's effects, drugs that slow the enzymatic breakdown of dopamine, and deep brain stimulation. While they are somewhat effective, today's Parkinson's treatments are only able to lessen the symptoms of the disease, as they cannot attack the root causes of the disease. However, new studies have shed light on Parkinson's Disease pathology. Those studies indicate that Parkinson's pathology may begin in the enteric nervous system.

The enteric nervous system (ENS) is the largest part of the autonomic nervous system. It is made up of hundreds of millions of neurons and is responsible for regulating the function of the gastrointestinal system. Because of its immense sophistication, the ENS can regulate the complex gastrointestinal system on its own, independent from the central nervous system (CNS). However, the ENS and CNS are linked by many afferent and efferent nerves that enable communication and the exchange of information between them. However, those same connections can also provide a pathway along which neurodegenerative diseases can spread. Scientists have postulated that Parkinson's pathology may begin in the ENS before spreading to the CNS and causing the disease's symptoms.

The ENS contains a unique type of neuron known as an enteric glial cell or EGC. EGCs can be found in the walls of the intestines and are crucial for the homeostatic regulation of many GI functions, including the regulation of the intestine's neuroinflammatory response.2 Under normal conditions, EGCs in the mucosa myenteric plexus are not activated. However, if the intestinal wall of an individual is compromised in some way, it may become permeable to the bacteria that inhabit the lumen of the small intestine.7 If able to pass through the intestinal wall, those bacteria will cause the EGCs of the small intestine to respond with a neuroinflammatory response. Sustained activation of EGCs results in an increase of the production of a misfolded protein known as α-Synuclein. α-Synuclein is a mysterious protein, as its true physiological function is not well known. However, it does play a crucial role in causing the dopaminergic cell death seen in PD patients.

α-Synuclein has been shown to build up in the dopa minergic neurons of Parkinson's patients, resulting in the death of those neurons.4 α-Synuclein also can be seen forming protein deposits within neurons known as Lewy bodies. In Parkinson's patients, Lewy bodies are often found in neural tissue and have high concentrations of α-Synuclein within them. The link between the production of α-Synuclein within the enteric glial cells of the ENS and the presence of α-Synuclein within the brain suggests that α-Synuclein may

somehow migrate from the ENS to the CNS. The exact method by which this process could occur was unknown for a long time. However, a study by Ahn et al. entitled "Initiation of Parkinson's disease from gut to brain by δ-secretase" shows how it could occur in humans. Researchers in this study looked to determine how α-Synuclein could move from the ENS to the CNS, which would demonstrate how the gut could affect Parkinson's disease pathology. They utilized the pesticide Rotenone to elicit Parkinson's-like symptoms in animal models. Rotenone is known to cause symptoms like gut dysmotility and the aggregation of α-Synuclein within the brains of animals. Also, Rotenone taken orally does not enter the circulatory system; instead, it solely acts on the ENS when it crosses the membrane of the intestines.4 These factors make Rotenone-treated mice good study subjects for Parkinson's.

The first thing the researchers looked at was α-Synuclein's interactions with a protein known as Tau. They found that α-Synuclein and Tau strongly bind to one another when they were cleaved by the protease Asparagine Endopeptidase (AEP). AEP cleaves the α-Synuclein protein at N103 and the Tau protein at N368. Interestingly, overexpression of the α-Syn N103 fragment in the brain has been shown to cause Lewy Body formation and motor dysfunctions.4 They also found that the complex created by the binding of Tau N368 and α-Synuclein N103 is highly cell permeable. Being able to easily cross cell membranes makes it possible for the α-Synuclein N103/Tau N368 complex to potentially leave the digestive system to enter other organs, such as the brain. That possibility was proven by a later experiment where Ahn et al. gave mice rotenone orally. After three months, immunofluorescence staining indicated that the α-Syn N103/Tau N368 complex was present in the vagus nerves of the mice treated with Rotenone. This indicated that the complex moved from the ENS through the vagus nerve to the brainstem.

