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The effects of migraines, anxiety and depression on concussion recovery

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THE EFFECTS OF MIGRAINES, ANXIETY AND DEPRESSION ON CONCUSSION RECOVERY

by

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Dedications

I would like to dedicate this manuscript to my parents, Karen and Timothy Howard.

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Abstract

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Concussion recovery has been a very relevant topic in the medical field recently. The impact that a concussion has on the patient post-injury has been a topic of debate. What has not been included in many of these studies has been whether or not certain factors in a medical history of patients under the age of 24 can predispose them to a longer concussion recovery. Medical factors such as depression, anxiety and migraines can result in different areas of the developing brain being compromised such as the hippocampus, anterior cingulate cortex, prefrontal cortex, striatum, and amygdala. It is not unreasonable to suspect that an injury occurring to a brain that is already compromised can result in a longer recovery duration. The purpose of this study is to determine if preexisting depression, anxiety or migraines play a role in recovery duration from concussion sustained as a result of a traumatic injury in the 13 to 24 age group. A retrospective chart review was performed using 170 medical charts from patients of Cooper University Hospital from the date range of 1/01/2010 to 11/19/2019. It was found that there was no interaction between gender and the effect of preexisting conditions on concussion recovery. It was also found that patients with a history of anxiety or migraines experienced a significantly longer recovery than those who did not. Depression was found to have no effect on the length of recovery. The findings from this study can be used to create a plan of care for patients of all medical backgrounds.

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Chapter 1

Introduction

Traumatic brain injuries, such as concussions, are serious injuries to healthy individuals who do not have pre-existing medical conditions. This is also true for the adolescent population. A brain injury occurring in someone who already suffers from a condition such as depression, anxiety or migraines could possibly exacerbate the symptoms and prolong recovery. The purpose of this literature review is to discuss how depression, anxiety and migraines affect the brains of both concussed and healthy adolescents. Due to the similarities in the brain areas affected by all these disorders as well as concussions, it is possible that someone who already suffers from one of the disorders would take longer than average to recover from a concussion. This could be due to the fact that an injury occurs to an already compromised brain. This result could also be compounded on a brain that is still developing and thus making the recovery even longer.

Brain Anatomy and Development

The brain controls a person's thoughts, memory, gross body movements, as well as vital organ functions. The anatomy of the brain can be compartmentalized into three regions which are the brain stem, cerebellum, and the cerebrum. The brainstem is the connection between the brain and the spinal cord and is comprised of three parts: the midbrain, the pons and the medulla oblongata. The main function of the brain stem is to regulate and control many unconscious body functions such as heart rate, breathing, and temperature.[1]

The cerebellum is located in the posterior aspect of the brain beneath the occipital lobes of the cerebrum. The main functions of the cerebellum are fine motor skills, postural stability and balance. The third part of the brain is the cerebrum which is the largest of the three sections. It is made up of a left and right hemisphere and controls functions such as the interpretation of touch, sight and sound, reasoning, emotions and learning.[2] All sections of the brain must work together to keep the body running efficiently, making no one section more important than another.

Adolescence(10-19 years old) is considered to be one of the most dynamic periods of human growth and development in terms of the rate of change within the brain.[3] This period is second only to infancy. Although the brain is at 95% of its total size by the age of 6, there are many changes that will occur past this age.[4] The brain continues to develop and mature into the mid-twenties.[5] Many of these changes occur on a neuronal level. Arian et al.[3] states that a significant amount of the brain growth and development that occurs during adolescence is the construction and strengthening of regional neurocircuitry and pathways. The areas of the brain that mature the most during this time are the brainstem, cerebellum, occipital lobe, parietal lobe, frontal lobe and temporal lobe.[3]

There are changes seen in the volumes and thickness of cortical gray matter and cerebral white matter through childhood and adolescence as well. Cortical gray matter follows an inverted U progression with there being increases in volume and thickness in early childhood which than begins to decrease through adolescence until it levels off in the twenties.[6] Gray matter volume reaches its peak volume in the frontal, parietal and temporal lobes between the ages of 12 and 16 while volume in the occipital lobes

continues to increase until 21 years of age.[7] Males and females do not develop at the same rate however. Gray matter volume in females peaks about 1 year earlier than it does in males. This has been attributed to the earlier pubertal maturity seen in females.[8] Cerebral white matter follows a more linear progression as it increases throughout childhood and adolescence.[6]

The Effect of Depression on the Brain

Major Depressive Disorder (MDD) is the leading cause of disability in the world according to the World Health Organization and is estimated to affect more than 350 million people.[9] Precursors to Major Depressive Disorder can be seen in patients as young as adolescents. It is approximated that 12% of adolescents will experience a depressive episode by the age of 18.[15,16] Gujral et al.[9] defines MDD as the significant impairment in social and occupational functioning. The exact cause and location of depression in the brain is not clearly defined but imaging and testing may provide an answer.

Many studies point towards abnormalities in the different regions of the brain as being the cause of MDD.[10,11,12,13,14] Pandya et al.[10] as well as Gujral et al.[9] both found that structural abnormalities in the hippocampus, anterior cingulate cortex, regions of the prefrontal cortex, striatum and amygdala have been most commonly found within the depressed brain of both adult and developing individuals(mean age of 21).

The hippocampus is said to be the most studied region of the brain when referring to depression.[9] This region of the brain is responsible for the regulation of the hypothalamic pituitary adrenal-axis which plays a role in the production of cortisol.[11]

Cortisol is a glucocorticoid which is a hormone that is released in high levels during times of increased stress. Gujral et al.[9] states that the hippocampus in depressed individuals can be about 5% smaller in terms of volume than that of a healthy individual. Jaworska et al.[17] found similar findings of hippocampal volume in still developing populations such as adolescents. If the hippocampus is compromised, such is the case with depression, the HPA-axis will not be able to function at as high of a level as it needs to, and the person is susceptible to high rates of hypercortisolemia.[11] Hypercortisolemia is a prolonged period of excess cortisol production. Chronic high levels of cortisol have been shown to affect an individuals affective functioning which cause cause issues with tasks such as the processing of emotions.[11]These changes will alter the way a person is able to handle stress, resulting in many of the symptoms seen with depression.

