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by Cara Currier | Art by Sarah Beasley

Despite Major Depressive Disorder’s widespread prevalence, depression has a reputation within our culture that can cloud our understanding of the condition. A few theories regarding its neurological origin have emerged, however, continuous research has opened potential avenues for causes, treatments, and preventative measures to advance our understanding and acceptance of this mental illness.

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ISSUE NOTES

ON THE COVER
Art by Sarah Beasley

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Sincerely,

Molly Lindstrom
Editor-in-Chief

EDITOR’S NOTE

The Grey Matters mission is twofold: first, to develop students into effective science communicators, and second, to make neuroscience research interesting and accessible to the public. Science journalism accomplishes each part of this mission by helping students write and illustrate in an informative yet engaging way that teaches the community about complicated neuroscience topics. Grey Matters recently established an education model for students that uses a series of editing and draft writing processes, as well as a Graduate Student Review process, to produce well-written and accurate articles for publication. While this model satisfies the first part of our mission, Grey Matters also participates in other activities to promote science communication in the wider community.

This spring, Grey Matters made a significant effort to satisfy the second half of our mission. First, we held our annual An Evening With Neuroscience event to bring community members together in a space that allowed for an exciting conversation and discussion with a panel of Seattle neuroscientists. We filled Kane Hall with over 700 people who were interested in learning about the brain! The event was an incredible success; we thank everyone who was able to come and encourage those who could not attend to do so next year. Grey Matters also participated in the Seattle March for Science on Earth Day to show our support for science research funding and the importance of science communication. Finally, our organization presented our journals at Art Neureau, an event organized by the University of Washington Neuroscience graduate program that exhibits fascinating neuroscience-related art each year. Whether it be through direct involvement with the community, activism in support of science, or communicating neuroscience through art, Grey Matters works hard as an organization to expand scientific knowledge in the entire Seattle area and beyond.

Sincerely,

Molly Lindstrom
Editor-in-Chief
When neurons were first discovered, the prominent perspective on neuroanatomy was "once it's gone, it's gone for good." The belief that neurons were frail strands that could never be repaired once damaged was a misinformed but universally held truth. However, once neural stem cells (NSCs) were discovered, it was theoretically possible for damaged neurons to be replaced. Neural stem cells have the potential to repair a multitude of neurological issues, including extensive neurological damage. These cells are multipotent, meaning they can differentiate into several neural lineages, unlike other cells, which are forever destined to be a single cell type. Such properties of neural stem cells give them interesting possibilities for future applications. Many incurable neurological conditions are categorized as neurodegenerative diseases, incredibly powerful diseases that target neurons for destruction. Thus, NSCs offer the potential to replace some of the structures that these diseases have destroyed.

NSCs are guided by the brain through a multitude of chemical and physical changes that determine the specialization of NSCs. When NSCs specialize, they will become exactly what the brain, and the body, requires for overall health. There are two types of stem cells: embryonic and adult stem cells. The main difference between the two is their potential for differentiation. Embryonic stem cells are pluripotent, meaning they can become any cell type in the body, while adult stem cells are multipotent, meaning they can only differentiate into the cell types of the tissue in which they reside. In the human brain, there are three primary lineages NSCs can follow: mature neurons, astrocytes, and oligodendrocytes [1]. These lineages ultimately form multiple cell types that help sustain a healthy mammalian brain, and all three lineages are necessary for proper cognitive functioning.

A study by Palmer et al. demonstrated how NSCs could be taken from the hippocampus and grown in vitro to form the three types of possible lineages [2]. Whether an NSC forms a neuron or an astrocyte depends on the kinds of growth factors the NSC receives, or in other words, the environment in which it grows. The microenvironment of the brain plays a crucial role in determining the cell type of an NSC. Palmer et al. were able to identify specific growth factors that lead to differentiation of NSCs, which introduces the possibility of lab-grown neurons [2]. Once researchers understand which pathways certain growth factors take, they can manipulate them after injury to stimulate neural regeneration. For example, if one growth factor or set of growth factors stimulates the development of a particular neuron type, physicians could inject those growth factors into a patient that, through injury or disease, is lacking that specific neuron type. With the combination of these introduced growth factors and transplanted NSCs, the body could regrow the missing or damaged neurons. This procedure of injection and transplantation has already been applied to neurodegenerative diseases such as Parkinson's disease, Huntington's disease, and Alzheimer's disease in hopes of managing or curing them.

“Everything may die, nothing may be regenerated”
Santiago Ramón y Cajal
Kim et al. conducted research on PD using embryonic stem cells. They noted that Parkinson's disease (PD), a neurodegenerative disease that leads to the destruction of motor neurons, is characterized by a loss of dopamine neurons responsible for fine movement. People with PD display a multitude of symptoms, ranging from mild tremors to the inability to walk due to muscular stiffness.

However, contrary to other studies, Redmond observed certain abnormalities that led to new theories on the mechanisms through which NSCs enact functional change [4]. While some human neural stem cells differentiated into dopamine neurons, there were a large number of neurons that differentiated into astrocytes that synthesized a growth factor called GDNF. GDNF promoted development of dopamine neurons from undifferentiated NSCs as well as aided the efficient production and release of dopamine from all dopaminergic-neurons. Redmond theorized that NSCs not only differentiate into the necessary cells, but also into cells that change the microenvironment of an injured area in the brain so that efficient neurogenesis and recovery might occur. This new theory suggests that NSCs do not just produce three lineages of cells, but produce a multitude of compounds and cell types that are important for neurogenesis in a multifaceted way [4].

**PARKINSON’S DISEASE**

A first step in applying NSCs to medicine would be to utilize their capabilities to manage diseases that are directly or indirectly associated with neuronal death. One of these diseases is Parkinson’s disease (PD), a neurodegenerative disease that leads to the destruction of dopamine-synthesizing (dopaminergic) neurons responsible for fine movement. People with PD display symptoms ranging from mild tremors to the inability to walk due to muscular stiffness.

Kim et al. conducted research on PD using embryonic stem cells that differentiated into dopaminergic neurons [3]. These neurons, when transplanted into Parkinson’s model mice, quickly began repairing the lesion responsible for the Parkinson-like symptoms. After nine weeks, mice that received the embryonic-based dopaminergic neurons had a significant increase in movement ability on the lesion side of their bodies when compared to the non-lesion side acting as a control [3]. Similarly, a study by Redmond et al. showed how undifferentiated human NSCs transplanted in primates with a chemical Parkinson’s model mice, quickly began repairing the lesion [3]. Similarly, a study by Redmond et al. showed how undifferentiated human NSCs transplanted in primates with a chemical Parkinson’s model mice, quickly began repairing the lesion [3]. Similarly, a study by Redmond et al. showed how undifferentiated human NSCs transplanted in primates with a chemical Parkinson’s model mice, quickly began repairing the lesion.

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**ALZHEIMER’S DISEASE**

Alzheimer’s disease (AD) is a neurodegenerative disease that eventually leads to neural death and brain shrinkage. This intense decrease in neurons results in memory loss, confusion, and delusions. AD destroys multiple types of neurons throughout the brain, making it a prime candidate for NSC testing. Blurton-Jones et al. conducted research on genetically modified rats, bred to model human AD, by transplanting undifferentiated NSCs into both hippocampi of the rodents [5]. The use of undifferentiated NSCs, as opposed to differentiated NSCs, demonstrates an undifferentiated NSC’s ability to correctly differentiate into the cell type most necessary for homeostasis in vivo. After four weeks, rats were given hippocampal-dependent behavior tasks such as the Morris Water Maze and a context-dependent novel object recognition test. Rats that were given NSCs experienced noticeable improvements on these tasks when compared to untreated controls, suggesting that transplanted NSCs could potentially manage symptoms of AD, since both studies found a neurotrophic growth factor (BDNF) that heavily influenced the outcomes of NSC transplantations [6]. BDNF, or brain-derived neurotrophic factor, acts as a regulator for undifferentiated NSCs. Neurotrophins are generally used by the brain as tools for altering synaptic connectivity. In fact, BDNF has been shown to be a critical component in the creation of memories in the hippocampus [6]. Blurton-Jones demonstrated how the presence of BDNF led to increased cognitive recovery when compared to NSCs that were BDNF-deficient [5]. The demonstrated necessity for neurotrophins such as BDNF is an indicator of their potential application towards neural regeneration through changes in the microenvironment of the brain. These findings give merit to Redmond’s theory on how the microenvironment plays a role in the behavior of stem cells. The different neurotrophic factors secreted in Blurton-Jones’s study and Redmond’s study, BDNF and GDNF respectively, indicates how stem cells are capable of changing the microenvironment of the brain to facilitate the production of the most necessary neuronal lineage of the particular brain area. Not only does this evidence demonstrate their capabilities, but it also exhibits the observed importance of modifying the microenvironment to better suit the stem cells’ needs.

