Brain Matters

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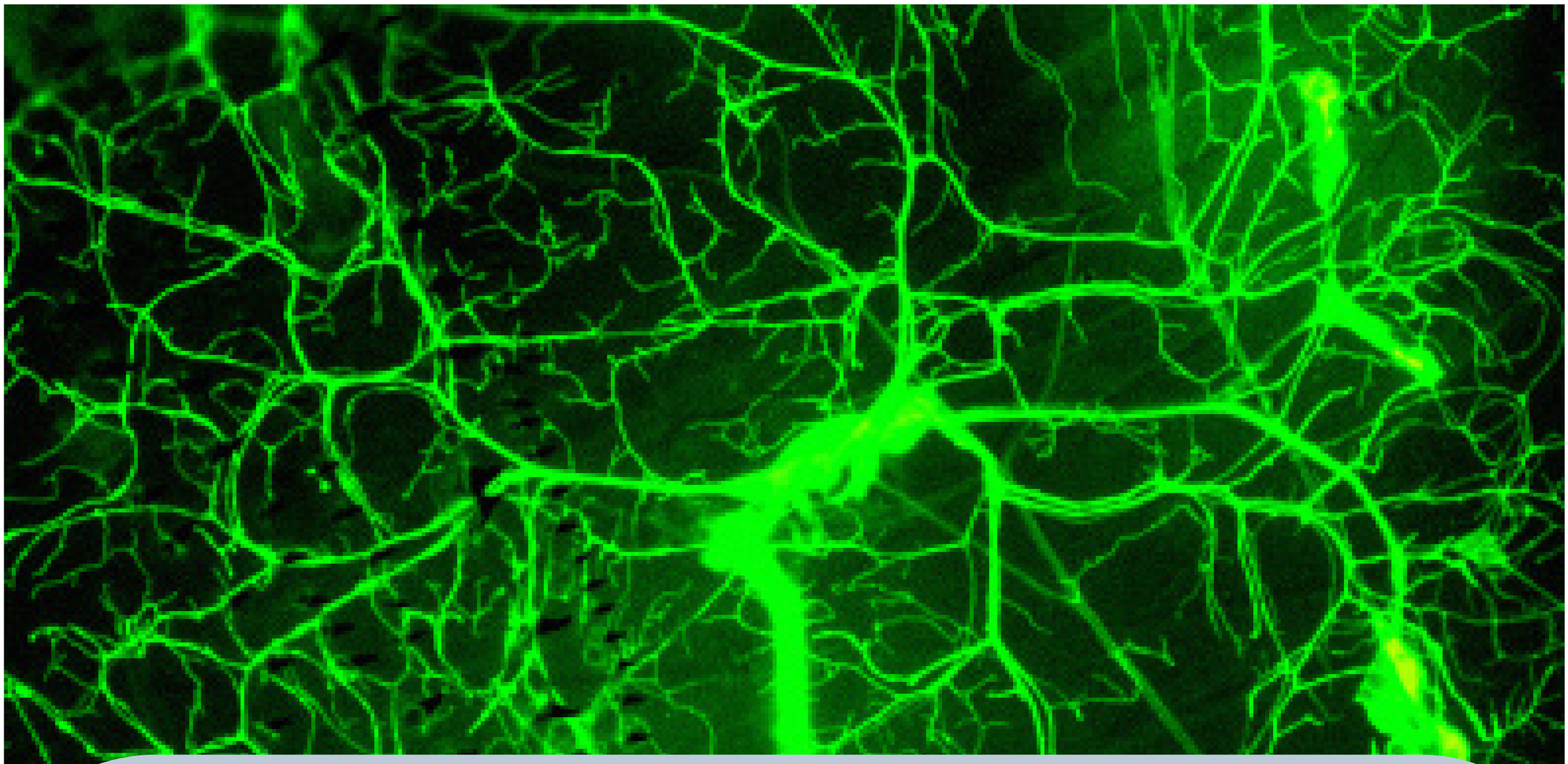

On the Cover: A beautiful brain with augumenter colors.
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Editor's Note

Thomas Romanchek
Chief-Editor

Thomas is a sophomore double majoring in Bioengineering and Psychology and does research with the Cellular Neuroscience Imaging Lab on campus. He is an editor for IJOIS and an active member of the Beckman Journal Club, two experiences which inspired him to start this journal. He is very excited to introduce "Brain Matters" to the UIUC community and hopes to broaden undergraduate interest in the field!

Fiza Bukhari
Assistant Chief-Editor

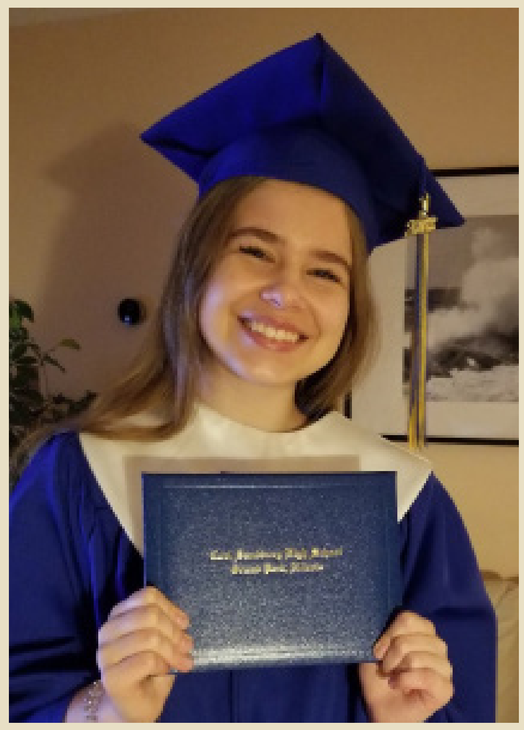
Fiza is a freshman majoring in Molecular and Cellular Biology on the pre-med track. In addition to her involvement in the Neuroscience Journal Committee, she communicates her Illinois experience by writing for the UIUC Admissions Blog. Just like her blog, she is thrilled to promote a neuroscience dialogue on campus!

Neil Doherty
Editor

Neil is a Freshman Molecular and Cellular Biology Major hoping to achieve the MCB Certificate in Neuroscience. He is a writer and editor for the "Brain Matters", as well as a member of the Undergraduate Psychology Association and the Philosophy Club at UIUC. He hopes to engage and inform the public about new advances in neuroscience, providing the foundation for sustained progress in science and medicine while also inspiring interest in the field in the student body of UIUC.

Laura Kilikevicius
Editor

Laura is a freshman majoring in biology and hopes to one day move into work in genetics. She is thrilled to be working on "Brain Matters" and hopes to broaden the knowledge of current neuroscience research across campus. Outside of the journal, she is an orientation leader on campus and is a Catholic Illini and Lithuanian-American club member.



Neelima Valluru
Editor

Neelima Valluru is a freshman at UIUC double majoring in Computer Science and Biology. She is currently interning at the Catchen Lab on campus and is working on a computational genomics project. She is also a member of the BMES and ESAA clubs on campus. She is very passionate about neuroscience and hopes to share current research in this fascinating field.

Emerson Fister
Editor

Emerson is a junior majoring in Psychology with a concentration in Behavioral Neuroscience and a minor in Integrative Biology. Outside of learning about Neuroscience, she is passionate about human-centered design and is an active member of the University of Illinois Design for America studio. She is delighted to collaborate and learn with the other students behind "Brain Matters".