The vagus nerve was identified as the main passageway by which the Lewy-body creating proteins traveled from the ENS to the substantia nigra (SN) to cause the symptoms related to Parkinson's disease. However, once at the CNS, scientists wanted to see if the α-Syn N103/Tau N368 could cause the endogenous production of α-Syn N103 in the SN. To answer this question, Ahn et al. injected mice the colons of mice with the α-Syn N103/Tau N368 complex. They found that once the complex got to the brain, it caused a local increase in the activation of AEP. Increased Ahn et al. noted that the mice showed "substantially impaired" cognitive function when compared to the control mice, demonstrating that they were experiencing dopaminergic cell death.

The findings of Ahn et al. demonstrate how the proteins responsible for Lewy body formation travel from the gut to the brain and cause dopaminergic cell death. The gut's effect on Parkinson's pathology can now be explained. First, leaky gut dysbiosis causes bacteria in the intestinal lumen to move through the intestinal wall. Those bacteria then cause a neuroinflammatory response from the intestine's enteric glial cells. Next, the EGCs start to produce abnormal amounts α-Synuclein, which builds up in the ENS. Then, the protease AEP starts to cleave α-Synuclein at N103 and Tau at N368. Those two fragments form a complex that can easily pass through cell membranes. Complexes then exit the ENS and travel to the brain via the Vagus nerve. Once in the brain, they cause endogenous production of α-Syn N103 by activating locally activating AEP. Finally, α-Synuclein builds up in the dopaminergic cells of the individual, causing Lewy body formation and cell death. Once in motion, this process would be difficult to stop due to the prion-like nature of the α-Syn N103/Tau N368 complex. However, it could be possible to create treatments targeted at preventing leaky gut itself.

It has been postulated that Parkinson's pathogenesis could be prevented by using drugs to alter the gut microbiota to prevent leaky gut and maintain the solidity of the intestinal wall.2 By using eubacteria and antibiotics, doctors could theoretically control intestinal bacteria populations to prevent them from getting through the intestinal wall and inflaming the enteric glial cells. Another possible treatment would involve the use of Fecal Microbiota Transplant (FMT). FMT involves the transplantation of fecal matter from healthy individuals into individuals with abnormal gut bacteria compositions. 9 This method is aimed at helping to reestablish a stable gut microbiota and therefore prevent conditions like leaky gut. Studies have shown that FMT has been effective in treating Ulcerative Colitis by helping to promote mucosal healing.9 Given leaky gut dysbiosis' role in Parkinson's progression, FMT could be a novel way to treat the disease.

For years, Parkinson's disease has been clouded in mystery; Its causes and pathology were a secret. However, new scientific discoveries have helped improve our understanding of the disease drastically. While we may not have all the information required to cure

Parkinson's, these new discoveries have brought us closer to finding treatments that target the disease at its source rather than mitigate its symptoms. The future of Parkinson's treatment is a little brighter, which is great news for the 10 million people who suffer from it.

Loneliness in the Mind

Hari Balachandran

In times of unprecedented levels of social isolation, loneliness has affected more people than normal. Loneliness is defined as a complex set of feelings encompassing reactions to the absence of intimate and social needs (Ernst, 1999). Typically, the terms lonely and alone are used interchangeably, but they are not the same. Being alone simply means being by oneself. A person being alone does not necessarily mean they suffer from the feelings of social isolation. Likewise, a lonely person may be in a room full of people, and still lack the sufficient personal connections to satisfy their social needs.

Loneliness, like other feelings, can be caused by a lack of positive emotional states and an excess of negative emotional states (Matthews, 2016). Examples of positive states include interactions with others, which leads to security and reduces the total energy needed to survive. An absence of these interactions can lead to loneliness, which is, in other words, a negative emotional state (Eisenberger, 2012). The negative state prompts a neurological change which pushes the organism to seek social interaction. The carrot of interaction and the stick of isolation constitute the feelings of loneliness, and push humans to a much more interconnected existence.

