GABA alterations in pediatric sport concussion

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ABSTRACT

Objective: To evaluate whether frontal-lobe magnetic resonance spectroscopy measures of γ -aminobutyric acid (GABA) would be altered in a sample of adolescents scanned after sport concussion because mild traumatic brain injury is often associated with working memory problems.

Methods: Eleven adolescents (age 14–17 years) who had sustained a first-time sport concussion were studied with MRI/magnetic resonance spectroscopy within 23 to 44 days after injury (mean 30.4 ± 6.1 days). Age- and sex-matched healthy controls, being seen for sports-related injuries not involving the head and with no history of concussion, were also examined. GABA/creatine + phosphocreatine (Cre) was measured in left-sided frontal lobe and central posterior cingulate regions. The frontal voxel was positioned to overlap with patient-specific activation on a 1-back working memory task.

Results: Increased GABA/Cre was shown in the frontal lobe for the concussed group. A decreased relationship was observed in the parietal region. High correlations between GABA/Cre and task activation were observed for the control group in the frontal lobe, a relationship not shown in the concussed participants.

Conclusions: GABA/Cre appears increased in a region colocalized with working memory task activation after sport concussion. Further work extending these results in larger samples and at time points across the injury episode will aid in refining the clinical significance of these observations.

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GLOSSARY

Cre = creatine + phosphocreatine; **DTI** = diffusion tensor imaging; **GABA** = γ -aminobutyric acid; **MRS** = magnetic resonance spectroscopy; **TE** = echo time; **TR** = repetition time.

Traumatic brain injury has been the subject of extensive MRI study over the past 20 years. While much of this work has focused on moderate and severe injury as defined by Glasgow Coma Scale score on admission, a growing literature focuses on milder traumatic brain injury defined as Glasgow Coma Scale score >13 to 15 with no loss of consciousness caused by sport mechanisms.¹ Indeed, many new studies now focus on the most mild spectrum of injury, often called exposure.² In sport terms, this is defined as the potential, counted, or measured head blows (e.g., football participation, soccer heading, sensor triggering) without necessitating a diagnosis of concussion.³ Although this injury category of risk represents the goal state for defining injury at its subtlest manifestation, the potential for outliers driving generalizations⁴ and whether head injury rotational mechanics can be adequately quantified via sensor technologies⁵ remain work for further optimization.

Commonly used imaging techniques of brain injury focus on structural or connectivity measures⁶ and task-based fMRI used to look at known vulnerable systems such as working memory.⁷ A growing body of literature outside traumatic injury aims to integrate fMRI and neurotransmitter results, with a focus on γ -aminobutyric acid (GABA) because of its measurement specificity. To evaluate the utility of this measure in children diagnosed with concussion and having

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persistent symptoms at clinic visit, we enrolled a pilot cohort of children with concussion compared with age- and sex-matched healthy controls.

METHODS Participants were recruited from patients seen at the Seattle Children's Hospital Sports Concussion Program and diagnosed according to the 2012 Zurich consensus statement.⁸ Healthy controls were recruited from the Seattle Children's Hospital Sports Medicine program.

Recruitment. One hundred eighty children were screened at clinic visits for inclusion in this study. Twenty-three were enrolled, with MRI data collected on 11 concussed children with persisting symptoms (5 male, 6 female, all right-handed, age 15.2 ± 1.2 years) and 11 healthy controls matched for age and sex who had sport-related injuries not involving the head and no history of concussion (age 15.2 ± 1.2 years, 2 left-handed). The sport activities related to injury for those participants enrolled in the concussion group were as follows: physical education (2), weight lifting (1), football (1), soccer (4), lacrosse (1), ultimate Frisbee (1), and skateboarding (1). Symptoms were assessed at the clinic visit with the Sport Concussion Assessment Tool 3 <http://bjsm.bmj.com/content/47/5/259> with chart notes also reviewed. Neuropsychological testing at the time of MRI (Wechsler Intelligence Scale for Children, Processing Speed, Digit Span, Delis-Kaplan Executive Function System, Symbol Digit Modalities Test) was an optional component of this single-time point study with 6 concussed and 9 control children volunteering for testing.

Standard protocol approvals, registrations, and patient consents. Informed consent for all participants and parents was obtained in accordance with the protocol approved by the Seattle Children's Hospital Institutional Review Board.