The Anterior Cingulate Cortex (ACC) has been linked to depression. Gujral et al.[9] breaks the ACC into the dorsal ACC, controlling high-level executive and motor functions, the subgenual ACC that plays a role in emotional and interoceptive processing and the pregenual ACC which affects cognitive and emotional processing. Pandya et al.[10] only separates the ACC into two parts, dorsal and ventral. The dorsal ACC is implicated in the cognitive aspects of emotions while the ventral ACC connects with the limbic areas of the brain such as the amygdala, dorsomedial thalamus and hypothalamus. The connection between the ventral ACC and the hypothalamus play a role in the function of the autonomic nervous system in regulating the stress response of the body.[10] Li et al.[12] published a study in which they stated that when someone is suffering from depression, the ACC undergoes cortical thickening. This change in cortical thickness can bring forth symptoms such as anhedonia, negative thinking and changes in emotional experiences.

All of these symptoms characterize MDD. A study performed by Kimbrell et al.[13] also found that the dorsal ACC has effects on the attentional and cognitive symptoms of depression including apathy, psychomotor slowing, impaired performance in selective and directed attention tasks and impaired executive function. Pannekoek et al.[20] found volumetric reductions in the anterior cingulate cortex of depressed adolescents. Their results showed that the ACC of the affected individual was 14.4% smaller than the healthy control. They found this reduction in the dorsal region of the ACC which is known for its role in higher cognitive processes such as cognitive control and focusing attention to relevant events.[20]

Another region of the brain that is affected by MDD is the amygdala. Kimbrell et al.[13] says that in more severe cases of depression, hypometabolism of the amygdala has been seen. Siegle et al.[14] focused on the amygdala and its activation to different stimuli seen on a functional MRI (fMRI). Siegle et al.[14] found that the amygdala is hyperactive in depressed individuals as compared to the control. They hypothesized that this is due to the amygdala's function in identifying emotional aspects of stimuli. Depressed individuals tend to dwell on negative thought as a result of an emotional stimuli. Siegle and colleagues believe that this is due to the increased activity in the amygdala.[14] They also found that the amygdala and the dorsolateral prefrontal cortex have an inverse relationship in depressed individuals. They saw on the fMRI that as the activation of the amygdala increased, there was a decrease in the activation of the dorsolateral prefrontal cortex.[14] Whittle et al.[18] discovered similar findings within the amygdala of depressed adolescents. These studies show that depression can impact all areas of the brain.

Jaworska et al.[17] examined the possible relationship between adolescent depression and physiological changes within the brain. The results showed that adolescents and young adults with depression presented with decreased hippocampal volume when compared to healthy controls.[17] These findings were consistent with the findings of Whittle et al.[18] who found that there was attenuated growth of the hippocampus, amygdala and putamen in the brain of adolescents with depression.[18] Accelerated thinning of cortical gray matter in the prefrontal cortex (PFC) of developing brains was a finding that was discovered in several studies.[15,18,19] Since the PFC is the region of the brain associated with emotional regulation, decision making, multi-tasking, impulse control, reflective thought, and other functions, a reduction would explain many of the symptoms seen with depression.[8] Physiological changes have been seen and studied in the developing adolescent brain and these changes could have a connection to adolescent depression.

Generalized Anxiety Disorder, Social Anxiety Disorder and its Effect on the Brain

Generalized Anxiety Disorder is a psychiatric condition that has been estimated to affect approximately 6% of the human population at some point during their lifetime.[21] Anxiety disorders, such as Generalized Anxiety Disorder and Social Anxiety Disorder, can be diagnosed in nearly one third of all adolescents.[16] The definition of Generalized Anxiety Disorder (GAD) has changed dramatically from its first appearance in the DSM-III in 1980 to its most recent publication in the DSM-5 in 2013. In the DSM-III, GAD was simply defined as generalized, persistent feelings of anxiety lasting greater than one month. In the most recent DSM-5, the definition has changed to excessive anxiety and worry about a number of events or activities and having it occur more days than not for at

least 6 months. Symptoms of GAD as defined in the DSM-5 include restlessness or feeling on edge, easily fatigued, difficulty concentrating, irritability, muscle tension, and sleep disturbances.[22] However, what exactly causes GAD has been hard to define since it is often seen comorbidly with other disorders such as MDD.[21]

Limited research has been conducted in the adolescent and pediatric populations to examine the origins of these disorders. Similar to adults, anxiety disorders in adolescents have been hypothesized to arise from functional changes in the fronto-limbic regions of the brain responsible for emotional processing.[24] Maron et al.[21] studied different regions of the brain, such as the amygdala and the gray matter, as well as different biomarkers within the human body to see if there are any differences between someone suffering from GAD and a healthy individual. One of the more significant findings was that patients with GAD have been seen to have an increase in volume of gray matter in the amygdala as well as increased right amygdala volume in females with GAD. These structural changes have been associated with prolonged reaction times on tasks that require tracking, suggesting impairments in attention.[21] Makovac et al.[23] did a study using fMRI for resting-state neuroimaging to see if there was a neurological difference between patients with GAD and those without. They found that the subject population (mean age of 29) with GAD had a decrease in connectivity between the amygdala and the prefrontal cortex (PFC) when compared to a healthy population. It is said that this decrease in connectivity leads to the PFC not being activated to aid in the regulation of anxiety, thus causing an increase in amygdala activation. The increase in amygdala activation hinders the body's ability to regulate emotion. The findings by Makovac et al.[23] support the findings of Maron et al.[21] in saying that two of the key

causes for GAD are compromises in both the amygdala and the PFC. Adolescent patients with GAD show significantly higher levels of activation in the amygdala when exposed to emotional stimuli as compared to health controls.[25] This finding support the findings found in similar studies performed with adults.[11] Increased activation was also found in areas of the ACC and PFC in anxious adolescents.[25] Research has shown that anxiety disorders are actually a result of changes within the brain that can be seen and measured in both adult and developing populations.