To study the neurological effects of loneliness, testing must often be done; however, given the ethical issues of isolating humans, rodents are used instead of humans. Rodents, like humans, are social animals, and have been shown to prefer interaction over isolation (Loo et al., 2001). While rodent models are not perfect substitutes for human testing, especially in the field of neuroscience, rodents have been used in the development of new drugs and are primarily used for their accuracy in modeling parts of human physiology and function.

The physical effects of loneliness are not centralized to one specific region of the brain. However, one particular region of note is the dorsal raphe nucleus (DRN), a region in the brain stem found in the midbrain and pons. To test methods that the brain uses to reward interaction and punish isolation, an in vivo calcium image was taken of rodents. In vivo calcium imaging works by using calcium indicators, special chemicals that light up when they bond to Calcium (II) ions. These ions are released within a cell when an extracellular messenger, such as dopamine, interacts with the cell. The entire process works like a series of dominos, as the dopamine movement triggers a release of calcium ions, which interact with the luminescent indicators that are then observed by researchers. Following a period of isolation, an increase in dopamine receptor activity in the dorsal raphe nucleus was found once the rodents were able to interact with other rodents (Matthews, 2016). The increased activity of dopamine, the "happiness hormone" brought about a pleasurable feeling to the rat. Similar to the rush a person might feel after exercise, this new rush incentivized the rat to pursue similar social activities, thus increasing their dopamine levels.

Another region important to understanding the effects of loneliness is the prefrontal cortex. The prefrontal cortex is a region of the brain that governs decision making, personality, complex thought, and moderation of social behavior. Within the prefrontal cortex, small-conductance calcium-activated potassium channels, or SK channels, were found to be responsible for the changes in the serotonergic neurons, neurons in charge of serotonin synthesis. Serotonin, the "feel-good hormone," is a mood stabilizer and is frequently produced when participating in group activities or exercise. The SK channels changed the serotonergic neurons by reducing the rate they fire following a period of social isolation, which resulted in mice having elevated levels of aggression, anxiety, depression, and antisocial behavior. However, a treatment of an excitation of serotonergic neurons was able to curb those behaviors. This treatment differed from previous trials, which used traditional pharmacological means to control serotonin levels within the mice. The new treatment was done using optogenetic and chemogenetic control. Researchers were able to excite the serotonergic neurons by changing the DNA in the mice themselves. The new DNA attaches either light-sensitive or chemical-sensitive receptors to the serotonergic neurons, which the researchers were then able to manipulate. These manipulations resulted in a decrease in aggression and an increase in social behavior in the mice (Sargin, 2009). Isolation deprived the mice of contact with others, which starved them of serotonin, and led to a variety of psychological issues. For this reason, treatments for loneliness may be found

by addressing the serotonin deficiency. Addressing the symptoms of serotonin deficiency, such as the aforementioned anxiety and depression, via anti-anxiety/depressant medication is likely the best place to start when attempting to curb the effects of loneliness.

There is another method in which social isolation can be observed within the brain. This is visible with the presence of the neuropeptide tachykinin 2 (Tac2)/neurokinin B (NkB), two different chemicals used to transmit messages between neurons in the brain. When mice were isolated for two weeks, Tac2 concentrations spiked across the entire brain. Like the previous study, aggressive behavior was noted in the animals, yet interestingly there were also defensive behaviors present in the mice. The presence of Tac2 triggered the "freeze" response in many mice. Prolonged loneliness, it was found, triggered fear responses in mice, in addition to anxiety and aggression. (Zelikowsky, 2018). The heightened fear response likely suggests that social isolation may have been causing harm to the mice. Fear is typically associated with the perception of danger, and being alone for nearly two weeks was enough for the mice to feel threatened by their environment.