**HUNTINGTON’S DISEASE**

As with the other diseases presented, Huntington’s disease is a neurodegenerative disease characterized by a loss of nerve cells in the brain that produces symptoms such as loss of coordination, speech difficulties, and changes in behavior. In addition, there is evidence suggesting that Huntington’s disease is linked to a specific genetic mutation on chromosome 4, known as the Huntingtin gene. The protein encoded by this gene is involved in the function of the brain, particularly those involved in memory.

The Morris Water Maze is a behavioral test designed to study spatial learning and memory in rodents. The rodent’s performance in this task can be used to assess the function or dysfunction of certain brain regions, particularly those involved in memory.
Neural Stem Cells: Completing the Puzzle

Neurodegenerative diseases have held humanity under their thumbs for too long. The profoundly negative consequences of these diseases have persisted due to a lack of effective cures and symptom management. However, recent research into neural stem cells offers hope to those who have had very little. Successful studies have demonstrated the therapeutic benefits of neural stem cells on neurodegenerative diseases of all types. People with Alzheimer’s, Parkinson’s, and Huntington’s disease could see significant improvement in quality of life through the use of neural stem cells. It is interesting to note that the neurodegenerative diseases in this list all affect different areas of the brain and thus have different functional effects. The beauty of stem cells lies in the possibility for regrowth in multiple brain regions to treat a wide range of diseases.

NSCs are the future of neuroscience and for good reason—the promising results of research could mean that diseases causing uncontrollable tremors, memory loss, and delirium can now be managed. Although this field is relatively new and requires years of additional research, there have already been incredible discoveries that will prove fruitful to the greater understanding of the brain. Perhaps years from now scientists will look back at our current treatments and question their efficacy after the revolutionary progress of NSCs. In other words, the great Santiago Ramón y Cajal was wrong—the future of neuroscience lies not in death and decay, but in growth and regeneration.

CONCLUSION

Neurodegenerative diseases have held humanity under their thumbs for too long. The profoundly negative consequences of these diseases have persisted due to a lack of effective cures and symptom management. However, recent research into neural stem cells offers hope to those who have had very little. Successful studies have demonstrated the therapeutic benefits of neural stem cells on neurodegenerative diseases of all types. People with Alzheimer’s, Parkinson’s, and Huntington’s disease could see significant improvement in quality of life through the use of neural stem cells. It is interesting to note that the neurodegenerative diseases in this list all affect different areas of the brain and thus have different functional effects. The beauty of stem cells lies in the possibility for regrowth in multiple brain regions to treat a wide range of diseases.

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DISTORTING PERCEPTION

by Enoch Chung
art by Sarah Beasley

The ability to see is often attributed to the eyes, but this is only the beginning of visual processing. It is estimated that one-third to one-half of the human brain is dedicated to processing aspects of our visual experience [1]. The eye’s primary function is to receive light and convert it into electrical signals that the optic nerve can then transmit to the brain. Neurons carry the signals from the retina, a layer of tissue in the eye that contains light-activated receptors, to the primary visual cortex (V1), located towards the back of the brain in the region known as the occipital lobe. Each layer of tissue in the brain then helps process the information to build recognition of visual stimuli.

This information processing occurs in a modular way, meaning that the brain has distinct regions, or modules, for processing distinct types of information. In the primary visual system, the visual world is interpreted as a set of lines. That information is then distributed to other areas of the brain, which use the lines to further construct the perception of shapes and then objects. For example, facial recognition is a multi-layered effort to integrate lines, circles, and other shapes to ultimately produce one coherent picture of a face. Due to this modularity, a breakdown or disconnection of pathways can lead to a variety of complications in visual processing. The brain provides the visual interpretation of our environment, and when something in this hierarchical and complex system is disrupted, the interpretation is skewed.

BLINDSIGHT

When a disruption occurs in the primary visual cortex, it can result in a condition called blindsight, or unconscious vision. This condition is characterized by an inability to visually perceive objects but a retained ability of the brain to identify visual characteristics such as position, motion, and size. For example, a person with blindsight can catch a ball thrown at them, despite not being able to see it. They pre-form their hand to the correct size and direct it to intercept the path of motion of the ball. There is a vast amount of visual information from the eyes, and only part of it contributes to the conscious sight we experience. Some of the information coming from the eyes contributes to unconscious vision, which gives us information about stimuli that we do not consciously perceive [2]. In blindsight, some aspects of unconscious vision are unaffected because the information from the retina goes through an alternate pathway relative to conscious vision. This pathway includes the superior colliculus, which is responsible for directing behavioral responses based on visual stimuli, and another area of the brain known as the extrastriate.
cortex, which can perform higher order processing such as motion. This alternate pathway of information allows for limited visual abilities such as detection of color, orientation, and motion of stimuli as part of the unconscious visual system. Research has shown that patients can consistently recognize these stimuli with significant accuracy, but the accuracy decreases with dimmer lighting conditions and more complex stimuli [3]. Current research is investigating the limit of unconscious vision in patients with blindsight. Ultimately, blindsight is the ability to perceive motion and act without conscious perception of visual objects.

**VISUAL NEGLECT**

While blindsight is the ability to interact with objects without seeing them, neglect is the ability to perceive visual objects without being able to manipulate or act upon them. A disruption in the firing patterns of certain neural networks, such as beta and theta networks in the fronto-parietal circuits, can result in this condition [4]. Patients with neglect may have trouble describing or interacting with stimuli in the visual field opposite to the side of the brain where the disruption or damage occurred, despite having no trouble visually perceiving the stimuli [5]. For instance, patients with damage to the right fronto-parietal circuits may struggle with everyday tasks such as eating because they have difficulty seeing but have difficulty linking what they see to something they know [8]. Patients can copy down shapes and objects as well as identify individual features of a visual stimulus, but are unable to identify the object that is presented to them. An example would be a patient who looks at a watch and recognizes all of its parts (the face, the hands, etc.) separately, but not as a cohesive unit they can name. Recent research has suggested that associative agnosia may be best categorized as a spectrum deficit, which means the severity can vary. Because of this, it is difficult to objectively assess each individual case [8]. What we know thus far is that the brain’s ability to process the information coming in remains intact, but the ability to link that input to semantic memories does not [9].

A subtype of associative agnosia, known as prosopagnosia, is a condition in which patients are unable to identify faces. Prosopagnosia results from a disruption between the part of the brain that can interpret shapes and the part of the brain that identifies faces. The disruption can either result from damage to the brain or can be congenital, wherein a person develops the prosopagnosia as he or she matures due to certain genetic factors. This disconnection has profound effects – patients can have difficulty identifying the faces of friends and family they have known for many years and may even struggle to recognize their own faces [10]. The anatomical study of prosopagnosia through damage is used to explore mechanisms and areas of the brain used to process faces. Early studies investigating prosopagnosia actually lead to the discovery of the importance of the right occipito-temporal cortex in facial recognition [11]. There is also significant research at present looking into congenital prosopagnosia, as the biological basis for the developmental manifestation of prosopagnosia is still under debate. At the moment, it is not clear what exactly occurs, but it is known that the mechanisms needed for facial recognition do not develop properly. Research suggests that the component of face memory is the most heavily affected [10].