Quentin Bu
Chief of Design

Quentin Bu is a junior majoring in Intradisciplinary Psychology with a minor in Creative Writing. In addition to her interest in cognitive neuroscience, she has past experiences in art, poster and graphic design. Quentin hopes "Brain Matters" can provide a platform for an academic discussion about the field of study at UIUC. She also wishes readers will have an enjoyable reading experience.

A Brief Review on the Nutrient Effects on the Brain and Implications

Do Yeon (Jason) Kim

Abstract Nutrients affect overall human health in various ways and their importance has been well-documented in numerous scientific articles. Recently, new evidence has suggested that diet plays a role in altering brain functions. Such findings have evoked speculation as to how diet can influence brain morphology and impact cognitive functions. Data from mice with modified diets and interpolated results from human studies with specific ingredients suggest that nutrients may act as a signaling molecule when broken down by cells to directly affect the brain itself. From well-controlled single diets to varying supplemental diets, new information has been found of how different diets influence brain functions and aging of the brain.

Introduction The human brain is a collective structure consisting of a myriad of neurons constantly firing signals to create, store, and recall memories. The major functional anatomy of the human brain is divided into four key parts: the parietal, frontal, occipital and temporal lobes (Hoffman, 2017). Each part comes with distinct functions. Although each part can be separated into its respective functions, it is important to note that brain structure as a whole is highly interactive. Therefore, the interactions of inner connections are not trivial and many questions about the function and architecture of the brain remain unanswered. Even with contrast to the remarkable complexity of the brain, scientists have used a relatively simple approach to determine the influence of nutrients on brain morphology and its function. Brain function and mental illnesses have often been associated with factors like mental stress and emotionality. In fact, in one study, researchers suggested that chronic stress leads to changes in brain structure and function (Chetty et al., 2014). However, at a molecular level brain functions can also be affected by tangible, physical factors such as nutrients. After all, the cellular make-up of the brain results from the fundamental building blocks received from foods in general. Hence, it is not surprising that food itself can affect the mental and cognitive functions of the brain. In one study, researchers have verified that tweaking the diet of mice models altered brain cell density, count, weight, and tissue morphology of the brain, leading to the belief that cognitive function and emotionality can be an influence as well (Lemon et al., 2016). It is believed that gut hormones affected by various foods can enter in and out of the brain, interacting with various receptors on the brain itself.

Nutrients affect Aging of the Brain Aging of the brain is commonly associated with a variety of negative changes including cognitive decline, sensory function loss, and neurodegeneration at the cellular level. Among the many symptoms of an aging brain, common characteristics include chronic oxidative stress, resistance to insulin, mitochondrial dysfunction, muscle, and neural atrophy, and increased levels of inflammatory processes; actual mechanisms behind these processes are complex and are the topic of another discussion in themselves. In general, mitochondrial dysfunction and oxidative metabolism are the two main sources of oxidative stress in the brain contributing directly to cognitive, motor and sensory damage (Antier et al., 2004; Wang and Michaelis, 2010; Yin et al., 2014). Neurons in the brain require a great deal of energy which is supplied by the ATP consumption occurring in membrane ionic pumps, synaptic transmission, and channel activity. As a result of such demand, this can lead to increased free radicals which may inhibit the enzyme NADH dehydrogenase and cause a defect in mitochondria. Impaired production of ATP from dysfunctional mitochondria increases reactive oxygen species in the brain which contribute to the commonly observed aging process (Shigenaga et al., 1994, Lenaz, 1998; Sastre et al., 2003). A recent study according to Lemon et al. (2016) has revealed the ways to prevent neural decline through the use of multi-ingredient dietary supplements (MDS). To explore these options, researchers from the study carefully chose key ingredients that have been proven to slow down or completely eradicate each of the five processes associated with aging. The supplements in the study were prepared in a liquid form and a 0.4 ml volume was soaked in a 1 cm x 1.5 cm x 1 cm piece of bagel and allowed to dry. Each mouse was given exactly one piece of the bagel with or without multi-dietary supplements every day. Each piece was eaten within 20 minutes to ensure that the mice received the equivalent and full dosage required for the study. Transgenic growth hormone (TGM) mice were used to model older specimens because the overexpressed growth hormone allows TGM to mature and age faster (Lemon et al., 2016). This allows researchers to study the effects of aging in a shorter period. Results of the experiment demonstrated that various improvements in brain function are due to the MDS treatment in the TGM mice. However, simple somatosensory tests, which included (a) landing response, (b) visual placing, (c) negative geotaxis, and (d) pinch reflex, did not show significant improvement compared to normal, untreated mice. This shows how further improvement from supplementation alone did not occur. However, there are other areas that have been improved to a certain extent. MDS treated TGM brain cells showed significantly greater density as opposed to the brain cells of 12-month-old untreated TGM mice, implying that MDS indeed slowed down the deteriorating effects of aging on the brain (Lemon et al., 2016). In terms of tissue morphology, supplemental mice had a 16% increase in the molecular layer (ML) and 18% increase in the granular layer (GL) of the brain (Lemon et al., 2016). The Mitrial cell layer also showed an increase of up to 29% in treated mice. Loss of mitral cells in aging rodents has been documented and the increase in these cells in the MDS suggests that treatment potentially prevented these neurons from age-related atrophy. In terms of behavioral influence on mice, the effect on the supplemented mice was significantly different from dim light to bright light. This suggests that supplemented mice demonstrated improved contextual discrimination which implies that aging MDS treated mice had stronger cognitive function than their counterparts. In motor coordination, the untreated 12-month TGM mice showed severely hindered coordination compared to same age untreated normal mice, but MDS supplement mice showed significant progress in terms of motor coordination (Lemon et al., 2016). This implies that nutrients play a critical role in the aging of the brain in various areas.

Gut to Brain Connection The Human body consists of complex systems of connections that interact with different parts of the body. For example, the enteric nervous system (ENS)

consists of more than 100 million nerve cells lining the gastrointestinal tract from esophagus to rectum. While the brain and gut may appear to be two different tissue systems with little interaction, it is highly probable that events in the gut can trigger reactions in the brain and vice-versa. A piece of great evidence about the gut-to-brain connection can be found in the interaction between insulin and specific signal transduction receptors located in the hippocampus. Insulin has been known to be a gut hormone produced in the pancreas and involved in changes in cognitive processing in the brain. As discussed above, the brain to gut connection plays a significant role in shaping the brain and further verifies the importance of nutrients.