These changes are not only seen in children and adolescents who have been diagnosed with an anxiety disorder but also in those who are the offspring of someone who is affected. Smoller et al.[26] states that offspring of individuals with anxiety disorders are six to nine times more likely to develop an anxiety disorder themselves. Results from Christensen et al.[24] showed that there were similar alterations in fronto-limbic activation in adolescents who did not exhibit symptoms of an anxiety disorder compared to those who are formally diagnosed.

Migraine and How it Affects the Brain

Migraines are said to affect approximately 15% of the world's population between the ages of 22 and 55.[27] Although more common in an adult population, migraines are also seen in the pediatric and adolescent population with a prevalence rate of 14.5%.[32,33] According to the WHO, migraine is the most prevalent and disabling neurological condition worldwide.[28] The International Classification of Headache Disorders (ICHD) defines chronic migraines as at least 15 days of headache occurring each month, including 8 days a month of headache attacks with migraine features, for

more than 3 months.[29,30] Studies have been conducted to understand what causes migraines and what changes occur within the body of someone affected.[27,28,29,30,31] The ICHD also breaks down migraines into two different categories: migraine with aura and migraine without aura. Migraine without aura means that it is a headache with a defined set of symptoms but no neurological symptoms that occur before or during the onset of the headache. Migraine with aura means that there are certain neurological symptoms that occur before or during the onset of the headache.[30] Aura symptoms that can occur include but are not limited to scotomas if the visual cortex is affected, numbness of the face or hands if affecting the somatosensory cortex, unilateral muscle weakness if the motor cortex is affected or aphasia if the speech cortex is affected.[27] The cause of these migraines and the effects that it has on the individual has not been extensively studied in the adolescent population. Studies done in the adult population have pointed towards lesions in the white matter of certain brain regions as well as volumetric changes in gray matter being a possible cause of migraines.[28]

Burstein et al.[27] states that migraines are more than just the normal headache. They believe that migraines are actually a neurological disorder that affect the cortical, subcortical and brainstem areas of the brain. Fillipi et al.[29] support this claim by also saying that migraines affect the cortical and subcortical areas of the brain that are responsible for pain processing such as the thalamus, hypothalamus, somatosensory cortex and the ACC. The hypothalamus seems to be the area that is discussed most frequently in several studies. Andreou et al.[28] states that decreased volume of the hypothalamus has been seen in patients with migraines and can help explain the frequency of their headaches. Fillipi et al.[29] also discusses changes that occur within the

hypothalamus when looking into migraines. There is an increase in hypothalamus activation during times of painful stimulation. They deduced that this increase in activation can result in the recruitment of other cortical areas that are involved in pain processing.[29] Finally, Burstein et al.[27] stated that the hypothalamus may be playing a key role in migraines because of its function with human circadian rhythms and maintenance of overall homeostasis. Neurons within the hypothalamus detect changes in homeostasis and activate nociceptors within the meninges.[27] With several studies supporting these findings, it is not unreasonable to say that the hypothalamus and the changes within it are a big piece of the puzzle that is the pathophysiology of migraines.[27,29]

Another area of the brain that has been linked to migraines is the brainstem. Coppola et al.[31] states that the brainstem both directly and indirectly controls the amount of cortical activation through the thalamus. This is important because it is said to have an effect on the pulsing sensation that is common with migraines. When the thalamus is activated, the meningeal nociceptors become sensitive to changes in intracranial pressure which can be altered by normal arterial flow through the brain.[31] This is what produces the pulsating feeling. Andreou et al.[28] also talks about the brainstem and the differences that are seen between migraine and non-migraine patients. They found that there were abnormalities seen in the white matter of the brainstem and cerebellum of migraine patients that was not seen in patients not suffering from migraines. Gray matter volume changes were also seen in several areas of the brain according to their research. The areas that these changes were found are responsible for nociception and analgesic dependence so it would be expected that these areas would be affected in a person who experiences

migraines.[28] The areas of the brain that are affected by migraines are similar to the areas affected by both Generalized Anxiety Disorder and Major Depressive Disorder.

Rocca et al.[32] conducted a study to determine if similar findings were found in pediatric and adolescent patients. The results showed that the migraine population had significant gray matter atrophy in the left middle temporal gyrus, right orbitofrontal gyrus, left inferior frontal gyrus and the subgenual cingulum.[32,34] This finding is significant as these regions play a role in nociceptive processing. Chong et al.[34] found reduced volume in white matter as well as altered connectivity in brain regions associated with nociceptive processing. Lesions in white matter have also been linked to pediatric and adolescent migraines. Candee et al.[35] conducted a study using magnetic resonance imaging to examine the structural changes within the brain of subjects with migraines compared to those who were healthy. The results show that in the subjects with migraines, there were lesions in the white matter of the brain.[35] Rocca et al.[32] had similar findings as they found lesions in deep and subcortical white matter. Although there is still need for further research, current findings show that volumetric changes in gray matter as well as lesions in cortical white matter may be linked to migraine disorders in the populations where the brain may not be totally developed.