**CAPGRAS SYNDROME**

Serious problems can arise when patients are able to identify faces but unable to emotionally respond to them. Such is the case of Capgras syndrome, a condition in which people have no problem recognizing faces but have trouble linking the face to the emotions that they typically evoke. Normally, in our everyday lives we display measurable emotional responses via the autonomic system, such as changes in heart rate and skin conductance, when we encounter people we know. People with Capgras syndrome have measurably decreased autonomic responses when looking at familiar faces [12]. A patient may see their mother and think that she is an imposter because, although they may recognize her, they do not feel the emotions associated with seeing their mom. Interestingly, some patients have no difficulties recognizing loved ones when utilizing their auditory system only. Loved ones can walk out of the room and call the patient, and the patient has little difficulty recognizing them solely by voice. A study published in early 2017 by Darby et al. investigated the role of single brain lesions in causing Capgras syndrome [13]. The study observed lesion positions of 17 different patients, allowing researchers to identify commonalities between the brain damage that caused the condition in different patients. Interestingly, every patient analyzed showed that the lesions all were connected to the left retrosternal cortex, which is the area in the brain that is activated by identifying familiar things [13]. The neural link between emotion and vision is crucial in our everyday social interactions, and more is to be discovered about it.

A significant portion of the brain is dedicated to visual processing. Information from the visual pathway builds up coherent pictures in our minds that can be distorted in a variety of ways if problems arise throughout our brains. Case studies on the effects of damage and developmental complications in the regions of the brain mentioned in this article have greatly broadened our understanding of the function of the visual system and have also shed light on other neural networks that work similarly in the brain. Because the visual system is so integral to our ability to connect with the world around us, the brain has devoted a significant proportion of its space to visual connections, and the concepts learned through researching vision can easily be applied to other systems that are more nuanced and difficult to study. Recent research on visual malfunctions make great case studies for how scientists can use small-scale experiments to make large strides in the understanding of a given field of science.

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The spinal cord is like a highway, sending and receiving information between the brain and the whole body. Our abilities to sense, move, and react are all transmitted as information along this highway. This neural connection is what allows for the travel of signals from the central nervous system, the main highway, to the peripheral nervous system, or the many exits that branch out to different regions of the body. The signals enable control of bodily functions, from big movements like taking a stride, to the fine motor control needed to play the piano skillfully. Impactful traffic jams on the highway can occur if a disruption, like a dilapidated road, stops the traffic from moving. As is with injury to the spinal cord, a disruption to the flow of neural traffic results in varying degrees of damage.

Spinal cord injuries (SCIs) occur in a variety of ways. Significant trauma, whether it is an athletic mishap, falling from significant heights, physical violence, gun violence, or motor vehicle accidents can cause SCI [1]. Most injuries to the spinal cord in earlier eras have been the result of trauma, war, and strenuous labor. The consequences of injury include reduced sensation, paralysis, and a diminished autonomy to carry out tasks [1]. Mapping out the multiple routes and avenues that pave the spinal cord and its extension throughout the body, along with the location of the injury on the spinal cord, is necessary to understand the effects of SCI on the body.

Starting from the bottom portion of the vertebrae is the sacral region. Injuries in this region generally result in some loss of function in the hips and legs, but the ability to walk is more than likely maintained [2]. Control of bladder and bowel functions may be disrupted due to damage in this region, causing incontinence. However, incontinence can be treated using equipment such as catheters to help alleviate urinary stress [1].

From the neck down, there are four sections of the spinal cord highway: the cervical, the thoracic, the lumbar, and the sacral. The vertebrae, the bones surrounding the spinal cord, split the spinal cord into smaller sections, and each region is associated with different motor and sensory functions. Hippocrates, the Grecian Father of Medicine, noted in his literature Anatomy of the Spine that there is an articulation of nerves and vessels that make up the spinal cord, providing information as to how our wiring reflects the functionality of the human body and how an injury could have a negative impact [1]. The location of the SCI determines the severity of impact on a person’s motor function, as well as which body parts are affected. The higher the injury is on the spinal column, the greater the disruption to neural activity, which in turn affects the function of the entire body.
Next up are the lumbar vertebrae, which serve as the trunk of the spinal cord. Injuries to the lumbar nerves generally result in reduced function in the hips and legs, as well as in bowel movement and bladder control. If leg muscle control and strength do not support the body in standing or walking, a wheelchair may be necessary for mobility.

Further up are the thoracic vertebrae, which trail up most of the back. The nerves from this region are associated with the upper chest, mid-back, the hands, and the abdominal muscles. Injuries to the thoracic spine will disrupt control of movement in those areas. Since disruption will also affect neural connectivity below, control of legs, bowels, and the bladder are also significantly reduced or lost. Paralysis from the waist down due to a thoracic SCI is what causes paraplegia. People with damage to the thoracic column still retain upper forelimb function, or most control of the arms, and would most likely use a manual wheelchair to navigate independently. Other accommodations that are available include modified cars, standing frames, crutches, and braces.

The final region that stands at the top of the human spine are the cervical vertebrae, which support the neck. Injury at the cervical level causes the most severe damage, disabling movement from the neck down. Internal functions such as breathing, speaking, and bladder control may be reduced as well. Paralysis of the legs, bowels, and the bladder are also significantly reduced or lost. Paralysis from the waist down due to a thoracic SCI is what causes paraplegia. People with damage to the thoracic column still retain upper forelimb function, or most control of the arms, and would most likely use a manual wheelchair to navigate independently. Other accommodations that are available include modified cars, standing frames, crutches, and braces.

By the mid-20th century, medical advancements in sterilization, surgery, and technology forwarded innovations for treatment in the field of spinal cord medicine. The breakthroughs made in trauma care and treatments came with the promise of promoting survivability and improving quality of life.

CURRENT TREATMENTS

Historically, the effects of SCI have proved to be incredibly difficult to reverse. Treatments were limited and failed to help people with SCI survive its debilitating effects. Egyptians used bronze catheters for urinary drainage, which was the earliest known form of treatment. Various forms of eastern medicine have been documented to alleviate spinal inflammation through use of splints and bedrest [5]. Catheters and wheelchairs have endured as devices that help those with SCI maintain an accessible and manageable quality of life. However, numerous medical and technological advancements helped make current treatments accessible for people with SCI today. Surgical advancements in the early 20th century have made the preventative means against spinal cord injuries possible. This includes spinal cord fusion surgeries, which are performed to brace the spinal cord using compression rods to treat scoliosis, spinal fractures, and dislocations. However, surgeries alone had little effect in promoting function in SCI patients [1].

More recently, functional electric stimulation (FES) has been explored and used in clinical studies to promote muscle movements. FES involves electric stimulation of muscular contractions via superficial placement of electrodes. Electrodes are taped onto the skin, at the site of interest (like an arm or leg) to help stimulate the muscles for supportive movement and exercise [3]. Stimulation at the lumbar cord can assist in generating responses and step-like movements at the legs [4]. FES has been used in therapies for the lower limbs to facilitate standing, walking, or cycling, whereas upper limb systems can enable functional grasping as well as limited, close-range arm movements [3].

SPINAL CORD CROSS-SECTION

Physical therapy, equipment, community, and self-care continue to be large components to the management of daily life for people with SCI. New discoveries and innovations in spinal cord rehabilitation bring us closer to uncovering solutions that could possibly remedy injury. Not only do treatments and continuous study help people with SCI manage life, but they also open a new road, or in the least a detour around what was damaged, to restore independence and improve quality of life.

DEVELOPING A DETOUR

Current research has focused on methods of stimulating the spinal cord to promote the restoration of limb function lost to injury. Just as was done with FES to stimulate muscle movements, techniques involve looking at the effects of electrostimulation and how it promotes the repair of neurons’ connectivity to each other [5].

Neuro-prosthetics can be implemented to promote neural activity via electrostimulation. This kind of electrostimulation involves application of subcutaneous (under the skin) or transcutaneous (through the skin) electrodes to an area of interest to receive electric impulses [3]. Forms of neuro-prosthetics include brain-machine interface (BMI) and neuro-modulatory stimulation [2]. When there’s a disruption in the road, traffic congests and mobility is halted. But if a detour is created around the road block, traffic flows again. These two forms of neuro-prosthetics can act to replace a blocked highway and allow for new traffic to flow and promote movement of the muscles.
A BMI is a device that records and decodes signals from the brain, which enables control of assistive devices, like a robotic arm. Signals from the brain towards the desired output veers away from the site of injury, allowing for neural communication to flow towards the effector muscle [2]. One experiment that focused on the capability of BMIs was conducted on monkeys [5]. A neural block was injected into a monkey to temporarily paralyze its wrist muscles. The monkey played a computer video game that required it to grasp and move a mouse to place the arrow in a box on the screen. The application of a brain-controlled spinal interface made it possible to send signals from brain cell activity directly to motor neurons innervating the muscle cells. The regions of brain cell activity were tracked based on the monkey’s wrist movement [5]. This was done by guiding the traffic of signals from the electrodes at the brain to the electrodes at the effector muscles. Data showed that movement was still possible with the BMI helping the monkey successfully use its wrist to complete the computer task [5]. Using a BMI is slower than taking the natural spinal cord highway, but nonetheless, the use of a BMI detour provides an effective measure of relieving spinal traffic congestion.