When scientists in the Zelikowsky study increased the expression for the Tac2 gene in mice that had not faced social isolation, the mice began to exhibit aggressive and anxious behaviors, similar to those that had undergone isolation. Thus, it was shown that Tac2 was likely the primary culprit for the feelings of loneliness in mice, and that more importantly, finding a way to inhibit that may cure the mice. As stated earlier, mice that were isolated displayed various hostile behaviors, such as chronic fear, increased aggression and an increased sensitivity to threatening stimuli. These mice were all found to have elevated levels of Tac2 in both the amygdala and the hypothalamus. Providing doses of Osanetant, a former schizophrenia medicine that also acts as a way to block the processing of NkB chemicals, showed a reduction in these traits, resulting in a mitigation of the effects of social isolation. Interestingly, the researchers discovered different effects when blocking the expression of the Tac2 gene in different regions of the mices' brains. When blocking the expression in the amygdala, the mice lost many behaviors related to the increased fear, such as hypersensitivity and chronic fear. When blocking the Tac2 expression in the hypothalamus, the mice retained the increase in fear, yet saw a decrease in the increased aggression brought about from social isolation (Zelikowsky, 2018).

Not only are there different chemical reactions that occur in the brain when a person experiences loneliness, but the shape of the brain is also subject to change. Using Voxel-Based Morphology, individuals suffering from chronic loneliness were found to have less gray matter in the Left Posterior Superior Temporal Sulcus (pSTS). This region of the brain is associated primarily with social perception. Accounting for other factors, such as empathy, other disorders individuals face, and the size of their social circles, there was a direct correlation found between loneliness and basic social perception. In other words, loneliness directly hindered an individual's ability to process social cues. It is unknown whether loneliness contributes to a loss in gray matter in the pSTS or if a person born with less gray matter in the pSTS is more likely to be lonely. Given the harmful, stress-inducing effects of an increase in Tac2 expression, and the fact that stress has already shown to cause neuron death in other parts of the brain, such as the hippocampus (Lee, 2002), it is not outside of the realm of possibility for Tac2 expression to result in a loss of gray matter. However, until further research is done, this question remains unsolved.

Loneliness is a rather insidious chemical process in the brain. Although mice were primarily used in testing, many of the processes observed are homologous in humans. It can be difficult to define loneliness, as the needs for every person changes. The difference between an individual's needs and the amount of interaction an individual feels is one way to determine how lonely a person feels. The important factor is not actual social interaction, but perceived social interaction. A poor perceived social interaction leads to a worse cognitive function, higher negativity, and greater chance of death (Cacioppo, 2009).

As shown in the 2018 study by Zelikowsky, a fear response in rodents was triggered after prolonged isolation. In humans, this likely manifests itself in a cognitive bias to social context (Spithoven, 2017, Kanai 2012). Loneliness was shown to lead to people having a much more negative outlook in all stages of a Social Interaction Processing model. An unfortunate circumstance of this behavior is that it becomes increasingly difficult for those with a negative outlook to gain the interaction they need, which leads to increasing levels of loneliness. In essence, a dangerous feedback loop is created. However, as more experimentation is done, more is being found to combat this issue. Serotonin treatments have already shown promise, and future

treatments to limit Tac2 production may yield fruitful results.

While these results are promising, no trials have been conducted on humans. For now, it has yet to be seen if one day a viable cure to loneliness can be found. Aside from pharmacological means, other forms of treatment are being explored. Technology has shortened the distance between people, and for individuals that are unable to meet face-to-face, it can serve as a way for them to connect. More research is needed to determine the effectiveness of technology in bolstering connections between humans, but as our world revolves around technology more, it will be interesting to see the effects of these changes. Given the recommended social-distancing policies due to COVID-19 in place at the time of writing, it will be interesting to see the short and long term effects of isolation. No doubt cases of loneliness amongst the population in the world have increased, but the extent to which social isolation has contributed to loneliness, and the societal outcomes of these cases have yet to be seen and studied. Future studies may combine the two ideas and attempt to discern a connection between a society's level of technology use and the effects of loneliness on the populace. Loneliness has become more prevalent in recent months. It is worth our effort to study and understand this debilitating disease.

