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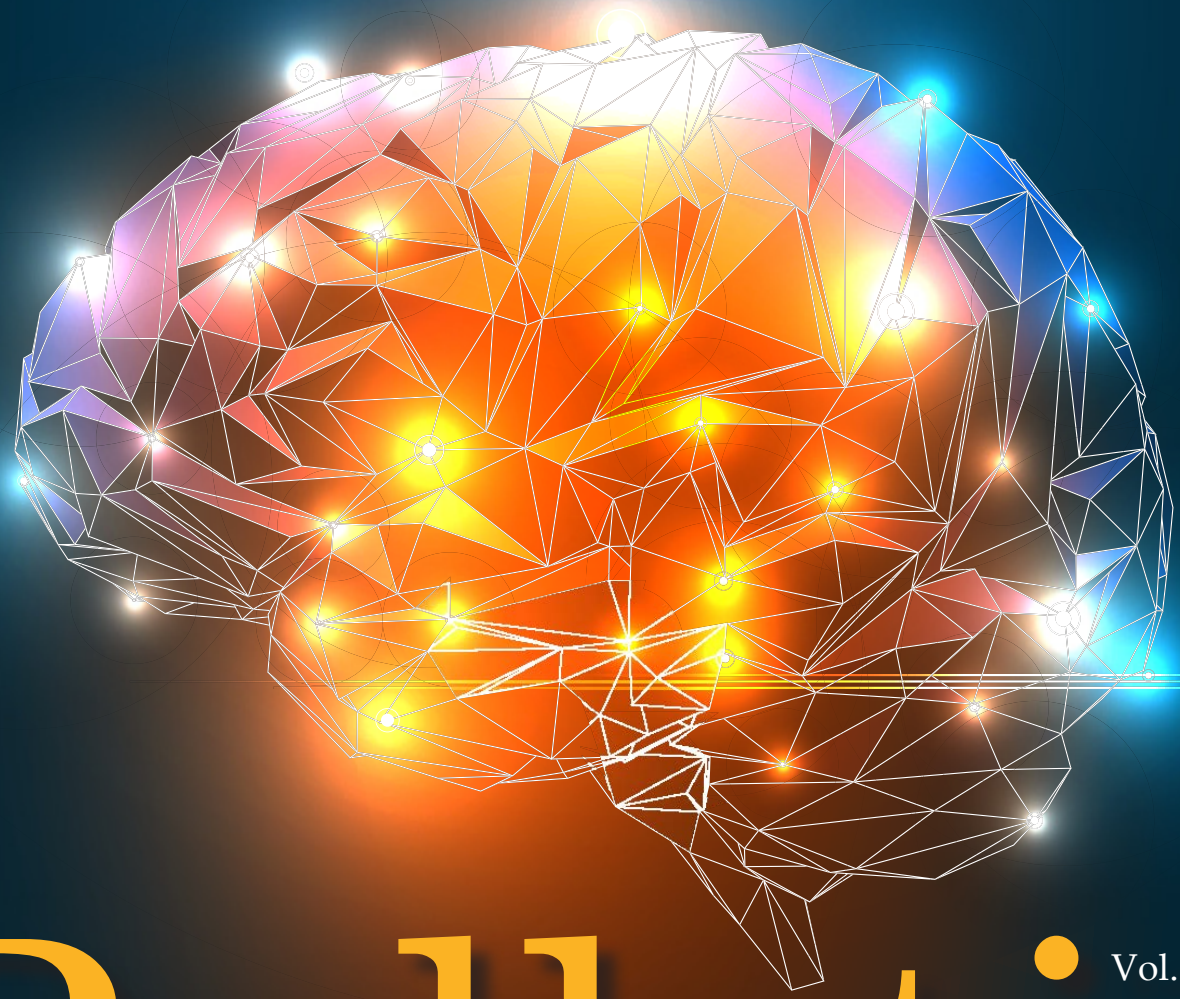

Bulletin

Vol. 31 No. 2

Student Corner

- *My Experience as a Graduate Student Focusing on Neuropsychology in Sports Concussion*