MRI study. Participants underwent a single imaging session on a Siemens 3T PRISMA scanner (Siemens, Erlangen, Germany) using a 64-channel head coil. Structural imaging included 3-plane localizers, a high-resolution sagittal T1 magnetization-prepared rapid gradient echo (512×512 matrix, echo time [TE] 3.5 milliseconds, repetition time [TR] 1,650 milliseconds, isotropic 1-mm resolution, 160 slices), axial susceptibility-weighted imaging (672×768 , TE 20 milliseconds, TR 28 milliseconds, 1.6-mm thickness yielding phase and magnitude maps), field map (64×64 matrix, TE 5.2/7.7 milliseconds, TR 488 milliseconds, 3-mm thickness), and axial diffusion tensor imaging (DTI) scan (b value 1000, 10 directions, field of view 230, slice thickness 3 mm, 44 slices; matrix = 128×128 , TE = 65 milliseconds, TR = 4,600 milliseconds). Next, an axial fMRI acquisition (64×64 matrix, TE = 30 milliseconds, TR = 3,000 milliseconds, 45 interleaved slices, 80 acquisitions) was performed with a working memory 1-back task with items (upper and lower case letters) presented at a rate of 2 seconds on a liquid-crystal display screen that was visible via a mirror mounted on a head coil. Left frontal lobe activation was identified from activation vs rest blocks (30 seconds) with maps generated in real time. Participants responded to the task via button press with the right hand denoting correct or incorrect response. These responses and latencies were written to a text file for offline analyses.

Two spectroscopy acquisitions followed fMRI: one localized in left frontal lobe as guided by the activation map generated from the working memory task and displayed on the scanner, and another placed in the central posterior cingulate cortex. Both acquisitions used MEGA-PRESS (Siemens Medical Systems, Malvern, PA) with a $3 \times 3 \times 3$ -cm voxel, TE of 68 milliseconds (with and without frequency selection), TR of 2,000

milliseconds, and 128 averages. Lastly, resting-state fMRI with eyes open was collected at slice positions similar to the task-based scan and slightly varying parameters (TE 27 milliseconds, TR 2,000 milliseconds, 33 interleaved slices, 192 acquisitions).

Analyses. MRIs were reviewed clinically by the study radiologist (D.W.S.). Automated processing of MEGA-PRESS data was done by Gannet.⁹ Magnetic resonance spectroscopy (MRS) data with off-resonance editing were processed in LCModel¹⁰ to generate non-GABA metabolite estimates. To measure the gray/white ratio underlying each measurement, T1 images were segmented in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>; UCL, London, UK) and masked by the spectral voxel location extracted from the raw spectral file with MATLAB (Mathworks, Natick, MA). Automated summation of pixels for each tissue class yielded gray/white ratio data. These masks were also multiplied by fMRI working memory activation maps and summarized to yield measures of median activation. DTI data were analyzed in batch in FSL (<http://fsl.fmrib.ox.ac.uk/>), and resting-state FMRI data were analyzed with CONN (<https://www.nitrc.org/projects/conn/>) as per our prior work.^{11,12}

Statistics. Paired parametric statistics were compared for GABA/creatine + phosphocreatine (Cre), gray/white fraction, and task performance. Regression analyses were performed to compare the association between GABA and median voxel fMRI task activation. Output maps from FSL (DTI) and CONN (resting fMRI) were examined for significant effects at $p < 0.05$ corrected for multiple comparisons without a priori masking. Exploratory analyses were performed for other MRS metabolites and neuropsychological testing data.

RESULTS One control had missing data because of claustrophobia, precluding MRI scanning, and 1 had missing latency performance data as a result of computer malfunction. One concussed patient's data were excluded because of motion artifact on MRI data and MRS failure. This yielded 10 (5 male, 5 female) participants per group. The clinic visit occurred 12 ± 8 days (minimum = 2, maximum = 28) after injury, with Sport Concussion Assessment Tool 3 symptoms ranging from 10 to 88 (mean 48 ± 25 , maximum = 132). Symptoms described in the chart notes for the concussed group were headaches (10 of 10), feeling in a fog (6 of 10), difficulty concentrating (9 of 10), confusion (6 of 10), and fatigue (8 of 10). MRI examination occurred at a mean of 18 days (SD 7, minimum 8, maximum 29 days) after the clinic visit. Measured from the date of injury, MRIs occurred for the group at a group recovery time point of ≈ 1 month (mean 30.4 ± 6.1 , minimum = 23, maximum = 44 days).

MRI study. No structural abnormalities, including any suggestive of traumatic brain injury (e.g., diffusion alterations, punctate hemorrhage, gliosis), were observed on the structural imaging scans.