Etiology and Biomechanics of Traumatic Brain Injuries

It is estimated that 1.6-3.8 million mild traumatic brain injuries occur each year in the United States.[36] Of the 1.7 million brain injuries that occur each year, it is approximated that 51% of these injuries occur between the ages of 1-24, a time of critical brain development.[5] Second only to motor vehicle accidents, sports-related concussions

are the second most common cause of head injury in this age group. The sports with the highest concussion rates are high school football for males and soccer and basketball for females.[7] Traumatic Brain Injuries (TBI), or concussions, can be defined as "any trauma induced alteration in mental status that may or may not result in loss of consciousness."[37] MacFarlane et al.[38] defines a concussion as a mechanical injury that leads to cerebral dysfunction without significant cell death. Brain injuries can be separated into two separate categories: focal and diffuse injuries. Focal injuries are typically more serious and can lead to cortical contusions or lacerations as well as intracranial bleeding. Diffuse injuries are a result of rapid acceleration and deceleration forces that cause a disruption to brain tissue. MacFarlane et al.[38] states that concussions are classified as diffuse injuries caused by acceleration and deceleration forces with a rotational aspect. The rotation from these forces create a temporary disruption within the thalamus and the midbrain, which can result in loss of consciousness. This acceleration/deceleration force can also cause what is referred to as a diffuse axonal injury (DAI). DAI results in multifocal lesions within the white matter as a result of the shear stress and tension on the tissue caused by the rapid acceleration/deceleration.[36]

Concussions can also occur without a direct blow to the head. Tong et al.[39] uses the example of a motor vehicle accident. When impact occurs, the seatbelt restrains the passenger from accelerating forward. Although the body stops moving forward, the brain continues to move forward until it makes contact with the skull, causing injury. Since the brain is not connected to the skull, there is nothing to secure it in place in times of rapid change. The impact of the brain crashing into the skull is what causes the damage to the brain without there being a direct blow to the head.

While resulting from similar mechanisms seen with concussions in adult patients, there is a higher level of concern with concussions in a younger population due to the ongoing development of the brain. Virji-Babul et al.[40] states that the still developing brain may be more susceptible to hypoxia, ischemia and traumatic axonal injury. Differences in energy metabolism, responsiveness to the environment and recovery from injury also make the developing brain more susceptible to injury.[5] Although the mechanism behind concussions in adults and adolescents is relatively the same, it is the fact that the injury occurs to a still developing brain in an adolescent that can be problematic.

The Effects of a Concussion on the Brain and Autonomic Nervous System

When a person sustains a TBI, it sets off an array of metabolic and neurochemical effects within the brain. The initial impact that caused the injury exerts shear and stretching forces on the brain which leads to a disruption in the cellular membranes. This disruption causes intracellular potassium(K^+) to rush out of the cells causing depolarization.[36] As the K^+ rushes out of the cells, extracellular calcium rushes into the cell. This alters the resting membrane potential of the cell which forces the sodium potassium pump to activate in an attempt to restore the body's homeostasis.[36] The sodium-potassium pump requires a great deal of adenosine triphosphate (ATP) to function resulting in an energy crisis within the brain. This energy crisis and the effects of it are the reason for the neurological dysfunction seen commonly with concussions.[38]

Leddy et al.[41] discussed that concussions can also cause problems within the Autonomic Nervous System (ANS). The ANS is controlled by the brainstem and its main purpose is to regulate cardiac and pulmonary systems throughout the body. It has been

seen that there is an altered level of chemosensitivity to arterial carbon dioxide ($PaCO_2$) in the blood.[41] Clausen et al.[42] found that female collegiate athletes had a lower sensitivity to $PaCO_2$ following their concussion. Being that the normal level of $PaCO_2$ usually fall around 40mmHg, the breathing rate that was observed in these athletes was significantly lower than expected for the amount of $PaCO_2$ recorded within their blood. The level of $PaCO_2$ in the blood has a direct correlation to cerebral blood flow (CBF). Cerebral blood flow will increase with increased levels of $PaCO_2$. This increase in CBF can result in symptoms such as headaches and dizziness.[41] Changes in CBF can also result in decreased endothelial and smooth muscle responsiveness due to increased levels of nitric oxide following trauma. This impairs vasoreactivity within the body and can leave the individual susceptible to chronic symptoms or even second injury.[36]

Allowing an athlete to return to play before their first concussion resolves puts them at a high risk for Second Impact Syndrome. Second Impact Syndrome occurs primarily in young patients under the age of 23 when there is a second trauma to the brain before the symptoms of an earlier concussion have subsided.[43] Scorza et al.[43] defines this as "a catecholamine surge from a second impact to the head that may cause vascular congestion, cerebral edema, increased intracranial pressure and ultimately death." There are many conflicting reasons for what actually causes second impact syndrome. Research has shown that the second hit exacerbates the vascular congestion within the brain and causes dysfunction within the trigeminal system.[44] This dysfunction hinders the brain's ability to regulate intracranial pressure, thus causing more damage to the brain.[44] Second Impact Syndrome could be problematic for an individual who sustains a concussion that coincides with a preexisting medical condition such as MDD, GAD, or migraines. An

individual may still be experiencing symptoms that they believe is caused from their condition but it is actually due to a prolonged recovery from a concussion. Downplaying these symptoms could put the individual at risk for Second Impact Syndrome as their brain has not completely healed from their concussion.

While the effects of a concussion on the brain is similar in both adults and adolescents, injuries in the younger population can result in more long-term consequences. Narayana et al.[7] reported that adolescents have shown impaired working memory and attention up to 2 years postinjury. With modern technology in terms of imaging becoming more available, researchers have been able to examine the possible physical changes that may occur in the adolescent brain as a result of a concussion. One of the most common findings were abnormalities in the white matter of adolescents and young adults following a concussion.[5] These lesions are similar to those seen with conditions such as migraines.[32,35] Virji-Babul et al.[40] used diffusion tensor imaging on adolescent patients who sustained and found that the changes within the white matter were still present up to two months following the injury. The findings of this study show that trauma that occurs to the brain as a result of a concussion is still present months later. These changes that are observed within different structures of the brain lead to the symptoms that can be seen in both adults and adolescents.