The neuro-modulatory system is another neuro-prosthetic which relies more on the modification of the spinal cord highway itself to promote neural connectivity [2]. Two major forms of neuro-modulatory stimulation include epidural and intraspinal microstimulation. Both forms assist in promoting functional limb movements through the restructuring of spinal circuitry. Epidural stimulation is where electrodes are placed on a vertebra. Intraspinal stimulation is more invasive than epidural stimulation, requiring electrode implantation to the spinal cord grey matter [2,3]. Studies performed on rats investigate axonal regrowth and regeneration triggered by electric stimulation during rehabilitation following injury [3,6]. In one study, the injection of enzymes like Chondroitinase demonstrated possible promotion of neural plasticity and improved muscle coordination following injury [7]. Additionally, Chondroitinase may possibly play a role in modifying glial cells, which help neurons form synaptic connections with surrounding neurons and build more intersections to allow for multi-route travel [8]. It is with high hopes that these conducted treatments may improve neural plasticity, or the ability for neurons to regenerate their own tissue and to modify their synaptic strengths, following trauma [3].

A combination of BMI and neuro-modulatory stimulation at the spinal cord provides a more natural promotion of motor neurons to replace the damaged ones [9]. But because injury at different regions along the spinal cord exhibit varying degrees of severity, the same treatment will almost always have differing levels of efficiency between individual injuries. Clinical studies are considering spinal stimulation using transcutaneous electrodes for human patients to reduce harm and cost of treatment [4]. As more research moves towards clinical trial, more study is necessary to determine what efficiency of movement can be maintained using neuro-prosthetics [10].

Current research is driving forward to investigate strategies in improving quality of life for paralyzed patients with SCI. Neuro-prosthetic techniques show the potential to form detours that serve as newly constructed routes and paths in the spinal cord for stimulating muscle movement and control. Hopefully, continued research into SCI will help produce a remedy for the effects of injury and restore function where it has been lost.

CONCLUSION

Although spinal cord injuries are far from being completely curable, developing treatments have paved new paths - mapping out the possibilities of restoring bodily functions for many people with spinal cord injuries. Fine motor control, large movements, and tactile senses all have the potential to be restored. All the while, education on living with SCI, including managing equipment, finding clinical treatments, community involvement, and the practice of self-care, continues to be necessary for people with SCI to help maintain quality of life. Study of the spinal cord has come a long way in the last century. Researchers continue to find new ways to repair and modify damaged tissue after injury and allow for communication between the brain and the body through a combination of neuro-prosthetics, enzymatic interventions, and electric stimulation promoting neural connectivity [1,6,8,4]. It will only be a matter of time until the road, once damaged by trauma and disease, is repaired and neural traffic on the highway can resume moving on the right track.

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INTRODUCTION
As we go through our daily routines, whether they be in a bustling coffee shop packed with sleep-deprived students or in the high-ceilinged library reading room, we are surrounded by the rustling pages of books, pings emitted by text messages, and emails full of words that we immediately consume. As we submerge ourselves in this plethora of words, we are perhaps blissfully unaware of the various connections and signals our brain must process. Why is it that we find the word eloquent quite different than vivid? What makes us cry when we read about the tragic end of one of our favorite characters? Why is it that we find the word buttery quite different than vivid? Must we process words and associating them with emotions in a much more complex and intertwined system than previously thought? The cortex as a dynamic unit

In order to understand language processing, it is important to have a firm grasp on the function of the frontal cortex. The cortex is the outer layer of the cerebrum composed primarily of grey matter (neuron cell bodies) and is divided into two parts by the longitudinal fissure that separates the left and right hemispheres. It is responsible for memory, perception, attention, thoughts, language, and consciousness and is considered to play a crucial role in the way our sensory and motor neurons create associations between words. Donald Hebb, a Canadian psychologist who pioneered the idea of neural webs, defines the cortex as a network of neurons processing stimuli from various input and output sources [1]. Recent research has revealed the cortex is not a static area of the brain that operates independently, but rather an “information mixing device” in which one neuron can carry information from many different sources [1]. This is directly associated with what Hebb calls “correlation learning,” a phenomenon where two or more systems of cells that are active at the same moment consistently become “associated” with one another so that activity stimulating one cell will stimulate the other [1]. Some words associated with those senses cause cells to detect stimuli in those areas, which is known as multisensory integration. For example, when reading buttery and voice, cells associated with food will be stimulated at the same time as those for recognizing sounds and the word voice. If this pattern is continued over time, the two words will automatically be associated with one another in the brain—known as neural efficiency [1]. As Hebb stated, “neurons that fire together wire together” [2]. In this way, our cortex acts as an information-mixing device that creates connections between different neurons and between different words and stimuli.

WORD WEB AND FUNCTIONAL WEBS
According to Hebb’s view, the cortex is composed of multiple functional webs, or networks of neurons from various sources, that carry associated information and reassembles it to create new information. For example, the smell of coffee, the taste of coffee, and the texture of the foam on top of the coffee is combined to create our perception of coffee [1]. This idea implies that if one part of the web is impaired, the corresponding part of the neuronal web will also be dysfunctional. An experiment to test this hypothesis was conducted on Macaque monkeys, where either the prefrontal cortex or the inferior temporal lobe was cooled while the monkeys were presented with different colored shapes. While this study focused on colors and shapes, it still demonstrates the functioning of word webs. Cooling one part of the brain by applying very cold temperatures over a short period of time to decrease neuronal firing activity, known as Targeted Temperature Management (TTM), caused the other part of the brain to also lose complete activity, implying that the two were directly associated with each other through a neuronal web. The monkeys who did not have their neuronal networks cooled displayed neuronal firing activity in the prefrontal cortex and in the inferior temporal lobe simultaneously, only firing when the exact combination of associated color and shape were shown [1]. A similar experiment, also done on Macaque monkeys, demonstrated that a sector of mirror neurons F5 in monkeys is analogous to the area in humans in the inferior frontal cortex, which is responsible for action imagery and language understanding [3-5]. Mirror neurons are neurons that fire both when an animal acts and observes the same action performed by another individual [3-5]. Similarly, patients that had diseases affecting the motor nervous system, such as motor neuron disease, had greater difficulty processing action-related verbs [6].
These studies support the hypothesis that more than one area of the brain processes and associates words, and that impairing or stimulating one part of the brain affects the other. Word webs would primarily consist of connections between neurons storing word formation data and neurons involved in processing activities and perceptions.

A more recent experiment also supported the theory of word webs and associated learning. Dr. Yuri Shyrov and his research team from the University of Cambridge hypothesized that words involving movements of different body parts should incorporate neurons in different parts of the sensori-motor cortices [2]. In order to test their hypothesis, they addressed brain activity related to semantic processing using a technique called mismatch negativity or MMN. This method allows the researchers to investigate long-term memory traces for words involving movements of different body parts—these words shown to demonstrate and reflect memory traces for elements in the brain. The MMN has recently been shown to provide further evidence that the cortex is much more akin to a web rather than a rigid information processor [7].

Research on how different words are perceived and processed in various parts of the brain categorized words into two groups: content and function words [7]. Content words are typically nouns, adjectives, or verbs. They are frequently associated with a physical object, such as table or cat. Upon encountering such a word in our daily lives, an episodic memory event may occur, where a particular memory from our past is associated with that word (such as connecting the word school with the physical activity of recess from first grade memories). Functional words, however, have linking purposes in words such as although or because. Through fMRI experiments that measured these episodic memory events in individuals, researchers noticed distinct lateral word processing between content and functional words. Sometimes, multiple parts of the brain would simultaneously light up when exposed to a content word or functional word, providing further evidence that the cortex is much more akin to a web rather than a rigid information processor [7].