Effects of Specific Nutrients on Cognition There is a belief that a deficiency of omega-3 fatty acids in rodents results in impaired learning and memory. In addition, even in humans, omega-3 deficiencies have been linked with increased risk of mental disorders such as bipolar disorder, schizophrenia, dementia and dyslexia (Peet, Laugharne, Mellor & Ramchand, 1996). According to current data, a diet rich in omega-3 fatty acids can promote brain health. On the other hand, high contents of trans and saturated fats adversely influence brain cognition as described below. In rodent studies, so-called "junk food" with high trans and saturated fat content led to a decline in cognitive performance in rats as well as reduced hippocampal levels of BDNF related synaptic plasticity in only three weeks of such treatment. This once again implies that nutrients have a huge role in brain health (Molten, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002). At a molecular level, broken down foods can become building blocks for signaling molecules to promote neural synaptic plasticity. Antioxidants and micronutrients, in particular, are other great examples known to influence learning capacity and memory performance of the brain. Various micronutrients with an anti-oxidant capacity can influence these functions. However, constituents that make up an "antioxidant" substance are great in number and only a few of them has been extensively evaluated separately. Two tannins (procyanidin and prodelphinidin), anthocyanins, and phenolics are well-known compounds with antioxidant properties commonly found in grapes, tea leaves, and seeds. Researchers evaluated their influence on mice, and polyphenols have been shown to increase hippocampal plasticity to enhance learning and memory performance (Casadesus et al., 2004). For example, alpha lipoic acid, which is found in meats such as the kidney, heart, and liver, and vegetables like spinach, broccoli, and potatoes, is a coenzyme important for energy homeostasis in mitochondria (Liu, 2008). Another example is a curcumin, curry spice, which has been shown to reduce memory deficits in animal models, implying that nutrients indeed have a positive effect on cognitive functions in the brain (Frautschy SA, et al 2001).

High Salt Diet on the Brain It is an accepted fact that the human body requires a sufficient amount of sodium to stay healthy and maintain functioning. However, a high sodium diet is detrimental to cognitive function and seems to have a role in a variety of cardiovascular disorders (Nwanguma and Okorie, 2013). A high salt diet undeniably has a critical role in shaping human health, yet the exact mechanism with which a high salt diet impairs cognitive function and learning remains unknown. However, it is well-documented that excessive salt intake has undesirable physiological effects. Various studies on animals have shown that such cases are true. Increased oxidative stress in cells, as well as the generation of reactive oxygen species which can turn into free radicals, can damage the brain over time. However, according to a study where scientists compared 4-week and 7-week high-salt diets in mice, it was found that the more salt was consumed, the more weight the mice lost. It is also important to note that in the same study, it is mentioned that the mice consumed a gradual increase in food and water (Ge et al., 2017). However, both short-term and long-term memories with mice treated with 7-week long high salt diets were impaired. The high 7-week salt group had disturbances in the hippocampal long-term potentiation (LTP). In addition, the same studied also showed that high salt diets induce oxidative stress and trigger metabolic reprogramming in the hippocampus (Ge et al., 2017). High salt treatment is associated with neurotransmitter release, implying that nutritional diet specification such as a high salt diet can affect brain function.

Conclusion In-depth analyses have shown that by tweaking and controlling diet, even aging of the brain can be slowed down and functions can be restored to normal levels. Further research is necessary to study the exact mechanism behind how specific nutrients can influence brain-cell interactions. Both high and low levels of brain functioning are affected by nutrients as evidence shows, which is why it is crucial to research and modify other experimental diets in order to promote the health of the brain.

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Brain Development of Schizophrenic Patients

Bailey S. Zinger

In the distant past, the symptoms and characteristics of schizophrenia were considered the behavior of other worldly spirits or beasts dwelling within a host's mind ("History Cooperative"). Although this idea is captivating, the symptoms of schizophrenia can be explained through scientific investigation. In 1910, Swiss psychiatrist Paul Eugen Bleuler coined the term "schizophrenia", derived from the Greek words "schizo", meaning split, and "phren", meaning mind (National Institute of Mental Health, 2016). Consequently, many people mistake schizophrenia for a form of dissociative identity disorder. A person who suffers from schizophrenia, however, does not change from one personality to another unrecognizable personality (National Institute of Mental Health, 2016). Schizophrenia is not a split personality disorder, nor is it the work of unseen spirits. Although the disorder is enigmatic, studies have been conducted to elucidate some of its symptoms and characteristics.

Schizophrenia is a chronic and severe mental disorder that affects how an individual feels, thinks, behaves, and perceives reality (A Brief History of Schizophrenia, 2012). Delusions and hallucinations are among the most common positive symptoms of the disorder, often resulting in experiences of derealization or depersonalization (Cannon, T.D., 2015). Derealization is a phenomenon in which the external world becomes seemingly unreal, for instance, a person experiencing derealization may describe it as a dream-like state in which sights and sounds are fuzzy and muted. Depersonalization, one of the most common symptoms associated with schizophrenia, is a state in which one's thoughts and feelings do not seem like his or her own (Cannon, T.D., 2015).

The onset of schizophrenia is typically progressive and presents itself between the ages of 12 and 35 (Cannon, T.D., 2015). A young individual demonstrating stark changes in thought or perception that manifest into delusions is considered a prodromal or high-risk clinical case. Schizophrenia is a disconnection between functional neural networks in the brain; since different psychotic symptoms of schizophrenia may involve different interactions amongst networks, high-risk clinical cases are of extraordinary importance to scientists as they can be marked and traced through the progression of the disorder (Cannon, T.D., 2015). The complexity of schizophrenia is what makes the disorder so difficult to diagnose. The root causes of schizophrenia vary widely and may include genetic variants, social stress, and neurological complications during childbirth or early development (Cannon, T.D.). Due to the complex nature of the disorder, two leading theories of schizophrenia onset have been considered, but there is not yet one sure method to diagnose and treat individuals with the disorder. The two theories discussed in this article include the neurodevelopmental model and the excitation-inhibition imbalance model. Brain disconnectivity due to *axonal pathology, such as disrupted myelination, and deficits in dendritic spines is thought to be the neurodevelopmental feature of schizophrenia (Cannon, T.D., 2015). One condition includes disrupted myelin, the sheath of protective plasma membrane extensions along axons of the nervous system (Snaidero, 2014). Disrupted myelin prevents high specificity of nerve impulses along axons, indicating the possibility of miscommunication amongst cells in regards to perception and memory. This condition is likely to have been expressed at birth in schizophrenic patients, but in some cases, this disruption may progress above a threshold of exposed psychotic symptoms despite normal neurological developments (Cannon, T.D., 2015). In other words, the neurological symptoms of schizophrenia are always present but are expressed later in life.

The notion of postponed symptom expression means that the disorder may be progressive and a method of mapping the brain over time is pertinent to discovering the patterns of the disorder. Thus, neuroimaging of high-risk clinical cases that did convert to the full psychosis of schizophrenia showed significantly greater thinning of the gray matter in the prefrontal cortex of the brain in comparison to healthy controls and those that did not convert (Cannon, T.D., 2015). These tests included subjects that had not previously been exposed to antipsychotic medications, ensuring that the medications themselves were not stimulating the acceleration of gray matter loss (Cannon, T.D., 2015). Networks that involve the medial prefrontal cortex play critical roles in memory formation and retrieval. These networks also indicate whether a person experienced their own memory or imagined the experience of another person (Cannon, T.D., 2015). This memory discrepancy can now be much better identified through the tracking of the thinning of gray matter in this region. "Reality monitoring" is defined as the ability to assess the characteristics of memory representations. The characteristics of the memory representations may reflect the neurological processing activity that occurs when a memory becomes encoded. This includes the marking of perceptual or actual details about an event and/or the associated thoughts and feelings at the time (Brandt, 2013).

