

**Title :**

Utilization of Routine MRI as a Neuroimaging Surrogate Biomarker for the Demonstration of Cerebral Cortical Atrophy in American Football Players with mTBI/Concussion and the Association with Chronic Traumatic Encephalopathy

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## **Abstract**

### Importance:

Players of American Football may be at increased risk of long term neurological conditions; particularly chronic traumatic encephalopathy (CTE).

### Objective:

To determine the Neuroimaging finding of Cortical Atrophy and the utilization of routine MRI Brain Studies in Football Players with Concussion as a Surrogate Biomarker for early Chronic Traumatic Encephalopathy.

### Design, Setting, and Participation:

Multicenter case series of 300 football players with a history of the Concussive Syndrome. Prospective study of the MRI Findings and evaluation to determine firstly the degree of cerebral Cortical atrophy by measuring the area of the Central Sulcus (CS) (Flowers et al. Works in Progress). The CS is one of the most important embryological and gross anatomical and histological landmark of brain anatomy but also the point of reference between gross functional sensory and motor neural connectivity and networks. Our preliminary research with servicemen returning from Middle East Conflicts with Symptoms from Mild Traumatic Brain Injury (mTBI)/Concussion, demonstrate early cortical atrophy of the Brain on routine MRI Brain studies using the measurement of the Central Sulcus area as a Biomarker for cortical atrophy..

### Exposure:

Participation in American Football in High School, College , Semi-Professional and Professional Athletes. Players should have a limitation of at least two known episodes of Concussion and Chronic Concussive Symptomatology.

### Outcome:

To demonstrate that the utility of routine MRI Brain may be utilized to show an association of cerebral cortical in football players and may be an integral point of reference early Chronic Traumatic Encephalopathy (CTE)

## **Technical Research Project Summary**

In the United States, an estimated 1.7 million people sustain a TBI annually, associated with 1.365 million emergency room visits and 275,000 hospitalizations annually with associated direct and indirect costs estimated to have been \$60 billion in the United States in 2000. Additionally, the Centers for Disease Control estimates that 1.6 to 3.8 million concussions occur in sports and recreational activities annually. Concussions are not limited only to the sport athletes but also to returning military personnel returning home with mTBI/Concussion from Blast-Injuries from conflicts in the Middle East. A concussion/mTBI results from an impulsive force transmitted to the head resulting from a direct or indirect impact to the head, face and neck. The symptoms of concussions/mTBI may present with a wide range of clinical signs and symptoms, including physical signs. Concussion and mTBI is a pathologically heterogeneous disease, including injury to both neuronal cell bodies and axonal processes. This study was designed to determine the relationship between neuroimaging markers of acute diffuse axonal injury (DAI) and cerebral atrophy months and years later from the time of injury. MRI imaging of 300 US Football players who suffered concussion will be included in this multicenter study. The area of the Central Sulcus of the Athletes will be measured on MRI studies with matched control subjects to give a more accurate assessment of Cerebral atrophy. The Area of the central Sulcus (CS) was measured and quantified in congruence to Volume of the sulcus. With knowing calculated known controlled Normal Central Sulcal anatomy Cortical atrophy of the brain of the Athletes will be measured. The correlation will be made with early Chronic Traumatic Encephalopathy (CTE).

## **Lay Research Project Summary**

Mild Traumatic Brain Injury (mTBI) is a pathologically heterogeneous disease, including injury to both neuronal cell bodies and axonal processes. This study was designed to determine the relationship between neuroimaging markers for concussion and Brain shrinkage months and years later from the time of injury. We performed magnetic resonance imaging (MRI) in 200 patients who suffered non-penetrating blast TBI. The area of the Central Sulcus were obtained in normal brain aged controls from outside medical center to give a more accurate assessment of brain shrinkage. The size of the CS was measured compared to the Volume of the sulcus groove on the brain. Knowing calculated controlled size of the central sulcus, the amount and degree of brain shrinkage is quantified. The Brain shrinkage in our current study was categorized into Normal, Mild, Moderate, and Severe proportionate for age using the Normal Controls for similar age with no history of mTBI. The Central Sulcus outline on Axial projections demonstrated the best tissue- cerebrospinal contrast on MRI and the ROI Freehand drawing along the Cortical gray depicted the best template for the evaluation to correlate with cerebral atrophy. In our preliminary work with young Veterans from the middle east conflicts with mTBI/concussion, we found that an increased size of the central sulcus of the brain following concussion can be utilized as a measure and marker for the evaluation of patients with concussion as well as a Standardization for brain shrinkage in young servicemen transferrable to the age range for players in the NFL as well as extending to older adults with and without clinical symptoms. This New Standardized Protocol may will be useful in the evaluation of younger athletes with Concussion and CTE as a guidance of early brain damage due to sporting injuries of the brain.