WORDS AND EMOTIONS

So how are we capable of taking all these words and experiencing different emotions and imagining different scenarios? There are two sensations that distinguish our perception of words: valence and arousal. Valence is the amount of pleasure one gets from a word, whereas arousal is a measure of how willingly one would want to approach or escape from the word, similar to the "fight-or-flight response" we might experience when we encounter a word [8-18]. There are two prevailing theories on how our brains are capable of emotionally processing words. Arousal theory states that the right hemisphere is more adept at processing words than the left, primarily supported by studies conducted on individuals with one hemisphere of their brain impaired, as presented with the macaque monkey study. Valence theory states that both hemispheres are active during emotional processing but to different extents depending on the valence of a certain word. There is, however, a third emerging theory called the circumspect theory, which combines the two aforementioned theories into one unified theory that analyzes both the amount of valence a word creates and the amount of arousal. Recent research by Dr. Moscovitch, a professor of psychology at the University of Toronto, claims that memory of a word is processed in the right portion of the brain whereas perception of a word is composed in the left, and together they create a complete picture of a word [8-18]. Continued studies show further evidence that emotional processing of words is not restricted to one or the other hemisphere; rather, both process it, which is more akin to a web-like model.

NEW VIEWS

Other recent research has introduced a new concept of word processing that incorporates the previous idea of word webs, but presents the sensory system as an input system that filters emotion and memory associated with a word and in effect dictates the actions of the motor system [19, 20]. In other words, the posterior portion of the cortex serves as a sensory information filter, and the frontal motor primarily functions under the control of the cognitive, posterior cortex system. This idea emerged after a neuroimaging experiment that studied specific motor activations by directing subjects to distinguish between speech sounds, word meanings, and sentence structures. Individuals with lesions in the inferior frontal regions of the brain, which are responsible for motor circuits involved in the comprehension of grammar and sentence structure, demonstrated greater difficulty than those who did not have lesions [19, 20]. This observation also supports previous hypotheses about word webs and neuronal associations between different parts of the brain [1].

CONCLUSION

Everyday language processing proves to be much more complicated than previously conceived. While we take in the multitude of verbal messages we encounter every day in the form of fliers, conversations, lectures, and books, our brain is busy making neural connections between different parts of the brain so if we ever encounter the word again, we have a specific memory or association coupled with it. For instance, the word geology might immediately recall the memory of learning geology in a classroom for one person or actually doing geology might immediately recall the memory of learning geology in a classroom for one person or actually doing geology might immediately recall the memory of learning geology in a classroom for one person or actually doing geology might immediately recall the memory of learning geology in a classroom for one person or actually doing geology might immediately recall the memory of learning geology in a classroom for one person or actually doing geology.
Every day, millions of students experience the feeling of almost indescribable emptiness caused by major depression, also known as major depressive disorder or simply depression. Major depression, one of the most prevalent mental health disorders in the world, is characterized by a loss of pleasure and interest in life. In 2015, approximately 7% of the United States’ adult population experienced at least one major depressive episode within the year [1]. Among college-aged students, major depression episodes had an even higher prevalence, affecting one in every ten individuals [1].

For a disorder that affects so many people, there is still much left to be understood, as the causes of major depressive disorder are incredibly complex. Accumulated research has revealed that neuronal growth, stress, hormones, and synaptic neurotransmitters—chemicals involved in neuronal communication—all play a role in the manifestation of major depression [2]. Although the growing body of evidence is now creating a much more intricate image of the disorder’s causes, clinical research and treatment tends to emphasize the role of neurotransmitters. The relationship between synaptic neurotransmitter levels and mood was first described by the monoamine hypothesis in the late 1960s [3]. This hypothesis states that a deficiency in monoamine-type neurotransmitters is the biophysiological basis for depression. After observing the unexpected effects of certain medications, psychiatrists hypothesized that depression results from chemical imbalances within the brain. However, new research is revealing just how limited the monoamine hypothesis is. A condition once thought to be caused by an imbalance in chemicals is now proving to be much more complex [2, 3].

THE HISTORY AND APPLICATIONS OF THE MONOAMINE HYPOTHESIS

Over the course of history, cultures have attributed the causes of major depression to various sources, ranging from unbalanced humors—the four bodily fluids thought to determine one’s health in ancient Greece—to evil spirits. Yet it was a chance medical observation in the early 1950s and the application of the scientific method to this great mystery that brought about one of the most well-known and applied perspectives of the modern era: the monoamine hypothesis [3].

The formation of the monoamine hypothesis began in 1955, when doctors at the Sea View Hospital on Staten Island decided to administer a new drug to treat patients with tuberculosis. The drug, called iproniazid, was a known inhibitor of enzymes that are responsible for the breakdown of a class of neurotransmitters known as the monoamines. The monoamine neurotransmitter class includes serotonin, norepinephrine, and dopamine [3]. Soon, the staff noticed a significant improvement in the mood of tuberculosis patients who had been withdrawn and depressed for months. This chance discovery of iproniazid’s effects on mood prompted more research that eventually led to the formal creation of the monoamine hypothesis. This also marked the formulation of the first modern biopsychological perspective on depression [3].

The monoamine hypothesis predicts that a deficiency of monoamine neurotransmitters leads to dysregulations in the mind’s control of mood [4]. This hypothesis revolutionized how healthcare professionals viewed and treated major depression. If major depression was caused by a deficiency in monoamines, then clinicians could treat the condition by simply prescribing a drug that increases these neurotransmitters. Although dopamine and norepinephrine play important roles in the regulation of mood, most of the early research that came out of this hypothesis focused on increasing serotonin [4].

While many people are unfamiliar with the formal name of the monoamine hypothesis, it has inspired the creation of a publicly recognized class of drugs – the Selective-Serotonin Reuptake Inhibitors (SSRIs). Although iproniazid was taken off the market for causing liver damage, its ability to increase the synaptic
concentrations of serotonin inspired further research. Soon, pharmaceutical companies were in hot pursuit of safer, alternative ways to increase serotonin levels [5]. Twenty years later, this research resulted in a second wave of antidepressants entering the market, most of which were of the SSRI family. SSRIs, like Prozac and Zoloft, increase serotonin levels by blocking presynaptic transporters, proteins that promote the recycling of serotonin back into the presynaptic neuron. By blocking these presynaptic transporters, SSRIs increase serotonin levels by increasing the amount of time serotonin has to accumulate within the synapse [4].

Over time, more drug families similar to SSRIs have developed that increase other monoamine neurotransmitters, like norepinephrine and dopamine [3, 4]. For example, several studies have shown the effectiveness of antidepressants that target norepinephrine. In the late 1990s, Dr. Pedro Delgado conducted a series of studies that explored the effects of monoamine depletion and various types of antidepressants on depression [5]. In order to study the effects of serotonin deficiencies, Dr. Delgado and his team decided to alter the diets of their participants so that the experimental group would not consume tryptophan, a necessary ingredient for the body’s synthesis of serotonin that is only acquired through the diet. If we are not able to obtain tryptophan from food, then our serotonin levels will decrease. For patients whose depressive symptoms had responded to SSRIs, more relapsed into depressive episodes during the tryptophan-deficient diet. Dr. Delgado’s studies powerfully supported the monoamine hypothesis, showing how an induced decrease in specific monoamine neurotransmitters can trigger a relapse into major depressive episodes [5].

THE LIMITATIONS OF THE MONOAmine HYPOTHESIS

Although the monoamine hypothesis inspired the creation of many drugs which effectively alleviate the symptoms of major depression, it has many limitations. Most notably, SSRIs take several weeks to elevate mood, despite the increase in synaptic monoamine levels after one to three days. Additional questions that seemed to weaken the monoamine hypothesis began to form as further research was conducted at the end of the twentieth century. In a 1994 study conducted at McGill University, male participants with and without a family history of depression were given a chemical mixture that was known to lower synaptic serotonin levels [3].