Prefrontal cortex regions are primarily involved in memory recollection. To verify this, a study was performed focusing on the inhibition of memory retrieval. In this study, subjects suppressed retrieval of some items from a study list, showing that the ability to retrieve those items was impaired and the medial prefrontal cortex was active during retrieval suppression (Peters, 1970). Therefore, reality monitoring of action memories is predicted to provoke activity in medial prefrontal cortex regions (Brandt, 2013) in specific structural variations, which correlate with differences in performance on reality monitoring tasks (Cannon, T.D., 2015). Schizophrenic patients are more likely to rely on familiarity-based mental processes, meaning activities and memories that are repetitive and easy to replicate due to prolonged exposure come more easily to them. This is due to the deficit in absolute or relational neural encoding, which reduces the ability to reference memories in context (Cannon, T.D., 2015). Considering this, disturbances in source monitoring during learning and memory encoding may cause disrupted belief evaluation (Cannon, T.D., 2015), the sensation of having difficulty discerning a belief from a fact or actual circumstance. Gray matter loss leading to disrupted belief in schizophrenia patients may explain why those with the disease become confused about what is real versus imaginary, and that the familiar begins to feel strange in the effect of derealization

*Axonal pathology refers to the laboratory tests conducted on samples of neural tissue including axons, the part of the nerve cell along which impulses are conducted. Samples are tested for various conditions such as disrupted myelination. The myelin sheath is an insulating cover over the axons in the brain that increase the speed of nerve impulses.

or depersonalization.

Another theory of schizophrenia onset is the excitation-inhibition imbalance model. The basis of this model is derived from the neurological developments of drug abusers, particularly in phencyclidine and ketamine abusers. These drug abusers experience similar symptoms to schizophrenia sufferers; the abusers' brains can be mapped and the findings applied to brains with schizophrenia. The effects of the drugs are driven by excitation of N-methyl-D-aspartate (NMDA) receptors in the brain, and these receptors in turn are activated by the excited state of the amino acid transmitter glutamate (Cannon, T.D., 2015). Cells associated with glutamine, glutamatergic pyramidal cells, converge, or synapse, onto some neurons that express the inhibitory gamma-aminobutyric acid (GABA) transmitter. These cells in turn project back to the pyramidal cells, completing a set of regional neurological circuits (Cannon, T.D., 2015). Pyramidal cells function by transforming synaptic inputs into a patterned output of action potentials. They are special due to their abundance in the brain and that they are able to send their axons long distances throughout the brain (Bekkers, n.d.). Since some pyramidal cells ultimately activate NMDA receptors, NMDA receptor hypofunction may result in an imbalance of excitation and inhibition that could contribute to some symptoms of schizophrenia (Cannon, T.D., 2015). For example, as NMDA receptor function continues to weaken, the previously learned memory interpretations show a directly correlating positive linear relationship. This process creates an altered environment for the development of new explanations of experience and phenomena (Cannon, T.D., 2015), such that an alien is controlling the patient's thoughts or beliefs.

Another interesting aspect of the excitation-inhibition imbalance theory is that mismatch negativity (MMN) potential is dependent on NMDA receptors. MMN is an electrophysiological potential generated when a stimulus occurs out of a series of standard stimuli that is different from the rest (a black dot amongst a series of white dots, for example) (National Institute of Mental Health, 2016). Since MMN is dependent on NMDA receptors, reduced MMN in all stages of schizophrenia is consistent with the inhibition of NMDA-mediated synaptic activity, and in turn these deficits in NMDA activity may drive the accelerated gray matter loss thought to be associated with schizophrenic cases (Cannon, T.D., 2015).

In all, the two theories discussed in this article describe some of the leading scientific evidence and speculation in the development of schizophrenia. However, many questions are still unanswered due to the complex nature of the disorder. What causes the process of gray matter deterioration? How does the inhibition-excitation imbalance come to be? Scientists and researchers are working toward answering these questions so that schizophrenics will receive more effective medical treatment.

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Neural Pathways of Anxiety

Luke LaLonde

What is Anxiety?

Anxiety is a generalized term that can be used to describe feelings of worry or uneasiness that almost all people deal with intermittently in their lives. Anxiety is a stress response to a potentially dangerous stimulus that causes an accelerated heartbeat and quickened breathing. While being stressed is uncomfortable, it's not necessarily unhealthy if it does not disrupt daily life. An issue arises in those who face prolonged or recurring stress. This type of chronic stress has often been shown to predispose individuals to anxiety disorders (Sanders, 2016), including various panic disorders, phobias, and social anxiety. Another type of anxiety disorder, generalized anxiety disorder (GAD), is characterized by constant and excessive uneasiness about routine life circumstances. GAD often leads to symptoms such as difficulty sleeping or unsatisfying sleep, which can then lead to issues like irritability, muscle tension, general fatigue, and trouble concentrating (The National Institute of Mental Health, 2018). There is no single cause for GAD, but there are many associated risk factors including hormone imbalance, early-life trauma, exposure to repetitive, stressful stimuli, and a relatively slight genetic influence.

Key Brain Areas

Anatomically, GAD involves abnormalities in the functioning of the limbic system, which is a phylogenetically ancient region of the brain that functions as a control center for emotions, mood, and drives (Martin, 2009). More specifically, the hippocampus and the amygdala are the two primary structures in the limbic system that play a role in GAD. The amygdala is an almond-shaped structure that transfers nerve impulses into hormonal signals, triggering emotional responses. It plays an important role in alerting the brain about potential threats. This is noteworthy because anxiety disorders, GAD in particular, are a result of prolonged overactivity of the amygdala, which causes the brain to be in a constant state of fear or anxiety (Patriquin, 2017). Obviously, a constant state of fear would make it difficult to relax for those facing GAD, ultimately resulting in the aforementioned symptoms of anxiety disorders such as fatigue and loss of sleep that eventually contribute to a multitude of additional symptoms. The other key brain region involved in GAD, the hippocampus, is responsible for encoding threatening events into memory and relaying information to the amygdala during the process of retrieval for a rapid response to threatening stimuli ("The Effects of Stress & Anxiety on the Brain", 2018).

Phylogeny

It is important to note the phylogeny of the structures associated with GAD. Phylogeny refers to the evolutionary development of a particular feature of an organism. As mentioned before, the limbic cortex is ancient. This means that the limbic system was preserved through evolutionary history, and because of this, it is relatively autonomous, involving little voluntary action. Anxiety disorders target the structures of the limbic system rather than higher cognitive centers of the frontal lobe such as the prefrontal cortex (responsible for decision making) or the orbitofrontal cortex (controls impulses). This means that anxiety disorders are not based on irrational thoughts but on threat assessment and an uncontrollable natural response to what part of the brain perceives to be a real threat, despite higher-order brain areas providing input that there is, in fact, no immediate danger (Martin, 2009). This helps to explain the difficulty involved in controlling nervous feelings that come with anxiety disorders, as the problem is not solved by simply being cognizant of the fact that there is no real threat. Instead, victims should take actions that will directly affect the sources of the problem, such as using medication to address neurochemical and hormonal imbalances.

Neurotransmitters and Endocrine System

Anti-anxiety medication is useful in many cases as a way to counter the neurochemical imbalances associated with GAD. There are a few ways in which neurotransmitter release can result in the overactivity of the limbic system. The first way is through decreased inhibitory signaling by the major mammalian inhibitory neurotransmitter, gamma-Aminobutyric acid, also known as GABA. This would result in a greater amount of uninhibited nerve firings in the limbic cortex which would consequently lead to overactivity (Martin, 2009). The second possibility is an excess of the excitatory neurotransmitter glutamate, which would result similarly with a greater amount of nerve firings and therefore overactivity of the amygdala.