During the fMRI working memory scan, task percent correct and latency of response did not differ between groups (table). For spectroscopy data, no statistical differences were observed for Gannet fit error or gray/white voxel fractions by anatomic

Table Means of GABA/Cre measures, gray/white fractions, and percent correct/latency of the 1-back task

Measure	Concussed		Healthy controls		Statistics	
	Mean	SD	Mean	SD	t	p
Frontal						
GABA/Cre	0.086	0.01	0.078	0.008	2.501	0.034
Fit error	10.065	1.678	11.19	1.650	-1.552	0.155
Gray/white	0.429	0.086	0.413	0.054	0.508	0.624
Cingulate						
GABA/Cre	0.091	0.009	0.097	0.005	-2.095	0.066
Fit error	9.340	1.106	9.770	1.146	-0.729	0.485
Gray/white	0.651	0.037	0.651	0.04	-0.038	0.97
Task						
Correct, %	0.958	0.022	0.942	0.042	1.018	0.342
Latency, ms	696.870	113.835	791.271	145.329	-1.534	0.169

Abbreviation: Cre = creatine + phosphocreatine; GABA = γ -aminobutyric acid.

location. Analyses of GABA/Cre in the frontal lobe demonstrated increases for the concussed group compared to healthy controls (table and figure 1). In contrast, the parietal cingulate cortex voxel showed decreased values in the concussion sample but not below the threshold of $p < 0.05$. Frontal lobe regression comparing group $\times$ GABA/Cre and fMRI median activation measures demonstrated an interaction ($\beta = 4.96$, $t = 2.74$, $p = 0.015$), with concordance between the control data ($t = 3.35$, $p = 0.010$) but not the concussed patients ($t = -0.28$, $p = \text{ns}$). Plots with correlation coefficients are shown in figure 2.

Exploratory analyses of choline-containing compounds, *N*-acetylaspartate, or glutamate referenced to Cre in the off-resonance spectrum demonstrated no differences for any metabolite by group (all $t < 1.18$ and > -1.4 , $p > 0.2$). A similar lack of group

differences was shown for the DTI data (measures of fractional anisotropy and mean diffusivity) by tract-based spatial statistics in FSL, resting-state fMRI connectivity matrices in CONN, and neuropsychological test scores in the subgroups receiving testing (all $p > 0.05$ corrected for multiple comparisons).

DISCUSSION In this pilot sample of teenagers with first-time concussions and persisting symptoms, frontal lobe GABA levels were elevated 1 month after injury. Supportive of this finding, the normally consistent relationship between GABA and working memory fMRI activation seen in the control group was disrupted. In contrast, decreased GABA was seen in medial parietal areas for the concussed group, a system that has broad functional implications for connectivity. Ascribing a theoretical basis to the direction of change is challenging. What we are seeing

Figure 1 GABA in frontal lobe

(A) Gannet output showing edited spectrum and (B) fitted GABA peak. (C) Concussed participants demonstrated elevated GABA/Cre ratio in frontal lobe as shown on the right. Cre = creatine + phosphocreatine; GABA = γ -aminobutyric acid.

Figure 2 GABA vs fMRI

Plot comparing GABA/Cr and median activation in the frontal voxel for healthy controls (open circles) and concussed participants (solid circles) with linear terms plotted. High concordance is shown between measures in the healthy controls but not for the concussed group. Descriptive examination of concussed individuals who seem to have become shifted off the control regression line did not reveal clear descriptive differences in injury type, location, or severity that would explain the results. Cr = creatine + phosphocreatine; GABA = γ -aminobutyric acid.

at this single postacute time point could be directly related to injury, recovery (a responsive change), or a mixture thereof, none of which can be discriminated without further longitudinal data. In terms of clinical relevance, GABA/Cr alterations after concussion could help to measure the arc of injury and recovery. Evaluating such measures in the context of “return to learn,” cognitive rest, or symptom resolution will be exciting avenues to explore in future work.