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Alcoholic disruption of function in neurophysiological pathways and retrogressive development in size and capability of cognitive neurobiological structures throughcontinual exposure

Juan Bautista

Introduction

Alcohol (EtOH) as a chemical disruptor that impedes on neural development, nutritional and hormone regulations, but has low salience amongst contemporary cultures as being such. In many societies alcoholic consumption is the universal pastime. It is a particularly popular form of socialization amongst young adults (18-22 years old). Of full-time college students 54.9 percent admit to having drunk alcohol in the past month when surveyed in the 2018 National Survey on Drug Use and Health. Out of those who drank in the previous group mentioned 36.9 percent also admitted to binge drinking (having 5 or more alcoholic drinks on a single occasion) []. The high prevalence among young adults is particularly dangerous because their brains are still developing and alcohol may accelerate some deleterious effects and disrupt synaptic rearrangement of the later stages of neural maturation. The factors behind the alcoholic trend within campus communities are numerous from a bacchanalian culture to emotional isolation. The general attraction to alcohol is that it releases inhibitions and psychological pressures.

But, this article will take a glance at some of the immediate and long term effects of both continual and binge alcoholic consumption on the nervous system. From a molecular perspective, alcohol induced mechanisms create damaging toxic reagents that in turn cause cellular hypoxia and aggressive autoimmune responses in neural sensitive regions. As alcohol continues to be abused the effects of these faulty irregular pathways accumulate and structural brain damage, neuropathies, and even detriment to genetic viability become evident.

Ethanol and Its Metabolism

Alcohol is classified as a depressant drug because it reduces brain activity by blocking NMDA, GABA, Serotonin, and Acetylcholine receptors from their corresponding neurotransmitters.

The binding of EtOH on GABA receptors in particular dims neural activity by oversaturating postsynaptic neurons with chloride anions. This elongated period of ion influx reduces the rate of action potentials delaying neural stimulation. The apparent changes in cognition following an episode of excessive alcoholic intake include: difficulty speaking (slurred), poor memory, slowed movements, loss of balance (vertigo), incapacitated motor coordination, stupor (unresponsiveness), and in some cases loss of consciousness.

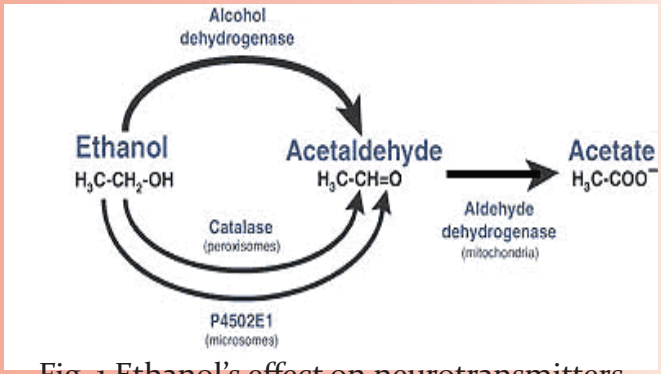

Fig. 1 Ethanol's effect on neurotransmitters

Ethanol (CH3CH2OH) is primarily metabolized in the liver by the enzymes alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). Alcohol dehydrogenase breaks down alcohol into acetaldehyde (CH3CHO), NADH, and H+. Then aldehyde dehydrogenase reacts with water to further break apart acetaldehyde into acetate (CH3COO-) and more NADH and H+ by products. The accumulation of NADH and H+ disrupt the natural pathway of gluconeogenesis. If gluconeogenesis does not proceed normally, an insufficient amount of bicarbonate would form and oxygen delivery would be set back. In addition to the hypoxia this case would also have acetate build up which would decrease the blood pH which may develop into metabolic acidosis. Metabolic acidosis severely impairs breathing and requires medical attention. But, continuing on with our metabolism of alcohol, acetate can then be converted to acetyl CoA through contribution of ATP and coenzyme A in the mitochondria. Progression stops here though, before completing the citric acid cycle, because the excess saturation of NADH from previous steps blocks regulatory enzymes (isocitrate dehydrogenase and α-ketoglutarate dehydrogenase). Acetyl CoA and ATP are

produced, and CO2 is not released. The cells affected experience energy deficits and toxic retention which may lead to cellular death. Over time these recurrent irregularities can lead to fatty liver, alcoholic hepatitis and lastly cirrhosis. Each stage further weakens the liver's ability to filter toxins as the organ dies.