It is also possible that some combination of these two could be at play in contributing to overactivity. Other chemical messengers that play a role in anxiety disorders are cortisol and norepinephrine, in this case acting as hormones. These two hormones are normally released in response to a threat for a limited period of time. They contribute to the accelerated heartbeat and quickened breathing that normally allow for faster movement and better perception when facing danger. ("The Effects of Stress & Anxiety on the Brain", 2018). However, the brains of those with GAD constantly perceive threatening stimuli, causing the extended production of these hormones that are only intended for short periods of time. There are trade-offs for the increased awareness these hormones provide over time. High cortisol levels contribute to weight gain, muscle weakness, and suppressed immunity as the body focuses on escaping momentary danger. (The National Institute of Mental Health, 2018). Another symptom of excess levels of both cortisol and norepinephrine is difficulty sleeping, which only exacerbates the stress response to real threats, perpetuating the release of these hormones.

Physical Effects and Ramifications

The short-term effects caused by GAD are apparent, as hormone imbalances and overactivity of nerves in the limbic system lead to sleep difficulties, lack of focus, weight-gain, and other symptoms (Patriquin, 2017). However, these are merely side effects of what can be destructive functional abnormalities in and of themselves. It seems as though the constant activity of the limbic system could have some effect on the utility of the nerves themselves. In short, there are more direct and lasting effects caused by GAD on the brain itself that should be

noted in order to view the full scope of damage caused by the disorder. One such effect is on the amygdala. As discussed, GAD is linked to overactivity in the nerves of the limbic system, in particular those of the amygdala, as it is the system primarily responsible for perceiving potential danger. It has been found that the normally almond-shaped amygdala gets larger in pediatric patients with GAD. This is likely to correspond with hypertrophy seen in the amygdala of lab animals, which correlates with expectation considering the abnormal activity of the amygdala in patients with GAD (Martin, 2009). Different, yet also alarming, results have been observed in the form of hippocampal damage caused by limbic hyperactivity.

While research is still in progress on the effects of GAD on neurodegeneration within the limbic system, new research is showing that prolonged stress and anxiety can potentially cause structural degeneration of hippocampal nerves ("The Effects of Stress & Anxiety on the Brain", 2018). This is especially concerning because the volume of the hippocampus and growth of new cells is directly related to stress resiliency in anxiety and mood disorders, suggesting that if there is structural damage to the hippocampus caused by GAD, it is making the brain gradually less resilient to the stress as it persists (Martin, 2009). Another recent observation from fMRI scans of GAD patients is the ratio of grey to white matter in the brain. Grey matter is the tissue of the central nervous system that contains the cell bodies, dendrites, and axon terminals of neurons, while white matter is made up of the connecting neuron axons (Sanders, 2016). Grey matter is found mostly in regions of the brain responsible for sensory perception, memory, and emotion, which is why it is possibly related to the hyperactivity of the amygdala, where an abnormally high ratio of grey to white matter has been found in studies of patients with GAD. Conversely, possibly related to neurodegeneration associated with GAD, a greater ratio of white matter to grey matter has been found in hippocampal regions of patients with the disorder (Hilbert, 2015).

Relevance

As time goes on and the human brain becomes better understood, more information is uncovered regarding the side effects and neurological damage caused by GAD. The good news is that neurodegeneration is not totally irreversible. The plasticity of the brain will allow for regeneration to some degree, but the earlier the damage can be reversed, the better ("The Effects of Stress & Anxiety on the Brain", 2018). However, with more potential damages being uncovered, it is becoming apparent that relaxation and avoiding the risk factors of anxiety disorders should be emphasized in daily life. This is especially pertinent to those with stressful jobs and students that face difficult assignments, exams, and other stressors on a regular basis. The positive news for people that lead stressful lives is that there are ways to avoid GAD, and the genetic contribution in GAD is not as substantial as other anxiety disorders, so taking measures to stay away from avoidable stressful situations can be quite effective (Martin, 2009). However, many people, especially students, still deal with GAD. Many face GAD along with MDD (major depressive disorder), with which it has high comorbidity that ranges up to 98% in treatment studies (Patriquin, 2017). It is important to not only know how to avoid GAD, but to also be aware of the ways in which it can manifest itself in daily life, the damage it can cause, and its relationship to other mental illnesses like MDD.

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Neurological Benefits of Mindfulness

Victoria Wu

René Descartes was a 17th-century philosopher who popularized the idea of Cartesian dualism, an abstract separation between the body and the mind, heavily influencing modern thought. People tend to think of their mind as separate from their brain and body, hence the term “Mind over matter”. Descartes believed that the connection between the mind and brain occurred at the pineal gland, which he called the “seat of the soul”. Because we now know that the pineal gland is responsible for secretion of melatonin, a chemical that contributes to the regulation of our circadian rhythm, we can now understand that this differs from the definition that it was the area where all our thoughts are formed. Additionally, from a biological standpoint, the “mind” as thought and abstract ideas originate from electrical and chemical signals in the brain (Lockhorst, 2013).

There is no separation between mind and body, for the brain works independently and outside of the body. The brain is simply another organ that functions as a piece of a machine, though the mechanisms are anything but simple. As a small error in syntax could lead to a myriad of unforeseen malfunctions in a computer program, minor changes in brain chemistry could lead to serious defects in the rest of the body. Studies have shown that chronic stress strongly correlates to psychological disorders, decreased function in learning and attention, and weakening of the immune system (Schneiderman, Ironson, & Siegel, 2008). However, for every action there is an equal and opposite reaction - the opposing process is mindfulness meditation, a technique that correlates with improvement in health. Effects have been most notable in patients with anxiety and depression, enhancing attention and reducing the risk of future cardiac ailments.

Mindfulness has proven to be quite an effective remedy in western medicine, despite its distant origin in Eastern Culture over two millennia ago. The practice of mindfulness, nonjudgmentally focusing the attention on the present moment to achieve mental clarity, originated in the Hindu traditions of Vedantism. Other methods of practicing mindfulness later developed with Buddhism around 400 B.C.E. The practice traveled West when Jon Kabat-Zinn, a medical professor, started the Mindfulness-Based Stress Reduction Clinic in Massachusetts. Mindfulness plays a large role in positive psychology, which focuses on people’s strengths and needs for fulfillment. Once mindfulness and detailed brain-imaging technology became prevalent in medicine, the door for research was opened. (Joaquin, 2017)

When researching emotion, fear is the easiest to observe. This is because behaviors associated with fear, such as cowering or running away, are physically exhibited. Fear is a strong emotion and necessary for survival, although it can become pervasive and interfere with everyday functioning. When this happens, it is a sign that a person may be suffering from an anxiety disorder. According to the National Comorbidity Survey by Harvard Medical School (Harvard Medical School, 2007), anxiety disorders are the most common psychological disorders in the United States.

Many medications and treatments for anxiety disorders are used to avoid feelings of fear, but mindfulness takes the approach of confronting and accepting them. Some people believe that focusing on the inner experience in a non-judgmental way can ease discomfort and promote a positive relationship with emotion. (Greeson & Brantley, 2009) Studies have found that it is very likely these people are correct in their hypothesis. According to Hofmann, practicing mindfulness over the short course of two months was found to reduce symptoms of panic and anxiety (Hedges’ g=.97). Mindfulness therapy could be another option as an alternative or addition to medication for anxiety and panic disorders. In a 3-year follow-up, 22 patients who had undergone an 8-week mindfulness-based stress reduction outpatient study were found to have maintained their stress reduction, measured on the Hamilton anxiety scale ($F(2,32) = 13.22$; $p < 0.001$) (Miller, Fletcher, & Kabat-Zinn, 1995).