Journal Section

- *Synopsis and Review of "Sandbagging on the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) in a High School Athlete Population" from* Archives of Clinical Neuropsychology

Professional Issues

- *Sex Differences in Sports-Related Concussion: A Brief Review*
- *The Role of Genetic Factors in Recovery & Outcome Following Sports-Related Concussion*
- *Assessment and Impact of Depression in Sports Concussion Evaluations*
- *Post-Traumatic Migraine Following Concussion: The Benefit of Regulation versus Rest*
- *Chronic Traumatic Encephalopathy: A Long-Term Consequence of Repetitive Head Impacts*

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2017 Award Recipients

Distinguished Lifetime Contribution to Neuropsychology
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Jennifer M. Morgan, Psy.D.

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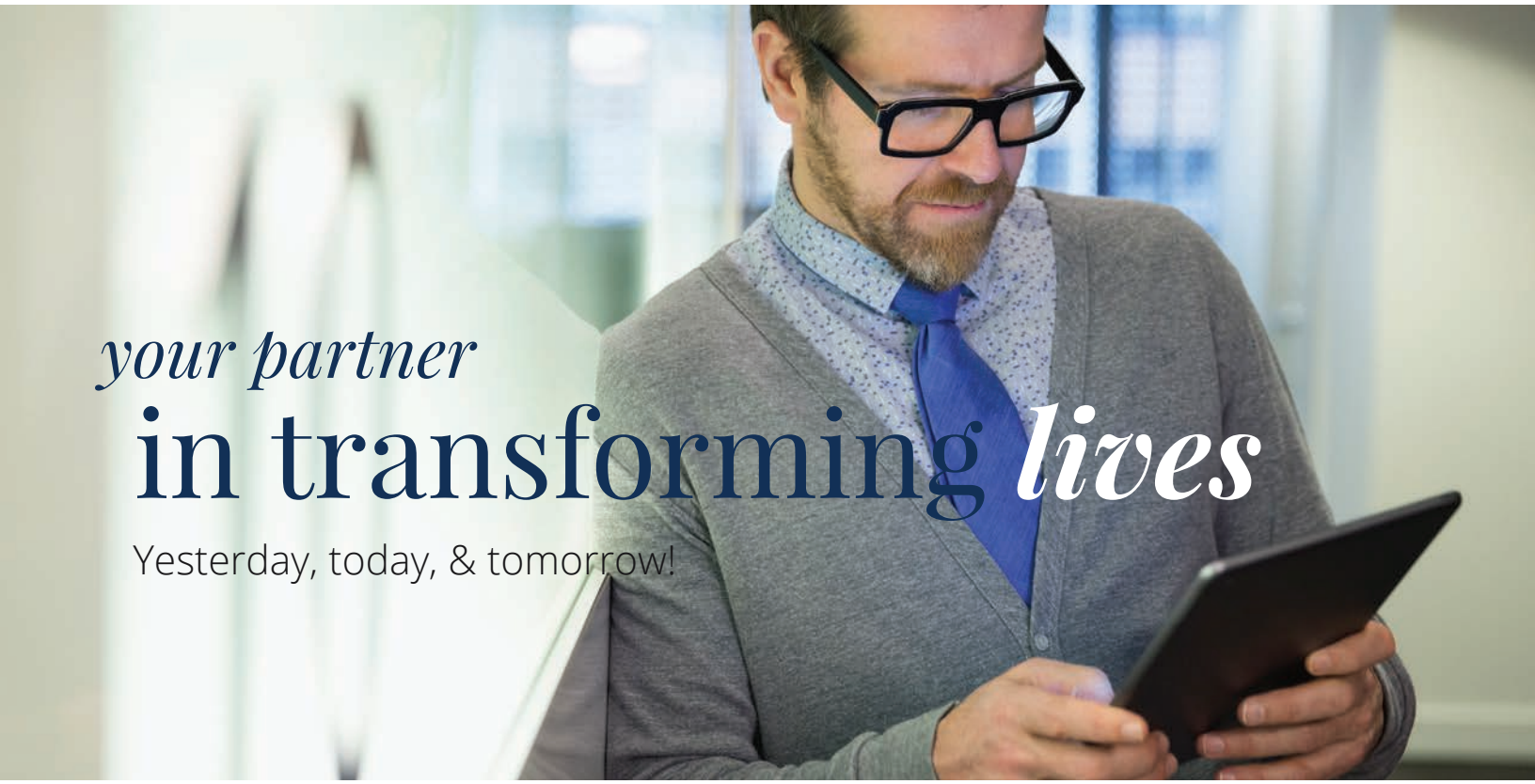
Ralph M. Reitan Award for Clinical Excellence
Ronald M. Ruff, Ph.D.