Oxidative Stress and Cellular Response

If alcoholic intake exceeds the oxidation rate of the stomach and liver enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) respectively, then other enzymes across the body will metabolize the alcohol and cause toxic products to linger in regions where they can do the most damage. The particular pace of oxidation in the average human body is roughly 100 milligrams of liquor for each hour per kilogram of body weight. To place this in context, about 8 grams of liquor will be discharged in an hour in the event that you weigh 180 pounds (81.6 kilograms), and 5 grams of liquor will be broken down in an hour if you weigh 110 pounds (50 kilograms). The oxidation rate is modified by sex, ethnicity/genetics, and health of the liver []. Once consumed alcohol is rapidly absorbed into the bloodstream. 20 percent enters from the stomach and the other 80 percent seeps in through the linnings at the beginning of the small intestine []. Because of this chemical's high solubility in fat and water, it does not need to be broken down to readily circulate and permeate across the blood-brain barrier. The brain is 75% water by mass and the diffused alcohol has an almost immediate effect in it[U.S. Department of Health and Human Services (1990)].

In the brain, the enzymes catalase and CYP2E1(Cytochrome P450) metabolize alcohol; this pathway is therefore called the cytochrome P450-dependent pathway. This pathway creates aldehydes and acetates similar to the primary alcohol metabolism

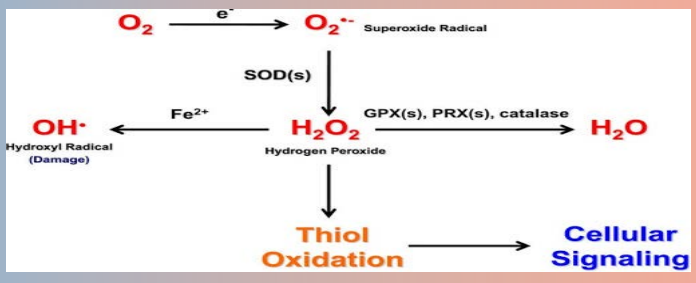

Fig. 2 Reactive Oxygen Species

pathway in the liver but differs in that it converts NADPH into NADP+ by implementing oxygen which forms oxidative free radicals in the brain. Free radical-mediated interactions occur within proteins, lipids, and dna. Oxidative degradation of omega 3 and omega 6 some polyunsaturated fatty acids undergo lipid peroxidation induced by ethanol intake (Burke and Ludden 1989).

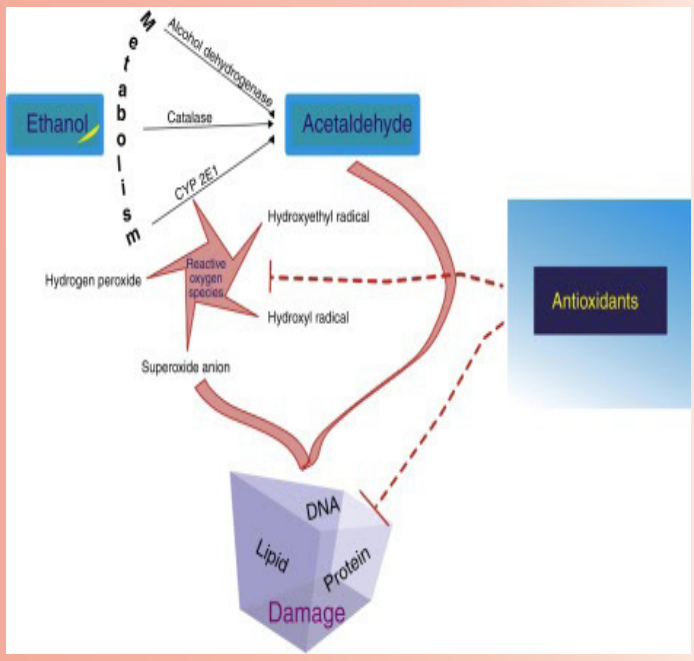

Fig. 3 Antioxidant Treatment and Alcoholism. In Molecular Aspects of Alcohol and Nutrition