The anterior cingulate cortex (ACC), associated with attention, is the brain area most consistently related to mindfulness during studies. The ACC functions to filter out distractions and direct attention to the object of focus. It was also found that the ACC is responsible for sustained attention (Wu et al, 2017). The fronto-limbic structures of the brain that control stress reduction and emotional regulation are also involved. Areas associated with attention and emotional regulation in the cerebral cortex were thicker in mindfulness practitioners compared to those who had never practiced this form of meditation. (Tang, Holzel, & Posner, 2015).

Depression is the second most prevalent psychological disorder the US population faces. Incredibly, mindfulness meditation not only lowers the feelings of fear in those with anxiety disorders but also raises the quality of life in patients with depression. As with anxiety, mindfulness meditation is helpful in symptom reduction, it’s unclear as to what neural mechanisms are responsible. More research is needed in these areas for full comprehension, but we do know a few of the brain areas involved as of now. The insula was found to have reduced activation during exposure to negative stimuli in those who practiced mindfulness. This brain area plays a large role in emotional experience and the decrease in activity corresponds to a decrease in rumination, a symptom of depression (Paul, Stanton, Greeson, Smoski, & Wang, 2012). Mindfulness-based cognitive therapy has been shown to reduce symptoms and prevent relapse of depression ($p=0.04$), though more research needs to be done on the neurological basis of these results (Barnhofer et al, 2009).

A benefit of mindfulness that is relatively well established is that the practice enhances attention (Tang et al, 2015). According to Lin et. al., “Results reveal that mindfulness as a meditative practice produced a reduction in the difference between the LPP response to negative high arousing and neutral stimuli across time” (Lin, Fisher, Roberts, & Moser, 2016). This means attention will be higher for more menial tasks, like studying, in addition to ones that automatically capture our attention, like video games. Studies have shown improved attention in long-term meditators. The cognitive decline that comes with age is reduced in these people, due to maintenance of the anterior cingulate cortex through meditation (Zanesco, King, MacLean, & Saron, 2018).

There is a strong connection to regulating breath and regulating attention. Focused breathing is a method of mindfulness meditation that requires sustained attention to the body and present moment. This is likely the most practiced form of meditation and it has long-term benefits

on attention and stress. Emotions, focus, and memory become clearer with this practice. Breathing directly affects our attention, which cycles with each inhalation and exhalation. Inhaling correlates to higher attention, exhaling to lower. Mindful breathing works to reduce noradrenaline to a "sweet spot." Too much noradrenaline can cause a jittery, nervous feeling while feelings of sluggishness may result when insufficient amounts are present. This mechanism reduces stress long-term, which benefits other areas of the body (Melnychuck et al, 2018).

Stroke is the fifth biggest killer in the US and heart disease is number one. Chronic stress is a risk factor for both. Those who suffer from chronic stress have high levels of cortisol, a stress hormone, which increases blood pressure. Increased blood pressure for long periods of time increases the risk of heart disease and stroke. Corticosteroid is another stress hormone as it. It suppresses the immune system by blocking the transcription of cytokines, proteins which regulate inflammation and immunity. Immunosuppression is the result of this chain of events, leading to adverse health issues over time. Suppression of the immune system impacts every system of the body and is linked to diseases like osteoporosis and obesity (Barshes, Goodpastor, & Goss, 2004). Acute, short-term stress is adaptive and will increase immune function, but chronic stress suppresses it (Dhabhar, 2009). Mindfulness meditation and focused breathing can be preventative for chronic stress, thereby reducing the risk of stroke and heart disease.

Although there is a need for more research on the neurologic mechanisms behind the benefits of mindfulness meditation, the studies given here show evidence that some benefits may exist. With age, decline in the ability to learn, solve problems, and reason is an issue common throughout all of humanity. Depression and anxiety are the most common mental disorders in the US. Stroke and heart disease are some of the top killers in our country. Mindfulness meditation is a method that has been found to reduce the symptoms of or prevent these ailments entirely. Additionally, it has been around for thousands of years due to its health benefits. Combined with new technology, increased understanding of the brain, and modern approaches to medicine, this practice could become more prevalent as a simple, natural treatment for many diseases.

Notes

1 LLP stands for Late Positive Potential. It is an electrophysiological measure of attention given to emotional stimuli.

2 Hedges' G is a statistical test measuring size of an effect, or how much one group differs from another. G is indicative of the number of standard deviations the groups differ by. For reference, g=.2 is considered a small effect and g=.8 is considered a large effect.

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The Origin, History and Science of Memory

Neil Doherty

Throughout human history, much of the brain and its functioning has been unknown. At first, the theory of mind was articulated by ancient Greek philosophers. Plato, for instance, declared that the Logistikon (interpretation of consciousness at the time) was, in fact, the thinking part of the soul. Aristotle subsequently proposed that the mind was an extension of the soul that involved knowing and understanding. Outside these two major contributions, not much else of the function of the human brain had been addressed, outside of its moral reasoning and decision making. Although the studies at the time had been primitive and informal, they did tackle many of the critical concepts about consciousness, will, and memory. However, memory seemed more tangential and was treated teleologically as a means of understanding consciousness. Up until the 20th century, very few people had questioned the extent, capacity, or mechanism of memory. It was lost in the deafening roar of debate over consciousness.

However, in 1885, the first account of memory as a function of crystallized intelligence had been proposed, with the advent of the famous Ebbinghaus curve from Ebbinghaus' Über das Gedächtnis (Memory. A Contribution to Experimental Psychology, 2016). Though it seemed rather self-evident, the scientific data proving that memory decreased over time was revolutionary. As a direct result of Ebbingahus' contribution, the study of human memory was thrust to the forefront of both psychology and early neuroscience. Eventually, Richard Semon proposed in his 1904 The Mneme that memories created an engram, a seemingly permanent change in the physical structure of the brain that can be measured (12). Later in 1949, psychology researcher Donald Hebb developed Hebb's Rule, the notion that memories were stored in connections between neurons known as synapses (65). This forms the basis of our current understanding of memory, scientifically supported by the continued efforts of modern neuroscientists from the 1950's onwards (most notably Dr. Karl Lashley, who in 1950 gave empirical evidence of engrams by eliciting episodic memories by electrically stimulating different parts of the brain with electrodes (Mastin, 2018).

Despite knowing about the nature of memory, there is little knowledge about what exactly constitutes memory, how it functions, and its relation to other cognitive processes. Currently, our understanding of memory is split between two interpretations of neural functioning: the modular approach and the holistic approach. The modular approach (first proposed by Jerry Fodor in 1983 when he published the book Modularity of Mind (2-5)) proposes that memories function differently in different parts of the brain as a result of a neural anatomical process known as functional specialization (neurons being functionally assigned different roles based upon localization and necessity (Wang, D. et al., 2014). To understand this approach, we must first understand how memories are formed.