Presentation of Symptoms/Post-Concussion Syndrome

Concussions can manifest themselves in a variety of ways with a wide array of symptoms. Harmon et al.[45] provided a list of symptoms that may be observed. This list includes but is not limited to headache, nausea, vomiting, balance problems, dizziness,

fatigue, sensitivity to light and sound, mental fog, difficulty concentrating or remembering, emotional changes, sleep disturbances, and many others.[45] The Berlin Guidelines, the standardized protocol for concussion treatment, breaks up concussion symptoms into six parts: clinical symptoms, physical signs, balance impairments, behavioral changes, neurocognitive impairment and sleep/wake disturbances.[46] However, not all of these symptoms will be present in every case. No two concussions present the same way making it important to recognize and understand which symptoms each patient is suffering from. Some symptoms may appear immediately following impact and others take time to develop so it is critical that the clinician is constantly monitoring a patient or athlete who they suspect may have suffered a concussion. An athlete who has sustained a concussion and has exhibited symptoms is not permitted to return to play on the same day of the injury per the newest guidelines.[46]

When a patient who is suffering from a concussion has persistent symptoms that do not seem to subside, they could have what is called Post-Concussion Syndrome (PCS). PCS is defined as the persistence of symptoms lasting several weeks to months.[7] Leddy et al.[47] states that "the etiology of PCS is controversial because there has been a lack of findings on standard neuroimaging." This has led to the thought that rather than being due to physical brain injury, PCS may be a sign of an underlying psychological illness, a reactive depression, a form of post-traumatic stress disorder, a consequence of pain, or a form of malingering.[47] According to Leddy et al.[47], this means that the presentation of PCS is thought to come from more of a mental origin than it does physical.

Children and adolescents will exhibit many of the same symptoms that adults do when they sustain a concussion. However, there have been some differences that have

been documented. Nasr et al.[48] explains that while older patients can exhibit psychosocial issues such as depression, anxiety or sleep disturbances, younger patients are more likely to exhibit symptoms such as disinhibited speech, aggression and irritability. This can be linked to the regions of the brain responsible for the regulation of emotions not being completely developed yet. Narayana et al.[7] adds that children and adolescents with a history of migraines, learning disabilities and ADD could experience more severe symptoms. Studies have also shown that damage to the frontal and temporal lobes commonly seen with concussions is linked to issues with learning, memory and behavioral disturbances.[40]

A main difference between adult and adolescent concussions is the need for the adolescent to return to school. There have been several studies conducted on how returning to school after a concussion either affects the patient's academic performance or exacerbates their symptoms.[49,50] Baker et al.[49] introduces the concept of "cognitive intolerance" which they define as the exacerbation of concussion symptoms from prolonged cognitive activity. It was found that the level of symptom exacerbation was related to the length and intensity of cognitive activity.[49] This means that the longer an individual tried to work on something or the harder the work was, the worse the symptoms became. Ransom et al.[50] conducted a similar study to determine how postconcussion symptoms affected academic performance. The results showed that symptoms such as headaches, fatigue and impaired concentration affected academic performance. The authors also explained that high school students had significantly more difficulties than younger students as they had an increased workload and had to balance

both academic and extracurricular activities.[50] Proper timing of returning to school is crucial to the recovery of symptomatic adolescents following a concussion.

Treatment and Recovery from a Concussion

The 2016 Consensus Statement on Concussion breaks down the management of concussion into the "11 R's". They consist of: Recognize, Remove, Re-evaluate, Rest, Rehabilitation, Refer, Recover, Return to Sport, Reconsider, Residual Effects and Sequelae, and Risk Reduction.[46] This is a step by step approach that has been accepted throughout the medical community. One of the most important aspects of concussion management is early recognition and removal from sport. Arguably the most dangerous aspect of concussions is the risk of sustaining a second injury for individuals under the age of 23, so being able to recognize the signs of a concussion and removing that person from activity is critical.[28]

Many assessments of concussions begin immediately following the injury, most likely on the sideline of the game or activity in which the affected was participating. There are many tools available to the individual performing the assessment such as the Sport Concussion Assessment Tool 5, abbreviated SCAT5, and the Pediatric SCAT5. The SCAT5 runs through a wide array of questions in areas such as memory, concentration, balance and symptoms present.[43,46] Once it is determined that an individual has sustained a concussion, they are no longer able to return to activity until they have been evaluated by a physician and have completed a graduated return to play program. The patient is not able to begin this return to play progression until they have been asymptomatic for at least 24hrs.[46] Treatment until that point is rest and treating the symptoms that arise until

cleared to return to play.[29] Once cleared by a physician to begin their return to play, the progression is as follows: symptom limited activity, light aerobic exercise, sport-specific exercise, non-contact drills, full contact practice, return to full activity.[46] The average time for complete symptom resolution and being cleared to return to play is between 10 days to 2 weeks so it is important for all clinicians to know how to properly manage concussion treatment and recovery.[29]