## Research Project Summary

Traumatic Brain Injury affects approximately 20 Million people yearly throughout the world and of that number approximately 75-80% are categorized as Mild Traumatic Brain Injury (mTBI)/Concussion. Although several advanced Magnetic Resonance Imaging protocols exist to evaluate Traumatic Brain Injury and mTBI including Tractography with Diffusion Tensor Imaging (DTI) and MRI Functional Imaging using BOLD techniques as well as MR Spectroscopy which are tedious techniques with lengthy examination time, routine MRI has not been established as the primary Magnetic Resonance Imaging examination for the evaluation of mTBI/Concussion. The reason for this oversight we believe is due to our intuitive focusing for the evaluation of microhemorrhages which we as neuroradiologists in the past have assigned our critical thinking capabilities to find as well as the Diffuse Axonal Injury white matter abnormalities which may be readily seen on routine MRI studies. As of date there has not been a specific neuroimaging biomarker to assess the effects of the injuries of mTBI as well as the clinical syndrome prior to and after a concussive injury.

Our preliminary study utilizing Routine MRI to evaluate young servicemen returning home from Middle East Conflicts in Iraq and Afghanistan with a history of blast injuries from Improvised Explosive Device (IED's) , Rocket Propelled Grenades (RPGs) and Motar explosions with a history of mTBI/Concussion ,demonstrate that 75-80% of our study population demonstrate a varied degree of atrophy with borderline and mild cerebral atrophy the most prevalent finding. The average age was documented at 31-years and the age ranged from 22-40-years old. Almost all participants were males and less than 0.5% of our study participants were females.

With similar age range from 22 to 40 years of age and an average age of 31-years of our study participants, this draws significant parallelism to the age of Athletes in the National Football League (NFL) who suffer episodes of concussion during their football career. The emergence of CTE as a more recent entity in NFL Players at the end of their career and more recently emphasized to the public with many news media stories but also more recent study from the Boston group emphasizes the need to find a biomarker to monitor NFL players during and at the end of their careers as well as other athletes participating in other sports may give credence also to our preliminary findings with parallelism of CTE. Although Computed Tomography (CT) is still utilized in the field of Medicine as the put through Neuroimaging technique for neurological related symptomatology many studies has shown that MRI is far superior to CT to image detailed anatomy of the brain and other body regions. To our knowledge our preliminary findings is the first to address the usage of routine MRI Imaging to help with the diagnosis and follow up evaluation for patients suffering mTBI/Concussion with implementation for further established protocols to monitor the degree of atrophy as well as the clinical Symptomatology of CTE in NFL Players utilizing routine MRI techniques similarly to our Preliminary study with servicemen and to evaluate for CTE similar to other neurodegenerative diseases.

Mild Traumatic Brain Injury (mTBI), or concussion accounts for approximately 75% of all brain traumatic injuries. This is the 1<sup>st</sup> study to show extensive generalized cortical atrophy on MRI imaging as a hallmark finding with this modality and a possible surrogate imaging marker in patients with mTBI/Concussion. Approximately 10-20-% of mTBI patients continue to experience neurological and psychological symptoms more than 1-year following brain atrophy has long been known to occur after Moderate and Severe head trauma but to date gross brain atrophy has never been reported utilizing Magnetic Resonance Imaging evaluation. This is the 1<sup>st</sup> study to show extensive generalized Cortical Atrophy with mTBI.

### **Cortical Atrophy Evaluation/Methods and Materials**

Axial FLAIR images as well as T2-weighted images were utilized for the evaluation and measurement of the Atrophy. The Central Sulcus was identified on the Axial images of the Controlled Patients with normal appearing brain morphology. Using AGFA Commercial PACS Software Freehand Drawing measurement tools, The Central Sulcus of patients were outlined with the freehand drawing technique with care not to include the cortical gray matter strip of the adjacent pre-and post central cortical gray The T2-weighted and T1-weighted images were not utilized due to averaging anatomical artifacts from the corresponding and adjacent gray matter strip lest the area calculated eliminated overlap with CSF may not fully be approximated. The FLAIR images were utilized due to the significant superior tissue contrast of Gray matter strip-Cerebrospinal fluid-Gray matter strip detailed visualized anatomy appreciated with excellent delineation and transition from cortex to CSF. Normal brain imaging which orientate parallel angulation to the skull base anatomy is utilized as routine alignment for slice acquisition. Slices are acquired from skull base to vertex of the caldarium with approximately 3-4 adequate visualization of the central Sulcus in profile delineated. The vertex of the brain is usually the top visual brain matter anatomy seen but the 2<sup>nd</sup> lower image on the Axial FLAIR acquisition of the Central Sulcus is normally the best sulci anatomy for adequate measurement of the area of the Central Sulcus which gives the maximum demonstration of the anatomy. The most superior brain cortical anatomy was not utilized to decrease overlap artifacts with the CSF in the high vertex sulci as well as due to the slight posteriorly curvature of the postcentral anatomy. On routine MRI imaging acquisition of the Brain, slice acquisition extends from and aligned parallel to the skull base to the vertex of the skull anatomy on MR imaging. Small amount of collection bias may incur if patient is moving then the measurement of the area of both the right and left central sulcus are acquired.

## **Facilities and Leverage**

Rush Medical Center, Chicago Illinois Department of Radiology

University of Illinois, Chicago Illinois Department of Radiology

University of Virginia Medical, Department of Orthopedics ,Charlottesville,VA

**Related Prior Grants:**

None



## **Budget**

Summary budget for the utilization of MRI Imaging at the Facilities listed  
Assistant Researchers.

Salaries

Travel

Administrative cost

Estimated: 2 Million Dollars over 2-years.