Memories are formed by converting external stimuli into usable electrical signals. Touch, for example, uses unmyelinated dorsal root ganglia (DRG) neurons to detect pressure and proprioception (body orientation), allowing for afferent messages to be sent via the depolarization of action potentials -electrical signals created by electrochemical gradients (see figures 1.1 and 1.2)(ch1_neuronv_biov2 8-26)- once exteroreceptive (outer body) and/or interoceptive (inner body) sensations have been detected. These messages then travel to the cortex via the gracilis muscle in the thigh, ascending up the spinal cord to the cunneatus, finally making their way to the second somatosensory cortex, which includes the amygdala and hippocampus (see figure 2.1). Proponents of modular theory then propose that memories enter the hippocampus from the Cerebral Cortex through the perforant pathway, which leads to the entorhinal cortex. This data then flows to the dentate gyrus where it is transferred to the pyramidal neurons of the CA3 region of the hippocampus, which sends the information to the axons of the CA1 region. The subiculum then relays the information back to the entorhinal cortex, which pushes out the data back into the cerebral cortex, where different memories are then divided to be encoded; repressed and emotionally episodic memories are sent to the amygdala and limbic system in people with PTSD or emotional trauma, while semantic memory is stored in the neocortex. Other information is mostly kept in the synapses between neurons via complex sequences of neurotransmitters stored in synaptic vesicles waiting to be released at depolarization into the synaptic cleft in both the hippocampus and the cerebral cortexes (see figure 3.1) (Rolls, E.T., 1996).

Holists suggest the very same anatomy,

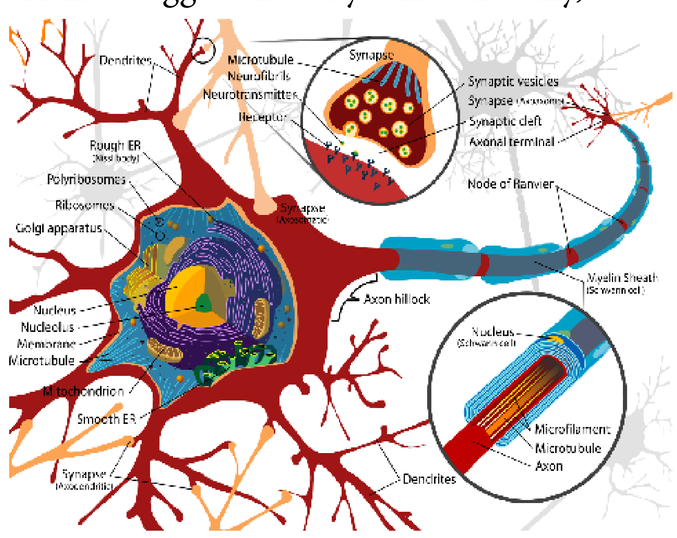

Figure 1.1 Diagram of neuron

however they maintain that memories are stored across the entirety of the cortex, meaning that all areas overlap with little specialization in memory storage beyond the distinction between the storage of explicit (conscious) memories in the cerebrum and implicit procedural (muscle) and episodic memories in the cerebellum and amygdala (Ramachandran, 2009). In essence, holists posit that memory storage is almost completely indeterminate and generalized across the entire brain. Both seemingly contrary theories have significant experimental support, meaning the prevailing theory is that memory is a mixture of both holism and modularity. As a result, more recent focus has been given to understanding the cellular mechanisms to better delineate between the two systems to determine their roles in very destructive disorders like Alzheimer's and PTSD.

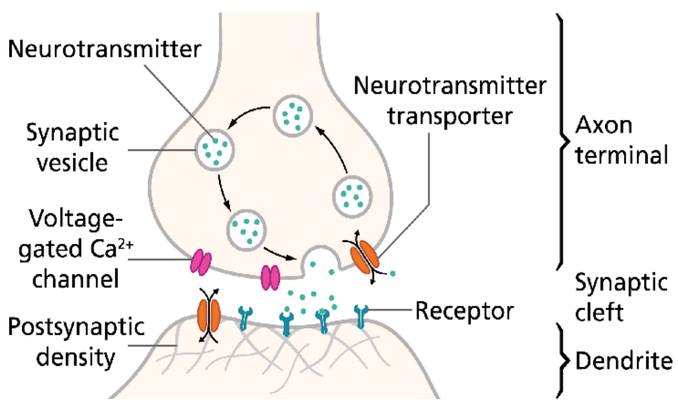

Figure 1.2: Image of the components of a synapse by which neurotransmitters are exchanged end signal transduction occurs.

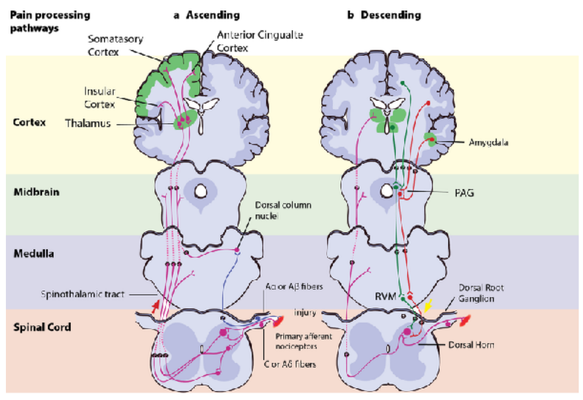

Figure 2.1: Image of the path by which sensory information is sent

After addressing the physiological distinctions for approaching memory, it's important to note that current studies on the procedure of recall have shown that memory has not been properly delineated from other cognitive processes as was originally thought. For instance, according to Tomita et al., functional Magnetic Resonance Imaging tests (fMRI) have determined that during voluntary recall, blood flow aggregation in regions of the frontal lobes associated with conscious thought increased, suggesting that feedback projections from prefrontal cortex to the posterior association cortex appear to serve the executive control of voluntary recall, not the previously believed sub-cortical regions responsible for unconscious activity. This implies that it is possible that memory and consciousness may not be separate at all. In addition, consciousness and memory have been discovered to emerge from the same cellular process. Memory is allegedly stored in complex sequences of pyramidal neurons that scientists now believe are capable of quantum computing by mechanism of tau protein synthesis in microtubules from ribosomes in the pyramidal neurons (orchestrated objective reduction theory or Orch-OR, also known as the Penrose-Hammerhoff model). The specific make up of proteases, tau proteins, and Ubiquitin proteins forms a complex system by which signaling occurs to quantum level differences, in which electron transmission is specified to particle level accuracy. This is also now considered the main mechanism of consciousness, as such neurons also associate with other high gray matter areas of the prefrontal and cerebral cortexes. This makes the data stored infinitely complex due to the extensively minute degree of error and incredibly high intensity of specificity (Atmanspacher, H., 2004). Though the Penrose-Hammerhoff model is a relatively new projection that is still being tested for validity, it does provide a possible explanation for why non-memory based conscious-driven parts of the cortex activate during voluntary recall. It should also be noted that the previously mentioned synaptic model for memory does imply that the synaptic cleft, which is associated with memory, is also responsible for signal transduction via neurotransmitters, indicating that there is some physiological correlation between the process of signal transduction and memory encoding and storage.