The symptoms that can occur as a result of a concussion as well as how long it takes to recover for an otherwise healthy individual has been studied extensively.[43,45,46,29] This course of recovery may be completely different for someone who had a previously existing condition such as MDD, GAD or a migraine disorder. Limited research has been conducted to see if there are any discrepancies between the recovery time of a healthy individual compared to someone who may have an existing condition. Terry et al.[53] conducted a study in 2019 comparing the concussion recovery rates of high school and collegiate athletes with and without a history of migraines. They recorded the time to return to school as well as to sport. They found that girls and women have a significantly higher rate of migraine history than boys and men with the percentages being 12.8% and 6.6% respectively.[53] They also found that the girls/women with a history of migraines returned to school at a slower rate than those who did not have the same history. However, there was no statistical difference in the time to return to sport. They also found that there were no differences in boys/men with a migraine history compared to those who did not. They attribute this slower rate to the fact that migraine disorders and post-traumatic headaches share a common pathophysiological pathway.[53]

Scott et al.[54] performed a similar study using deployed US Military members. They were searching to see if co-morbidities affected the course of recovery for service members who sustained a concussion while deployed. They defined a comorbidity as "chronic, previously diagnosed or recent onset clinical condition identified by the treating neurologist as potential contributors to the clinical presentation following concussion."[54] The conditions that were studied were anxiety, depression, PTSD, migraines, and insomnia. They found that a single comorbidity alone did not impact the service members' recovery rate but when they had multiple, their rate of recovery was significantly slower.[54] They deduced that these conditions exacerbated the symptoms that the patients were experiencing and, in most cases, caused the length of recovery to be longer. Lau et al.[55] also performed a study looking at how premorbid conditions can affect the rate of recovery. The difference between Lau et al.[55] and Scott et al.[54] is that Lau used only male high school football players in their study. However, the results that they found were similar. It was found that the football players who had a history of migraines or headaches before their injury took significantly longer to recover than those who did not share the same history.[55]

Guerriero et al.[56] published a study focused solely on school-aged children. They defined school aged as patients between the ages of 5 and 22.[56] The results show that females were more likely to experience longer recoveries times compared to men regardless of premorbid pathologies. They also found that patients ≤12 years old with a history of migraines or headaches had a significantly longer recovery time. However, there was no statistical difference in recovery time for patients >12 years old.[56] The authors also stated that as patients got older, there was an increase in reporting of

premorbid conditions. They attributed this to the patient being more likely to explain what they are feeling themselves as they get older instead of relying on their parents to speak for them during childhood.[56]

Although several studies have been conducted showing possible relationships between pre-existing conditions and length of recovery, there are still gaps in the research. Many studies group together all the conditions and form a blanket statement encompassing all of them.[53,54,56] Also, some studies, such as Guerriero et al., primarily involved children and not older indivduals.[56] Further research would benefit from separating MDD, GAD, and migraines to truly determine if one results in a longer recovery time than another. These answers would help some clinicians to better treat their patients in varying stages of brain development based off of their medical history.

Discussion

Disorders such as Major Depressive Disorder, Generalized Anxiety Disorder and migraines not only show as symptoms that someone experiences, but they also cause changes within the structure and functions of the brain in both adolescents and adults. However, the fact that the brain is still developing in adolescents adds an increased level of risk. Research has shown that traumatic brain injuries such as concussions affect many of those same areas as MDD, GAD, and migraines. An individual who suffers from MDD, GAD and/or migraines could be expected to take longer to recover from a concussion than what is normally seen. This could be due to the fact of an injury occuring to an already compromised brain. In order to provide the best care possible for these

individuals and all individuals who sustain a concussion, it is important for all clinicians to be well versed in the recognition as well as the management of concussions.

Problem Statement

Disorders such as depression, anxiety and migraines can create problems in a person's life. In addition, it can also affect the individuals brain. Youth, adolescents, young adults and adults have found ways to cope with their disorders. Some turn to athletics as their coping mechanism. The risk of sustaining a traumatic brain injury such as a concussion is always present in athletics. There have not been many studies done on the effects of concussions on a brain that is already suffering from a disorder such as depression, anxiety or migraines in adolescence and young adulthood. Also, there have been minimal studies looking at if sustaining a concussion on an already compromised brain can impact recovery times. These studies should be primarily focused in the adolescent and young adult populations. Investigating this gap in the research can help provide better care to those who are affected by multiple conditions.

Purpose and Specific Aims

The purpose of this study is to determine if preexisting MDD, GAD, and migraines in adolescents and young adults(13-24) plays a role in recovery duration from concussion sustained as a result of a traumatic injury. This is a retrospective chart review with the following specific aims:

1. To evaluate how certain health history factors (migraine history, depression, anxiety) can affect the length of concussion recovery in this population.
2. To compare the difference in recovery rates between patients with and without one or more of these factors.

Hypothesis

It is hypothesized that the presence of migraine history, depression and/or anxiety in a patient's medical history will result in a longer recovery time from a concussion than those without the presence of any of the stated factors among this population.

Chapter 2

Manuscript

Abstract

Concussion recovery has been a very relevant topic in the medical field recently. The impact that a concussion has on the patient post-injury has been a topic of debate. What has not been included in many of these studies has been whether or not certain factors in a medical history of patients under the age of 24 can predispose them to a longer concussion recovery. Medical factors such as depression, anxiety and migraines can result in different areas of the developing brain being compromised such as the hippocampus, anterior cingulate cortex, prefrontal cortex, striatum, and amygdala. A longer recovery duration could be expected due to an injury occurring to an already compromised brain. The purpose of this study is to determine if preexisting depression, anxiety or migraines play a role in recovery duration from concussion sustained as a result of a traumatic injury in the 13 to 24 age group. A retrospective chart review was performed using 170 medical charts from patients of Cooper University Hospital from the date range of 1/01/2010 to 11/19/19. It was found that there was no interaction between gender and the effect of preexisting conditions on concussion recovery**.** It was also found that patients with a history of anxiety or migraines experienced a significantly longer recovery than those who did not. Depression was found to have no effect on the length of recovery. The findings from this study can be used to create a plan of care for patients of all medical backgrounds.