Acute and chronic intoxication created Acetaldehyde is very unstable and forms covalent adducts with the surrounding constituents. This should be done within the liver as it decreases enzymatic activity, inhibits microtubule assembly, and increases catabolism of proteins (Lieber; Sorrel and Tuma). Acetaldehyde condensates can incur detection by the immune responsive proteases and thereby damage the conjugated tissue (Israel et al., Lin et al). Aldehyde also activates production of acetaminophen, benzene, CCl 4, halogenated hydrocarbon at toxic levels and pro-carcinogens (nitrosamines, and azo compounds) [].

In an experiment sponsored by the University of Texas Southwerstern Medical Center, Immunocytochemical localization of animal brains administered EtOH discovered immunoglobulin antibodies, B-cells (InterLeukin-4), and T-cells (CD4-L) clustered in very high amounts (Kozlowski and Sterzl). The Researchers predicted that cytokine IL-4, recruited macromolecular immunoglobulin proteins into the brain that

rallied with CD4-L and caused neuronal endocytosis in brain's of the animals fed EtOH. Alcohol promotes inflammatory response in neuronal and glial cells by activating signalling pathways (MAPKs, IKK), increasing production of inflammatory mediators, cytokines, and transcription factors involved in apoptosis and injury response (AP-1, NF-kB) [Alcohol and Neuroinflammation: Involvement of Astroglial Cells and IL-1RI/TLR4 Receptors Vol. 25 Num. 3/ 2006]

Malnutrition

Chronic alcohol use can cause malabsorption of important nutrients. Health expert for Bright Hub magazine, Kimberly Roberts, offers insight into the unhealthy effect of alcohol in one's diet "Individuals that abuse alcohol also tend to fill their caloric needs with drinks, as opposed to food. When they do eat meals, they tend to be unhealthy. This is because alcohol is an addictive carbohydrate. Consuming large amounts of this type of carbohydrate increases cravings for more unhealthy carbohydrates, as well as salts and sugars."

Chronic alcoholic consumption can lead to a cycle of eating low nutrient foods. But long term alcohol malnutrition has a wide spread strain on many systemic organ functions. It inhibits secretions of digestive enzymes, neglects natural metabolic pathways (glycogenesis) and damages the cells lining the intestines and stomach impairing their ability to absorb nutrients into the bloodstream. Vitamin B 6 (pyridoxine), 2 (riboflavin), 1 (thiamin), and folate are some of the nutrients crucial to brain health (nutrient transport, cell growth, homeostasis, which are in lowest proportion within alcoholics (Leevy et al).

Alcohol is associated with cerebral deficiency of folate, a B vitamin soluble in water. Folate is involved in metabolic processes such as that produce neurotransmitters (glutamate) and aid in DNA synthesis. Deficiency of Folate and other B-vitamins contributes to accelerated neural degradation and initiation of disease (Molero-Luis M et al. 2015). For example Fetal Alcohol Syndrome (FAS) is prevalent disorder in which a pregnant woman (even at early stages in which she may not be aware of the pregnancy) consumes alcohol that suppresses nutritional flow (folate in particular) resulting in neuronal malformation (Shibley IA Jr, Pennington 1997).

Thiamin deficiency for example is related to Wernicke-Korsakoff syndrome of ophthalmoplegia, cerebellar dysfunction, and cerebral degeneration.

Morphological Changes in the Brain

Cerebral Cortex

Hippocampal Formation

-reduction in thickness

- reduction in the numerical density of granule cells

Prelimbic Cortex

-Degradation of Myelin sheaths

Cortical subcortical atrophy

Associated Neuropathies

-Multiple sclerosis like symptoms

Genetic Damage and Heritability of Alcoholic Symptoms

-Predisposition

-Fetal AS

-Lower iq unrelated to poor upbringing

Some Regeneration is possible with abstinence of alcohol and lifestyle changes

Decrease or reverse the decline of brain matter

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