An interesting advancement in our current understanding of the connection between memory and consciousness can also be found in stroke victims, specifically those that suffer from cerebral ischemia -brain damage caused by lack of blood flow to the brain- (Mayo Clinic, 2018) Patients who have such debilitating strokes have the potential to develop a condition known as Capgras Syndrome, a unique disorder affecting a person's ability to relate memory to emotional experience. This rare disorder preserves the pathways for visual recognition within the posterior occipital lobe and temporal lobe, along with emotional centers of the brain such as the amygdala, parts of the diencephalon, and the basal ganglia. However, the connection between the two in the parietal lobe (now believed to be the fusiform gyrus) is damaged, producing an inability to share the processed information between the limbic system and the occipital lobe. As a result, the ailing patients are incapable of recognizing loved ones or processing emotional memories properly. Despite being able to recognize people of little significance in their lives and being able to experience emotion, these patients report being surrounded by impostors replacing their loved ones, hence the colloquial name "imposter syndrome". (Ramachandran 158-174) The problem, however, presents a surprising revelation: emotional memories are separable from conscious activity. In patients with Capgras Syndrome, there is a remarkable ability to consciously forget an individual within a short span of time; however, patients do exhibit an unconscious emotional response that is caused by an emotional "memory" of qualities of the individual. In other words, when someone with Capgras Syndrome catches up with an old friend, they fail to recognize the friend cognitively, however they unconsciously feel the typical emotions they would around said friend, indicating that emotional memory might be processed separately from conscious memory, only to interweave with consciously streamlined data in the fusiform gyrus. (Ramachandran, 2009) Similarly, people with severe anterograde amnesia who are incapable of forming new crystallized memories are reportedly able to retain unconscious emotional memory storage, sometimes even exhibiting consistent behavior in spite of not understanding why or how they started the behavior (Sacks 23-43)

Post Traumatic Stress Disorder, another

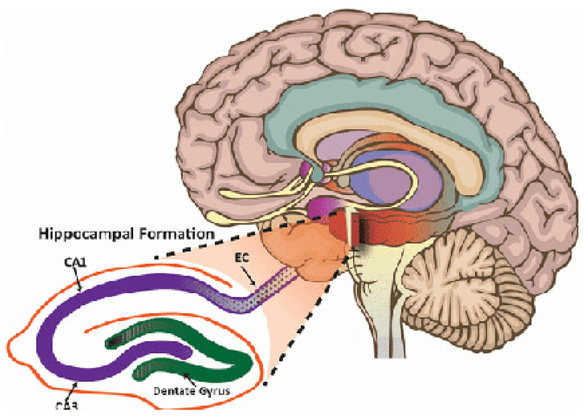

Figure 3.1: diagram of the hippocampus and position in the brain

debilitating neuropsychological condition, has revealed that the human brain is capable of altering its capacity of memory storage drastically. PTSD is a result of the overuse of corticotropin-releasing factor (CRF) in the hypothalamic-pituitary-adrenal axis system. In the brain, the thalamus circulates CRF to facilitate the release of adrenocorticotropic hormone (ACTH) from the pituitary gland, resulting in the adrenal gland releasing epinephrine. The epinephrine then operates in a negative feedback loop with norepinephrine by mechanism of auto-inhibition through presynaptic α2-adrenoceptors. This negative feedback loop prevents overproduction of cortisol and their consequent overstimulation of the pituitary gland, hypothalamus and hippocampus. (Bremner, J.D. et al., 1970)

Normally, this noradrenergic response is used to maximize utility (more blood flow, more actin filaments prepared by ionized channels, more ready action potentials, and generally faster reflexes in physiological structures) in survival circumstances, increasing activity in the sympathetic nervous system in preparation for dealing with external threats. However, people with PTSD create CRF in extreme excess due to both genetic and epigenetic influences. Some people are born with more hypothalamic corticotropin-releasing factor mRNA, meaning more glucocorticoid protein synthesis occurs (Bremner, J.D. et al, 1970). Others can have previously unexpressed genes triggered by the environmental factors causing the use of more telomeres which are responsible for cortisol production (Yang, B.Z. et al., 2013). This overabundance of CRF and cortisol has been shown to cause some impairment of intellectual ability in both crystallized and fluid intelligence. According to Dr. J. Douglas Bremner M.D et al., "Brain imaging studies have shown alterations in a circuit including medial prefrontal cortex (including anterior cingulate), hippocampus, and amygdala in PTSD… Stimulation of the noradrenergic system with yohimbine resulted in a failure of activation in dorsolateral prefrontal, temporal, parietal, and orbitofrontal cortex, and decreased function in the hippocampus."

Interestingly, these studies show that not only are memory and verbal ability reduced, but the very process of accessing memory is completely altered during triggered episodes. During post-traumatic episodes, it seems that hippocampus activity is lower than normal while most brain activity is centered in the limbic system; specifically, the amygdala, posterior cingulate, gyrus, and parahippocampal gyrus are active in these periods. The reduced brain activity in areas associated with conscious memory retrieval explain the seemingly random and uncontrollable onset of traumatic episodes and most likely occur due to overstimulation of the sympathetic nervous system. In other words, the mechanism of PTSD is most likely related to an overstimulated fight-or-flight system exercising dominance over the less developed cognitive system of the brain. The dominance occurs due to the limbic system being a far more responsive and developed brain structure, one that operates on hormonal messaging that is longer lasting than simple synaptic signaling. PTSD thus shows that memories are in fact not entirely voluntary and occur due to several diverging mechanisms rather than one (Bremner, J.D. et al., 1970).

To summarize, memory has been a relatively uninvestigated subject. However, with the advent of modern neuroscience and growing prevalence of memory disorders, it has become a scientific phenomenon worth investigating. Memory has been linked to many phenomena, branching emotion, consciousness, instinct, and genetics in a melting pot of complex neural functioning. Memory may well be the key to understanding the connection between mind and matter, consciousness, intelligence and human emotion.

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Writer's Bio

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Jason is a senior majoring in Agricultural & Biological Engineering, in nanoscale engineering concentration. He will attend graduate school in the Fall of 2019 for biomedical engineering. Jason is also involved in other RSO's such as Illini Biohackers, Illini Algae and the American Society of Agricultural and Biological Engineering. He is always willing to learn new topics and challenge himself.

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Luke is a freshman majoring in Molecular and Cellular Biology. Along with writing for the journal, he works as a research assistant in the Saif Lab of Cell Mechanics and Nanoscale Materials on campus. He is excited to see "Brain Matters" continue to grow throughout his time at UIUC.

Victoria Wu, Writer

Victoria is a sophomore completing and Independent Plan of Study in Neurotheology and a minor in Chemistry. She is the founder and president of Juvenile Detention Center Tutoring at UIUC. Outside of academics, she enjoys travelling, reading, long runs, and yoga. She is looking forward working and learning with the collaborators and readers of NJComm at UIUC.

Bailey Zinger, Writer

Bailey is a sophomore in bioengineering and has interests in neuroscience, computational biology, and imaging. Apart from writing for Brain Matters, Bailey is currently working as a research assistant in machine learning applications to problems in medicine. She is excited to help facilitate general knowledge and interest in neuroscience topics through Brain Matters.

Neil Doherty, Writer

*See Editor's Note

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About Undergraduate Neuroscience Journal and Undergraduate Neuroscience Society

The Undergraduate Neuroscience Society (UNS) is an academic student organization that strives to promote, educate, and hold events that help undergraduates gain a deeper understanding and appreciation for the field of neuroscience. Events such as Brain Awareness week and fundraisers for the Brain and Behavior Research Foundation are held. The Neuroscience Journal Committee, a subsidiary of UNS, has created a journal entitled “Brain Matters”. This journal promotes a neuroscience dialogue on campus by publishing student research about topics from neuroscience, psychology, and biology.