Participants

Of the medical charts reviewed between the ages of 13 and 24, 170 met inclusion criteria and were included in the study. A subject list was generated from the date range of 1/1/2010 to 11/19/19 using the ICD-10 and ICD-9 codes found in Tables 1 and 2.

Table 1

ICD-10 Codes

ICD-10	
S06.0XOA	Concussion without loss of consciousness
S06.0X9A	Concussion with brief loss of consciousness
S06.0X1	Concussion with loss of consciousness 30 minutes or less
S06.0X2	Concussion with loss of consciousness 31 to 59 minutes

Table 2

ICD-9 Codes

ICD-9	
850.0	Concussion without loss of consciousness
850.9	Concussion without loss of consciousness
850.5	Concussion with brief loss of consciousness

From this subject list, charts that were included in this study were those of both males and females between the ages of 13-24. They must have been evaluated by a

physician of Cooper University Hospital and diagnosed with a concussion. Charts were excluded if the subject fell outside of the selected age range, the presence of concussion was ruled out or if they have a history of one or more concussions. Patients were not required to sign a consent waiver as no identifying factors are published in this study that can be traced back to the subject. The final subject pool consisted of 100 females and 70 males. Out of the 100 females, 52 were found to have either depression, anxiety or migraine history and 48 did not. Out of the 70 males, 20 were found to have one or multiple preexisting conditions and 50 were not. Patient demographics as well as the sports that patients participated in can be seen in tables 3 and 4.

Table 3
Patient Demographics

Gender	**# of Patients**
Male	70
Female	100
Total	170
Age	
13-16	103
17-20	61
21-24	6
Total	170

Table 4
Breakdown of Sports Participation

Sport	# of Patients
Baseball	5
Basketball	7
Cheer	13
Color Guard	1
Dance	3
Field Hockey	9
Football	24
Golf	1
Gymnastics	1
Hockey	3
Ice Skating	1
Lacrosse	16
Non-Athlete	6
Rugby	1
Soccer	46
Softball	13
Swimming	2
Tennis	1
Track and Field	2
Trampoline	1
Volleyball	7
Wrestling	7
Total	170

Instruments

For this study, we used Cooper University Hospital's electronic medical record system, Epic. Epic is a cloud based electronic medical record(EMR) system that is used by Cooper University Hospital as well as all of their satellite offices. All data that was extracted from the patients' charts was entered into a spreadsheet that was created by the study team (Figure 1).

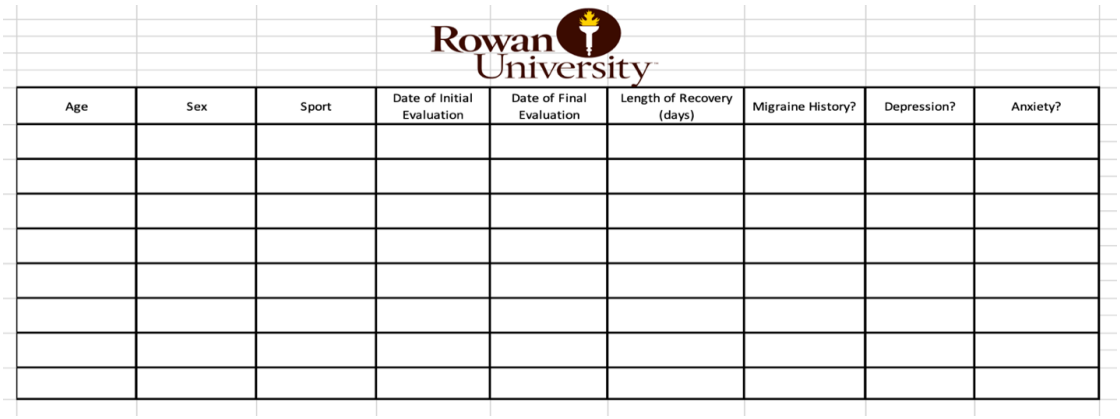

Figure 1. Blank Data Sheet

Statistical Analysis

IBM SPSS 26 was the statistical software that was used for data analysis. A 2x2 ANOVA was used to determine if gender influenced the effect that preexisting conditions had on length of concussion recovery. The dependent variable in this test was the length of recovery. Independent t tests were used to determine which of the conditions out of depression, anxiety and migraines had a significant effect. The independent variable in these tests were whether or not the subject had the condition and the dependent variable was the length of recovery.

Results

There was no interaction found between sex and symptoms ($p=0.428$). It was found that individuals who had at least one of the studied conditions had a longer recovery (59 days) than those who did not (21 days). This was considered to be statistically significant ($p<0.001$). There was also no impact of sex on recovery as males had an average recovery of 32 days and females had an average recovery of 41 days. This was considered to not be statistically significant ($p=0.851$).

First looking at migraine history, it was found that individuals who had migraines had longer recovery times (72 days) than those who did not (30 days). (p=0.025). Similar findings were found for those with a history of anxiety. Individuals with a history of anxiety had longer recovery times (52 days) than those who did not (31 days) (p=0.026). The data from these tests can be seen in tables 5 and 6.

Table 5

Migraine Data

Condition	Recovery Time(Days)	P-Value
Migraines	72	0.025
No Migraines	30	

Table 6

Anxiety Data

Condition	Recovery Time(Days)	P-Value
Anxiety	52	0.026
No Anxiety	31	

This test also showed that individuals with a history of depression did not have longer recovery times (49 days) when compared to those who did not (35 days). (p=0.255) The data from this test can be seen in table 7.

Table 7

Depression Data

Condition	Recovery Time(Days)	P-Value
Depression	49	0.255
No Depression	39	

Patients are often seen to have depression and anxiety comorbidly.[9] An independent t-test showed that the recovery time for patients who have both depression and anxiety comorbidly was not significantly different than those who did not have these conditions together. (p=0.432) The average recovery time for patients who had depression and anxiety was 46.3 days compared to 35.8 days for those who did not have these conditions together and 21.1 days for those who had no previous conditions.