Over the course of the study, the moods of the participants and their serotonin blood levels were monitored. Interestingly, most participants experienced no change in mood despite a definite decrease in serotonin blood levels [5]. Mood changes were observed only among participants who had a family history of depression. If the monoamine hypothesis were totally true, mood changes would be expected in all participants—not just those with a history of depression. The McGill study would be just one in a long list of studies that began to question whether the monoamine hypothesis alone could accurately explain the biological basis of major depression [3].

In 2006, more questions were raised after the results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D study) began to be analyzed [6]. In one of the first federally funded comprehensive studies on the treatment of major depressive disorder, patients across the nation that were diagnosed with moderate to severe major depression were given the option to participate in STAR*D. The STAR*D study consisted of four different levels of treatment. All participants started the study taking the same SSRI (level one). Those who did not experience remission of depressive symptoms went on to try out a new medication or combination of medication and psychotherapy at the second level. Although many types of antidepressants were tried at each level (disregarding level one), 30% of participants who stayed with the study did not experience remission after going through all four levels. The increase of norepinephrine, serotonin, and dopamine by the various drugs could not cure all instances of major depression. The McGill and STAR*D studies both presented the scientific community with results that could not be explained by the monoamine hypothesis alone [4, 6].

NEW PERSPECTIVES AND RESEARCH

As more research revealed the missing gaps left by the monoamine hypothesis, more comprehensive hypotheses and theories began to take shape. Within the last twenty years, research in the field of endocrinology—the medical study of glands and hormones—has led to the formation of the neuroendocrine hypotheses for depression. Neuroendocrine hypotheses describe how hormonal responses to stress contribute to major depression [7]. Biological responses to stress are specifically shown to cause hyperactivity in the hypothalamus-pituitary-adrenal (HPA) axis, a system that encompasses many complex hormonal interactions within the body. Changes in such a far-reaching system can have dramatic effects. The slightest increase in activity of the axis can trigger chain reactions that result in large changes in mood. When we encounter a stressor or like social rejection or the death of a loved one, our hypothalamus secretes hormones that tell the pituitary gland to release specific directing hormones. These directing hormones are essentially messengers that travel through the bloodstream to our adrenal glands. Once the adrenal glands receive these directing hormones, they begin to secrete the stress hormone cortisol, among other hormones. Together, these three structures play critical roles in the body’s registration of and response to stress [7].
In 2007, Nicole Vogelzangs and colleagues conducted a study that tested the connection between depression, cortisol, and metabolic syndromes. Vogelzangs defined metabolic syndromes as a cluster of risk factors that increase one’s risk for cardiovascular disease and diabetes [8]. Interestingly, the results showed that depression and high urinary cortisol levels were significantly associated with each other and with metabolic syndromes. Similar hormonal relationships are observed in the mice model of depression [8]. A recent 2017 study by Dr. Shetty and colleagues found that levels of corticotropin, a hormone associated with stress and fear, increased in mice that had been socially isolated [9]. These mice also demonstrated depressive behavior. Many other studies that examine the common relationship of diabetes (a disease that affects the endocrine system) and major depression provide further evidence for the neuroendocrine hypothesis [10]. Although the monoamine hypothesis accurately predicts the changes in neurotransmitter concentrations, it does not predict nor explain the hormonal changes that are also observed in depressed patients [8, 9, 10].

An accumulation of research in the last fifty years has allowed the psychological community to develop a new theory for understanding the causes of major depression. The neurogenic theory of depression states that an impairment of new neuronal growth (neurogenesis) in the adult hippocampus, a brain structure well known for its role in emotional regulation and memory consolidation, is a biological basis of major depression [11]. In 2013, Dr. Huang and colleagues used Magnetic Resonance Imaging (MRI) to examine the hippocampal volumes of participants with and without major depressive disorder [12]. The study's results showed a significant difference in the volume of the hippocampus between those with major depression and the healthy controls. Participants with major depression had less tissue in their lower dentate gyrus, a specific fold of hippocampal tissue known for its ability to undergo neurogenesis. Scientists now think this fold of tissue could be the key to understanding the hippocampus’ role in mood disorders. Other studies have shown that a reduction in the size of the hippocampus and an increase in degradation activity (neuron death in the brain) are commonly seen in the post-mortem brains of people who suffered from major depression [11, 12, 13]. Additionally, many studies show that prolonged usage of effective antidepressants can trigger the birth of new nerve cells and reverse hippocampal shrinkage [14]. This may explain why it takes so long for the mood of patients on antidepressants to improve, despite the rapid increase in monoamine levels. This could also mean that monoamine neurotransmitters play a role early on in the etiological timeline of major depression that culminates in the inhibition of hippocampal neurogenesis. A low serotonin level by itself does not tell the full story of depression. New research is currently exploring neurotransmitters that directly impact neurogenesis (e.g. ceramide). New studies are also showing an association between high cortisol levels and low hippocampal volume, indicating a crossover of the neuroendocrine hypotheses and the neurogenic theory [9]. One of the clearest demonstrations of this crossover was discovered in a 2016 study conducted by Columbia University [16]. In the study, researchers discovered that serotonin receptors on mature mouse neurons were responsible for the various antidepressant effects of SSRIs. An increase in binding to these receptors was shown to trigger other pathways that resulted in the neurogenic and hormonal responses associated with effective antidepressant usage. This new research demonstrates how the monoamine hypothesis interacts with both the neurogenic theory and the neuroendocrine hypotheses to

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form a clearer picture of the biological basis of major depression [14, 15, 16].

NEW APPLICATIONS IN TREATMENT
As researchers continue to enhance our understanding of the intricate biological mechanisms that underlie major depression, pharmaceutical companies and physicians are taking a more individualized treatment approach. The accumulation of research reveals that there is no one drug type that perfectly "fits all." New pharmaceutical research is exploring the antidepressant effects of atypical chemical compounds known to increase hippocampal neurogenesis. In a recent 2016 study, Dr. Ma and colleagues at the Shenyang Pharmaceutical University administered a traditional Chinese medicine herbal compound called Xiaochaihutang (XCHT) to mice [17]. Interestingly, mice who had expressed depressive symptoms showed a noticeable change in behavior after receiving XCHT. In addition to an increase in hippocampal volume, depressed mice began to eat more and exhibit less aggressive behavior. By making neurogenesis the end goal of biochemical interventions, pharmaceutical researchers may be able to decrease the time it takes antidepressants to alleviate symptoms. Further studies have also demonstrated the potential for unusual substances, like plant pigments and grape seed extract, to be used as antidepressants. In addition to already in-use SSRIs, these substances have been shown to promote hippocampal neurogenesis and improve mood [18, 19, 20]. The neurogenic theory is inspiring a new frontier in pharmaceutical research that examines a wide range of compounds for potential neuronal growth-promoting and antidepressant properties [17, 18, 19, 20].

New research is also revealing the effects our daily activities and habits can have on our brain's ability to regulate emotions and hormones, and generate new neurons. Within the last ten years, a substantial body of research has examined the beneficial effects aerobic exercise can have on major depression and neurogenesis after impairment, leading many healthcare professionals to advise major depression patients to participate in regular aerobic exercise [21]. Additional research in the field of endocrinology also reveals the effects sleep can have on our mood and hormone regulation. Many studies show that sleep deprivation and an increase in wakefulness during sleep increase cortisol levels and the risk of developing major depression [23, 24]. Perhaps the most preventive action we can take against major depression is to prioritize exercise and rest in our daily lives [21-24].

Although our understanding of major depression has significantly progressed, we are still far from knowing everything about the biological basis of this disorder. However, the future is looking bright. Our biological understanding of major depression has never been this comprehensive. Acknowledging the intricate nature of this disorder will only improve how we treat those who suffer from its symptoms every day.

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Through the melatonin pathway, light entrains the ‘headquarters.’ SCN announces the end of melatonin’s shift, so no sends a telegram to the SCN. Seeing the telegram, the clocks. When light enters the eye, it flips a switch that body, going up to each receptor and adjusting their headquarters. In the dark, melatonin walks around the shift messenger, and the SCN as the messenger morning [5,6].

