Neuroinflammation in Chronic Sports-Related Repetitive Brain Trauma

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Target Audience: Clinicians and scientists interested in sports-related head injury and chronic traumatic encephalopathy.

Purpose: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that is caused, in part, by repetitive brain trauma (RBT) such as those experienced by millions of youth, high school, college, and professional athletes involved in contact sports[1]. CTE is characterized by accumulation of phosphorylated tau protein[2]. Post-mortem studies have shown microglial activation with tau deposition as well as neurodegeneration[3]. Microglial activation has been found to be the source of neurotoxic factors such as reactive oxidative species (ROS). In order to counteract damaging ROS, the brain utilizes glutathione (GSH), a natural anti-oxidant that binds to ROS to neutralize their affect[4]. GSH levels in the brain can be measured using ^{1}H magnetic resonance spectroscopy (MRS) and reductions of GSH in neurological disorders such as multiple sclerosis[5] and schizophrenia[6] have been associated with neuroinflammation. ***Our goal is to measure GSH levels in individuals that are greatest risk for developing CTE: retired National Football League (NFL) athletes with a history of RBT.*** If neuroinflammation plays a role in CTE and brain injury, it could provide a potential new therapeutic target with existing anti-inflammatory treatments that may be effective for this devastating disorder.

Methods: In a prospective study, 75 retired professional NFL athletes with at least 10 years of play including at least two seasons in the NFL in a position with high exposure to RBT (ie linemen, linebackers, defensive backs) and history of symptoms associated with CTE were recruited. From this group, 10 NFL players (ages 58.0 $\pm$ 6.6, range: 46-69 years) were selected prior to analysis to age-matched (ages 57.7 $\pm$ 7.1, range: 45-69 years) to 10 healthy professional athletes such as Major League Baseball, with no history of head injury and neurologically normal. All subjects were scanned in at 3T widebore MRI (Siemens TIM Verio) using a 32 channel head coil. Short-echo single voxel spectroscopy was acquired in the posterior cingulate gyrus (PRESS, TE=35ms, TR=2s, 128 averages, 2x2x2 cm^3) with linewidths < 14 Hz as shown in Figure 1. This region of interest (ROI) was selected on the basis that it has been shown to be sensitive to brain injury[7]. MRS data was then processed offline using linear combination model analysis (LCmodel, Provencher) using a basis set that contains GSH. GSH values were normalized to total creatine (Cr+PCr). Data was tested for normal distribution and paired t-test was conducted to compare the two groups.

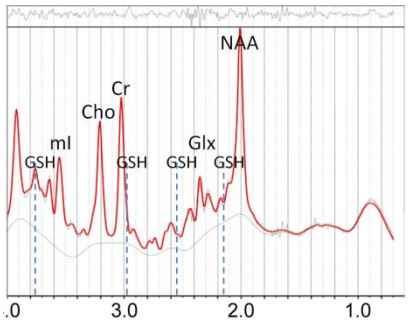

Figure 1. Representative spectrum of an NFL. Metabolites are labeled, GSH positions shown in blue lines.

Results and Discussion: The glutathione levels of the NFL athletes were significantly decreased (p=0.0164) compared to that of the control athletes with no history of repetitive head injury. In all cases except the youngest player, all NFL athletes had lower GSH levels when compared to age-matched controls as shown in Figure 2. There did not appear to be an overall reduction of GSH and therefore reduced GSH could not be attributed to age alone. There is the possibility that normalizing to creatine may influence the results given studies that have shown increased Cr in subacute mild brain injury which recovered after time[8]. In this chronic stage of injury, residual increased Cr is not likely however ongoing studies will clarify this possibility.

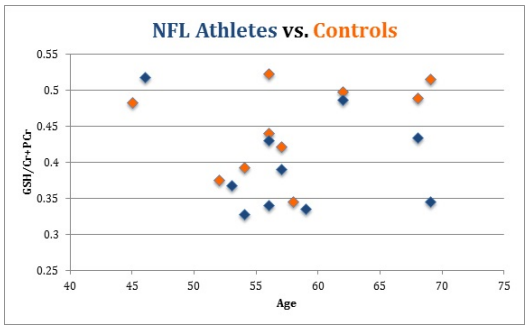

Figure 2. Scatterplot of GSH and Age. NFL subjects are shown in blue. Controls are shown in yellow.

Conclusion: We demonstrate for the first time reductions in GSH in chronic sports-related head injury in professional athletes at greatest risk for developing CTE. These results provide the possibility of novel treatment pathways which can then be monitored non-invasively using MRS.

References: 1) Goldstein et al. Sci Transl Med 2012; 4:134-60 **2)** Baugh et al. Brain Imag Behav 2012;6:244-54 **3)** Ojo et al. J Neuropathol Exp Neurol 2013;72-137-51 **4)** Lull and Block. Neurotx 2010;7:354-65 **5)** Srinivasan et al. MRI 2010;28:163-70 **6)** Do et al. Eur J Neurosci 2000;12:3721-8 **7)** Lin et al Brain Imag Behav 2012;6:208-23 **8)** Yeo et al. J Neurotrauma 2011; 28:1-11.