Discussion

The purpose of this study was to determine if individuals who had a history of depression, anxiety, or migraines were at risk for a longer recovery from concussion than those who did not have this same history. It was found that the influence of the preexisting conditions on length of recovery was not dependent on the gender of the subject. Due to gender not having an influence on the duration of recovery, there was no need to separate the data into two genders for further analysis. Our results found that individuals who had a history of migraine or anxiety had significantly longer recovery times than those who did not. This finding was consistent with current literature such as Terry et al.[53] and Scott et al.[54] However, depression was found to not have an effect on

duration or recovery. This was not consistent with current literature. This could be due to the fact that there was a small number of patients in our study with depression. These findings partially supported our initial hypothesis. It was hypothesized that all three of the conditions would have an effect on the length of recovery and while the findings with anxiety and migraines supported this, the findings with depression did not. Anxiety and migraines could be significant for several reasons. The level of stress that adolescents and young adults are under could be one possible reason. This amount of stress, whether it be from school or pressure from peers to return to a sport, can become too much. This can trigger bouts of anxiety and even migraines in some indivduals. It would make sense that this could affect the course of recovery from a concussion as this age group is subject to increasing levels of stress. Finally, an independent t-test was run to see if patients who had both depression and anxiety have a prolonged recovery as the two conditions are often seen comorbidly.[21] The results showed that the difference in recovery times was not statistically significant. Clinicians can use the findings of this study to identify which of their patients may be at an increased risk of a prolonged recovery based off of their medical histories. They can also use these findings to encourage their patients to have their preexisting medical conditions under control.

Disorders such as Major Depressive Disorder, Generalized Anxiety Disorder and migraines have effects on the brain that can result in physiological changes in certain areas. Research has shown that traumatic brain injuries such as concussions affect many of those same areas. Due to the similarities in the brain areas affected by all these disorders as well as concussions, it could be hypothesized that someone who already suffers from one of the disorders would take longer than average to recover from a

concussion. Research has been done trying to uncover the severity of the effect that these conditions have on recovery. Terry et al.[53] and Scott et al.[54] both conducted studies to determine if migraines affect the rate of recovery from concussions in their respective populations. Although they did not use the same populations, with one using high school and college athletes and the other using United States military members, they both found similar results. Terry et al.[53] went even further and also found that girls and women took longer to recover than boys and men did. While our results did not find the same in regard to gender, it did show that individuals who suffer from conditions such as migraines are susceptible to longer recovery times from a concussion.

Guerriero et al.[56] conducted a study that focused on school aged children from the age of 5-22. While our study focused on patients ages 13-24 this study provided a good base to form our study off of. The main finding from Guerriero et al.[56] was that children ≤12 years old with a history of preexisting conditions had a significantly longer recovery time and that there was no difference for children >12 years old. Ages of the patients was not a variable that was studied in our research but would be interesting to pursue in the future. Overall, our findings were consistent with many articles and studies that have been previously published.

Chapter 3

Conclusion

Concussions are becoming a more prevalent injury in the medical field and there needs to be a solid understanding of how it can affect all individuals. While there has been an abundant amount of research done on the topic, there is still research that can be done to further the understanding of concussion recovery.[30,31,32,33] Our study was aimed to fill one of those gaps by answering the question of how depression, anxiety, and migraines can affect the rate of recovery following the injury. Our findings suggest that patients who are suffering from conditions such as depression, anxiety and migraines prior to injury are susceptible to a significant longer recovery. With this information, clinicians will be able to identify younger individuals who are at an increased risk and be able to develop a plan of care should that individual sustain a concussion.

Limitations

One of the limitations of this study was that we were limited to only one health system, Cooper University Hospital. This limited the number of medical charts that were available for use in the study. Along with limited charts available, we were also restricted to only using charts of the doctors that are employed by Cooper University Hospital. While this restricted our subject pool even more, it also limited the range of care that each of the patients may have received. Although the care of concussions is for the most part standardized as per the 2016 Consensus Statement on Concussion in Sport from the 5th international conference in Berlin, every physician has their own way of interpreting these guidelines.[46] What the physicians from one health system do for their concussion patients may not be identical to what physicians of other health systems do. This creates a

variability in care that may have an effect on recovery outside of what the study was looking for.

Another limitation of this study is the fact that patients filled out their medical history forms on their own or had a parent do it for them. This opens the opportunity for response bias when it comes to disclosing previous concussions and existing conditions they may have. Unless the subject has been a patient of Cooper University Hospital for their entire life, there is no way to prove if the information provided on the health history form is accurate. This could be problematic to the study because if they fail to disclose a history of previous concussion, the patient may have been included in the study when they should have been excluded per our exclusion criteria. This is considered a limitation because undisclosed medical history can potentially have an impact on recovery and invalidate the data.

Future Work

While our results supported current research that has been published, future research should be conducted to address any limitations that our study may have had and further expand upon what we studied. As anxiety and migraine history were both found to be significant in our study, each should be studied exclusively in further research. One question that should be researched is if a certain sport puts these individuals at risk for longer recovery times. Another avenue that should be studied more extensively is the effect of age on length of recovery in patients with preexisting conditions. It would also be interesting to further the research on the effect of family medical history on concussion recovery. Although the patient may not have a condition such as depression or anxiety, it could be beneficial to determine if a family history of these conditions plays

a role. These questions should be researched in order to further close the gaps in knowledge when it comes to concussion recovery and will allow clinicians to provide better care to all individuals. With this knowledge, physicians will be able to take a more thorough history and be able to explain to the patient how their recovery process may differ due to their medical history.

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