The Night Shift

Melatonin essentially serves as a ‘darkness hormone,’ as light suppresses its secretion [5]. Melatonin courses through the body and is received by a variety of receptors, most of which are within the SCN itself. Two known melatonin receptors, MT1 and MT2, receive and relay information depending on the timing of melatonin release. The MT2 receptors appear to be responsible for the shifting and re-aligning of the circadian rhythm with the solar day, whereas the MT1 receptor promotes drowsiness and sleep. Throughout the day, melatonin will follow a regular cycle in the body, appearing prior to sleep, peaking between two and four in the morning, and dropping off near the morning [5,6].

For easier visualization, imagine melatonin as a night-shift messenger, and the SCN as the messenger headquarters. In the dark, melatonin walks around the body, going up to each receptor and adjusting their clocks. When light enters the eye, it flips a switch that sends a telegram to the SCN. Seeing the telegram, the SCN announces the end of melatonin’s shift, so no more melatonin leaves HQ to set receptor clocks. The arrival and departure of melatonin thus signal the beginning and end of the day, as controlled by the SCN ‘headquarters.’

Through the melatonin pathway, light entrains the circadian rhythm, which sets and regulates the biological sleep/wake cycle [7]. Suppression of melatonin earlier in the day ‘advances’ the circadian rhythm, promoting earlier wakefulness. Likewise, light exposure later in the day, like the prolonged solar day in the summer, will extend the biological day. In this way, the body optimizes when certain processes occur and can prepare for resting hours ahead of time as well as prime the body for waking by raising internal body temperature [7,8].

GOING TO BED WITHOUT A NIGHT LIGHT: EFFECTS OF BLINDNESS ON THE CIRCADIAN RHYTHM

Without entrainment, even light-perceiving individuals may develop “free-running” cycles that deviate from the 24-hour cycle. Light-perceiving individuals include all people who can detect light, including the legally blind who may have useless but present vision. Concerning circadian entrainment, any individual with functional ipRGCs are ‘light perceiving,’ while those without ipRGC signaling are ‘non-light perceiving.’ In non-light perceiving people, the circadian rhythm may become very out of sync with the regular pattern of their social and work lives, creating problems like circadian rhythm sleep disorders. These include delayed sleep phase syndrome (DSPS) and advanced sleep phase syndrome (ASPS). DSPS and ASPS both feature regular 24-hour cycles that are either set later in the day (delayed) or earlier in the day (advanced). For example, an individual affected by ASPS may wake up very early and become sleepy in the afternoon. More common is the “free-running” cycle, in which the circadian cycle runs longer or shorter than the solar day, and so becomes increasingly out of sync. This type of cycle would be kept in check by the regulating mechanisms of melatonin and light, but may drift free in a non-light-perceiving individual [9].

Several studies conducted on the blind report that at least half of non-light perceiving individuals suffer from circadian rhythm sleep disorders [4]. These non-light perceiving individuals report difficulty going to sleep, waking, and staying awake throughout the day, as the rhythm of their biological system doesn’t correspond with the environment [9]. Digestion and metabolism may be disrupted if meals are consumed during the biological night, leading to increased levels of glucose, insulin, and fat after meals. This may cause an increased risk of diabetes and heart disease [6]. Irregular sleeping patterns can also interfere with normal life. Some choose to sacrifice their social lives and work in order to follow their own internal clocks. This choice enables them to function at full capacity, but prevents them from matching their schedule with those of their family, friends, and co-workers [10]. Others choose to find medication and treatment to fix their circadian rhythm so they can better integrate with society.

While stimulants and depressants can force a patient to sleep at certain times, they only address the symptoms and not the misaligned circadian rhythm [11]. Strategies for treating the root of the problem suggest administering melatonin, which has been shown to correct free-running circadian rhythms disorders as well as delayed- and advanced sleep onset disorders [10]. Patients are told to take the hormone a few hours prior to the desired bedtime, mimicking the normal cycle of melatonin. This has worked for numerous patients, although those with extremely deviant cycles may not respond to treatment. Recent developments have provided similar strategies using drugs such as Ramelteon, which mimics melatonin but is designed to target MT1 melatonin receptors with greater affinity than melatonin to induce sleep onset. Alternative strategies without medication include non-photic entrainment, in which a rigid daily routine is maintained to try to keep the circadian rhythm in sync [5].

Circadian entrainment provides a great many benefits, and occurs naturally with the rise and fall of the sun. Yet, many people in the modern age do not take advantage of their circadian rhythm, disrupting the natural cycle by staying up far past dusk with electronic devices [12]. Through continual exposure to light, people desynchronize their circadian rhythm voluntarily; instead of operating under constant darkness, they work under continual light. Take advantage of the system provided through nature, but don’t turn a blind eye to the clock.

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A fifty-year-old man with glioblastoma—one of the most invasive and aggressive types of brain cancer—had failed to find a treatment that worked for him; radiation, anti-tumor chemotherapy, and surgery showed no stable improvement [1]. Finally, doctors decided to perform an experimental procedure called CAR T cell therapy, a form of treatment involving genetically altering the DNA of T cells and reinjecting those engineered cells back into the cancerous areas in his brain. The therapy had been successfully used to treat blood cancers in the past, but researchers hypothesized that the treatment could be altered to treat more invasive cancers. This case would be one of the first attempts to use the treatment on solid tumors through this specific approach [2].

This attempt was highly successful: every tumor the patient had regressed by 77-100%; the number of immune cells in his cerebrospinal fluid increased, suggesting that the injected cells were working correctly; and the patient experienced no major side effects throughout the process [1]. After exceeding all expectations, he was able to return to aspects of normal life. These results raised new questions about the experimental therapy’s success and its implications regarding cancer treatment in the future.

Cancer is one of the leading causes of death worldwide. Although it can take multiple forms, the disease always emerges through the same general pattern. Cancer stems from the dysfunction of the human body’s own cells—a rogue, random, spontaneous growth of cells that do not respond correctly to the body’s signals and gradually invade the entire body [3]. As technology advances over time, so does our understanding of the disease and our ability to treat it. Modern medicine offers many different means of treating cancer, like surgery and radiation, but certain types and locations of a patient’s cancer can make treatment more difficult. Moreover, the side effects from radiation and chemotherapy can be immensely painful and debilitating. Rather than attacking the body with foreign chemicals like most modern therapies, CAR T cell therapy takes the patient’s own blood cells to formulate a treatment that can be directly localized to the cancerous areas or injected into the patient’s bloodstream.

CAR T cell therapy uses chimeric antigen receptors (CARs), synthetic receptors that target specific surface molecules on cancerous cells and attack them by using the killing/cytotoxic capacity of T cells, a type of white blood cell that is responsible for recognizing and destroying infected or mutated cells in the body.
body [2]. T cells remain in the body after their initial response to create longer lasting immunity against pathogens. The T cells are taken from the patient’s immune system and are altered by a process that takes approximately twenty-one days. First, the patient’s blood is broken down on a gradient after centrifugation to separate its red and white blood cells [1]. The isolated T cells are then treated with a viral agent that has been modified to carry a CAR that is synonymous to an antigen expressed by the patient’s tumor. This virus will permanently alter the T cell DNA and enable the cells to recognize and attack cancerous cells instead of the infected cells they normally destroy in the body [2]. In the initial patient’s case, the T cells expressed a CAR that recognized a tumor-associated antigen interleukin-13 receptor alpha 2 (IL13Rα2), a gene highly expressed on glioblastoma cancer cells, which enabled the altered cells to attack his solid tumors [1]. The engineered T cells were injected directly into the patient’s tumors several times over the course of treatment and carefully assessed to see how the affected areas responded [2].

The success of this experimental treatment—an almost complete removal of brain tumors through genetically modifying immune cells in the patient’s body—supports CAR T cell therapy as a possible means of treating all types of cancer moving forward. But, although the initial attempt was more successful than expected, more attempts to treat cancer using this method must be performed before the process becomes regularly used in the field of medicine. Many aspects must be considered before it can become a leading form of cancer treatment. Manufacturing chimeric antigen receptors is highly intricate and expensive, and each cancer case requires specific care regarding the genes targeted by the reengineered receptors [1,2]. There is also no way to know if all forms of cancer would respond the same way to CAR T cell therapy. For instance, research accumulated from every attempt to treat blood cancer has shown that certain forms of leukemia are more susceptible to treatment than others [2]. Immune tolerance to self-antigens and the lack of guidelines for successfully locating the necessary target molecules are other significant barriers in providing more patients with this form of treatment. Currently, researchers are looking for other ways to alter the DNA of patients’ T cells for the expression of the CAR. The optimization will ultimately lead to a shorter and more efficient transformation of a patient’s T cells [2]. Regardless, the primary success fosters optimism that it may soon be possible to treat cancer without having to endure the unpleasant side effects of chemotherapy or radiation—or that we are steps closer to finding a cure.