GABA is the major inhibitory neurotransmitter and is an important factor in both normal cognitive function and the sequelae of traumatic brain injury.¹³ While spectroscopy has now been widely applied in traumatic brain injury, primarily to look for markers of neuronal loss before the development of DTI¹⁴ (for review, see reference 15), to the best of our knowledge, no study to date has evaluated changes in GABA. Relative to structural markers of injury (e.g., *N*-acetylaspartate and choline-containing compounds¹⁶), GABA is unique in that levels have been shown to be associated with cognitive functioning. For example, correlation of magnetoencephalography measures of gamma band activity (likely mediated by GABA¹⁷), fMRI, and GABA was demonstrated in the visual cortex in response to a visual discrimination tasks.^{18,19} Similar findings have been found for motor control and GABA in the supplementary motor area,²⁰ tactile discrimination and GABA in the sensorimotor cortex,²¹ and gaze shifting and GABA levels in the frontal eye fields.²² In 2 of these studies, control regions, chosen to assess cortical GABA levels remote

from the site of interest, demonstrated no concordance to performance.^{21,22} Although GABA level changes do not incorporate measurement of other factors (e.g., receptor density changes, enzyme alterations), the concordance between GABA and discrete task performance supports the need to evaluate this biomarker in conditions in which structural changes may be difficult to characterize.

Evidence on a cellular level also supports that GABA may be a particularly important marker of injury and recovery in concussion. Alterations in GABA, especially GABA transport, have been seen in trauma models, both fluid percussion injury²³ and shear injury to the developing brain.²⁴ GABA-mediated inhibition can increase after injury such as stroke in response to transport and receptor dysregulation, and the corresponding increase in tonic inhibition may be deleterious to recovery from injury.²⁵ Intervention, by pharmacologic inhibition of specific GABA subunits, improved motor function recovery in an animal model.²⁵ This is a proposed mechanism for impaired recovery after cortical injury, with pharmacologic interventions potentially available to reverse this process.²⁶ GABA changes may alter postconcussive motor plasticity.²⁷ However, excessive impairment in GABA can also lead to deleterious effects such as seizures, and the understanding of the complexities of GABA after injury is critical to guiding future interventions.²⁸ It is plausible that our finding of elevated GABA is imaging evidence of changes known to occur with cellular injury.^{23,24,28} The selective change in the frontal lobe would be

consistent with the increased vulnerability of this region to traumatic injury.

The potential that GABA provides a protective effect or corresponds to the postconcussive cognitive symptoms or impairment often observed remains unresolved from this work. While no child in the study was experiencing headaches that would be classified as migraines, literature supporting GABA elevations in this condition provides interesting fodder for consideration.²⁹ If elevated GABA occurs as a byproduct of injury, it could be envisioned to influence local activity. In general, elevated GABA is associated with improved tuning and performance, suggesting that GABA elevation could be the result of recovery attempts or possibly increased cognitive effort to perform the task as well as healthy controls. Somewhat concordant with this idea, increased activation in the frontal lobe has been described after injury or in impaired states.³⁰ The correlation between GABA and fMRI activation has been studied,^{21,31–33} with how well abnormal tissue fits these associations not known. Our GABA voxels included areas outside the strongest activation, but we did find a GABA/fMRI ratio in the frontal lobe that was consistent across the healthy control sample and much higher, and varied, in the concussion group. Elevated GABA was not seen in the other area studied, the medial parietal lobe. Thus, there is some selectivity to the GABA elevation, suggesting that it is related to the function of this brain region or perhaps the task load being applied. This seems possible but, without differences in behavioral performance between groups, premature to conclude. Whether the GABA elevation is causal or only indirectly associated with postconcussive symptoms, it may provide an objective measure for following disease progression and offering a target for modulation.

AUTHOR CONTRIBUTIONS

Seth D. Friedman: designed and conceptualized the study, performed data collection and analyses, wrote the manuscript. Andrew V. Poliakov: set up the fMRI task, oversaw data collection, analyzed DTI and fMRI data, participated in writing the manuscript. Christopher Budech: oversaw patient evaluation by MRI/MRS and neuropsychological testing, contributed to manuscript editing. Dennis W.W. Shaw: evaluated images for trauma features, participated in manuscript editing. David Breiger: oversaw neuropsychological evaluation and related analyses integrated into manuscript. Thomas Jingui: oversaw enrollment, criteria for inclusion, manuscript drafting. Brian Krabak: participated in study enrollment, revision of manuscript. David Coppel: oversaw neuropsychological evaluation and related analyses, helped to revise final manuscript. Tressa Mattioli Lewis: responsible for patient enrollment, inclusion criteria revision, paper editing. Samuel Browd: participated in clinical oversight and general oversight of study activities. Jeffrey G. Ojemann: designed and conceptualized the study, performed critical interpretation of data, and wrote the manuscript.

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DISCLOSURE

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DISCLAIMER

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