Outstanding Dissertation Award
Victoria C. Merritt
The Influence of The Apolipoprotein E (Apoe) Gene on Neuropsychological Outcome Following Sports-Related Concussion

Nelson Butters Award for Research Contributions to Clinical Neuropsychology
Karra Harrington
Using Robust Normative Data to Investigate the Neuropsychology of Cognitive Aging

Federation of Associations in Behavioral and Brain Sciences (FABBS) Early Career Impact Award
Ozioma C. Okonkwo, Ph.D.



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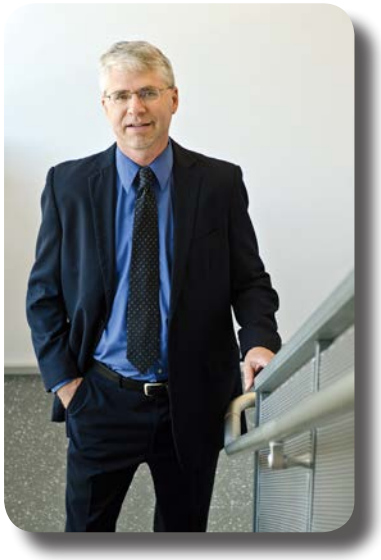
Editor's Corner



Peter Arnett, Ph.D.,
NAN Bulletin Editor

As the Editor of the *NAN Bulletin*, I am delighted share our latest issue with you, where we focus on sports-related concussion. Sports-related concussion has garnered tremendous interest in the popular media of late, especially regarding some recent findings on repetitive head impacts in American Football associated with Chronic Traumatic Encephalopathy (CTE). Of greater significance for readers of the *Bulletin*, clinical neuropsychologists have played an increasingly important role in the sports concussion landscape. I first began studying sports concussion in earnest in the early 2000s, after taking over the management of the Penn State Neuropsychology of Sports Concussion Program that was initially developed by Drs. Ruben Echemendia and Margot Putukian in the 1990s. So the focus of our current issue is of particular interest to me. We have much to offer you in this issue to help update your knowledge of some core issues in the neuropsychology of sports concussion.

In the Professional Issues section of this *Bulletin*, there are five articles that address core issues of interest in sports-related concussion. Tracey Covassin and her colleagues start out this section with a brief review of the current status of our knowledge of sex differences in sports-related concussion. Victoria Merritt and Nicole Evangelista follow this with an incisive review of some recent data on genetic factors that may predict recovery and outcome following sports-related concussion. Two of my current students (Erin Guty and Megan Bradson) and I then discuss the importance of assessing depression in sports concussion evaluations, and provide some guidelines for how this could be done clinically. Melissa Womble and Micky Collins then provide a succinct and compelling discussion about the benefits of regulation versus rest in addressing post-traumatic migraine following concussion. Finally, Michael Alosco, Megan Mariani, and Robert Stern provide a timely review of CTE, offering an even-handed discussion of a topic that is often sensationalized in the popular media.

The Student Corner section of the *Bulletin* includes a discussion by Erin Guty, a graduate student who currently works as the coordinator of the neuropsychology of sports concussion program at Penn State. She provides some telling insights about what it is like to run this program, and discusses how her research interests in sports concussion evolved out of her clinical work. Finally, John Randolph provides an astute review of a recent *Archives of Clinical Neuropsychology* article by Higgins and colleagues focusing on sandbagging performance on the ImPACT.