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The characteristics of the human microbiota are remarkable and perplexing. It is an incredibly diverse biome, consisting not only of a variety of bacterial species but also of the occasional virus and protozoan [5]. The human microbiota generally consists of approximately 100,000,000,000,000 (that’s 100 trillion) bacterial cells, thus accounting for 90% of the cells in the human body [1]. The largest, most widely studied community of microbes can be found living in the lower gastrointestinal tract [5, 6]; however, microbes also populate our mouth, our inner elbows, and even the creases behind our ears [7]. The species of microbes that are present at each site vary between different individuals. While all humans share a core microbiome, variation in microbiome composition depends on factors such as diet, genetics, and even recent kissing partners [8].

Based on genomic analysis from the Human Microbiome Project, some fundamental metabolic functions are common to all microbes populating humans, whereas other metabolic functions are exclusive to single microbial species and are uniquely useful to the human host [7]. The functions of genes in the microbiome require further study, as the vast majority (78-86%) of genes present in our body’s large microbial communities have unknown functions [7].

For the most part, the relationship between humans and their microbial tenants could be described as mutualistic, meaning that both organisms benefit from the interaction. Bacteria residing in the intestine help their human hosts by synthesizing and excreting vitamins, completing metabolic functions that human cells cannot perform, preventing pathogen colonization in the intestine, producing chemicals necessary to stimulate epithelial cell growth and metabolism, and stimulating the development of the immune system. The role of bacteria in maintaining human health is further demonstrated by the fact that imbalances in microbiota composition, called dysbiosis, have been found to be associated with numerous diseases [5]. Some of the diseases with the most well-characterized connections to dysbiosis include obesity and gastrointestinal diseases such as Crohn’s disease, ulcerative colitis, irritable bowel syndrome, and colorectal cancer [5]. In the latter half of this last decade, research in the subject area of the microbiota and human health has also begun to explore the relationship between the microbiota and the central nervous system, yielding exciting insights into both neurological diseases and brain development [6].

WHAT IS THE HUMAN MICROBIOTA?

Modern research of host-associated microbial communities has been made possible by advances in microbial research techniques that were made in the 1980s [1,2]. Previously, research of bacteria had largely been accomplished through analysis of pure cultures of bacteria grown in a Petri dish; however, bacteria in culture are generally not representative of the rich diversity of bacterial species present in a given environment, such as the gastrointestinal microbiota. On top of this, many bacterial species—including most of the microbes that populate the human gastrointestinal tract—are difficult to culture [5]. These shortcomings of culture techniques eventually gave rise to the development of techniques for studying uncultured bacteria, including ribosomal RNA sequencing techniques as well as techniques for directly cloning and analyzing DNA from environmental samples, called metagenomics [1, 2]. Armed with these methods, the scientific community has gained vast insight into the nature and impacts of host-associated microbes through studies such as the Human Microbiome Project, which was established in 2007 to sequence and analyze the health impacts of the human microbiota [4].
gastrointestinal dysbiosis are autism spectrum disorders, Parkinson’s disease, and multiple sclerosis [6]. Numerous studies have demonstrated characteristic abnormalities in the microbiota composition of the gastrointestinal tract of children with autism, which align with previously noted abnormalities in blood metabolite concentrations [12, 13]. A 2016 study by scientists at the California Institute of Technology demonstrated in a mouse model that Parkinson’s disease could only occur when gastrointestinal microbes are present and that symptoms of the disease could be worsened in mice upon colonization with gastrointestinal microbiota of a human Parkinson’s disease patient [14]. Abnormal trends in gastrointestinal microbiota composition have also been observed in multiple sclerosis [11]. However, in many cases of demonstrated connection and even contribution of the microbiota to neurological diseases, the reason for the association is poorly understood [5].

The effect of the microbiota on the brain has more permanent consequences in the context of development. The conditions of the brain—and of all organs—during development are critical because their effect on development will be reflected in the functioning of the organ throughout an individual’s life, a phenomenon called developmental programming [15]. In one study, researchers in Japan examined the effect of microbiota on the development of the hypothalamic-pituitary-adrenal (HPA) axis, a neuroendocrine system which controls the physiological response to stress [16]. The researchers first identified that mice lacking microbiota, called germ-free mice, exhibited an exaggerated HPA response to stress relative to mice with normal functional microbiota. They then colonized the germ-free mice with normal microbiota to determine whether the HPA response to stress in the germ-free mice could be normalized. They found that colonization with normal microbiota at a young age resulted in partial normalization of the HPA stress response in germ-free mice, whereas colonization at a later stage of development did not result in normalization of the HPA stress response. A similar result was found in a study conducted by researchers in Sweden in 2011, wherein it was found that certain differences in anxiety-related behaviors between germ-free mice and mice with a normal microbiota could be normalized by colonizing germ-free mice with normal gastrointestinal microbiota at a young age but not at a later developmental stage [5]. These studies are significant because they demonstrate that the state of the gastrointestinal microbiota during development can cause permanent changes in the physiological functioning and gene expression of the brain.

The implications that this demonstrated relationship between microbiota and brain development could have for humans are quite profound. Studies have shown that the development of the gastrointestinal microbiota in humans is an entirely postnatal process that begins with maternal microbial transmission via breastfeeding and lasts for 2-3 years [17, 18]. Malnutrition during those early years of life causes the development of the gastrointestinal microbiota to be delayed. As such, the gastrointestinal microbiota of undernourished children does not fully reach a mature configuration and is not sustainably brought to a mature configuration by therapeutic food interventions, which are common treatments for malnutrition [19]. Given the relationship between brain development and the composition of the microbiota, some scientists hypothesize that this persistent immaturity of the gastrointestinal microbiota could contribute to the impaired cognition observed during adulthood in severely malnourished individuals. However, extensive research into this subject has yet to be conducted [18].

CONCLUSION

Inquiry into the connection between neurological health and the gastrointestinal microbiota is an exciting endeavor because it affords intriguing opportunities to develop novel therapeutic interventions. For example, scientists have just begun to explore in greater depth the application of probiotics—microbes which are administered for a health benefit—to psychiatric disorders. One systematic review published in the Journal of Neurogastroenterology and Motility in October 2016 assessed 38 published studies of the positive effects of probiotics on central nervous system disorders, demonstrating that probiotics have been successfully used to ameliorate symptoms of depression, anxiety, autism spectrum disorder, and obsessive-compulsive disorder [20]. Additionally, some scientists encourage the application of fecal microbiota transplantation—a treatment in which microbiota are transplanted from a healthy donor to a patient in the form of feces—to neuropsychiatric disorders associated with dysbiosis. The technique has been successfully used in treating a number of gastrointestinal disorders, and several studies have been conducted in the past few years on the use of fecal microbiota transplants to treat Parkinson’s disease, multiple sclerosis, and autism [21, 22].

Given the burgeoning research currently surrounding the relationship between the gastrointestinal microbiota and the brain, these innovative treatment approaches certainly represent an appealing and promising approach to addressing neurological conditions. However, continued progress in this field will require overcoming a number of limitations on our current understanding of the gastrointestinal microbiota. For instance, scientists do not currently have clear parameters for defining what a healthy or normal gastrointestinal microbiota configuration looks like [3]. Additionally, due to the complexity of intermicrobial and host-microbe interactions within host-associated microbiota, it is difficult to pinpoint the effects of imbalances in the abundances of individual species on the host. Taken together, these limitations have made it difficult to progress from researching correlations between diseases and microbiotic imbalances to researching the possible causal role of the microbiota in certain diseases. In order to move past these barriers, further methodological and technological advancement and innovative applications of current research techniques will be required [3]. However, with such technological advances being within reach, further research in this exciting and fast-paced field of study promises to yield greater insight into the role of the microbiota in neurological diseases, development, and health.

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