Of note, Dr. John Randolph has continued to serve as Associate Editor of the *Bulletin*, and was instrumental in working with me on completing this issue. We also appreciate the continued help from the members of the NAN Publications Committee, especially the chair of this committee, Dr. Lee Ashendorf, who provided valuable input on the contributions to this issue.

Peter Arnett, Ph.D.
Professor & Director of the Neuropsychology of Sports Concussion and MS Programs at Penn State University
NAN Bulletin Editor

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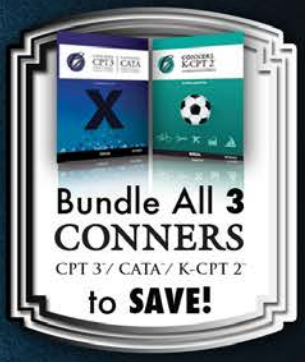

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Student Corner

My Experience as a Graduate Student Focusing on Neuropsychology in Sports Concussion

Erin Guty, M.S.
Penn State University

Starting in my second year of graduate school, I took over the role of Coordinator for Penn State's Sports Concussion Program within the clinical psychology department. The program is headed by my advisor, Dr. Peter Arnett, and it serves the majority of athletes who are competing in varsity sports at Penn State and involves both baseline and post-concussion neuropsychological testing. Dr. Arnett and I interpret the results of post-concussion testing and provide a written report with recommendations that team physicians and trainers can use when making return to play decisions. As the program's coordinator, one of my roles is to schedule sessions with the athletes who are referred by their trainers for testing. Another responsibility is ensuring that our undergraduate research assistants are thoroughly trained on our testing battery so that they can perform baseline tests. Athletes are often referred to receive baseline testing when they have specific characteristics that may make any potential post-concussion data difficult to compare to a normative sample. Such characteristics can include history of ADHD or a learning disability or a history of multiple head injuries.

The fact that our program allows for well-trained undergraduates to complete baseline neuropsychological testing provides a unique opportunity for our students who in many labs would find their research experience restricted to data entry and management. While that is a critical piece of a research assistant's role, many of our undergraduates have ambitions of going to graduate school, so this additional testing experience is quite valuable to them. Because of this, coordinating the Sports Concussion Program has also provided me with an opportunity for mentorship. By participating in multiple steps in the data collection process, including performing neuropsychological testing, our undergraduates often have more exposure to the data and it allows them to better formulate their own research questions and ideas. It's a privilege to be able to work closely with our research assistants and guide them as they begin the process of becoming independent researchers.

It was through my own experience of testing athletes post-concussion, scoring and interpreting their results, and writing related reports that I was able to further my own research questions. Often concussions present non-uniformly, with individuals reporting different symptoms and demonstrating varying functioning afterwards. A common measure of symptoms following concussion is the Post-Concussion Symptom Scale (PCSS), which is a self-report measure of symptomatology[1]. Previous work in our lab explored the PCSS using factor analysis and demonstrated that symptoms from this scale cluster together into four specific factors: cognitive, sleep, affective, and physical[2].

After having experience working with these athletes and observing the variable ways in which concussion can produce symptoms and affect cognitive functioning, I began to wonder whether these distinct symptom clusters could explain some of the functional variability that is observed following concussion. These questions gave rise to my Master's thesis project which explored how specific symptom types may be differentially related to cognitive performance and impairment on neuropsychological tests. Previous research has explored the effect of overall symptom reporting on cognitive functioning following concussion with the general consensus that more symptoms are related to poorer cognitive outcomes. However, whether specific types of symptoms were mainly driving that effect was a relatively unexplored topic. It was also unknown whether specific symptom types differentially affected specific domains of cognition such as memory or attention and processing speed. My master's project aims to shed some light on these questions, and this research is due in part to working face-to-face with the athletes who are affected by concussion. My interactions with the athletes is one of reasons that my research questions relate back to clinical relevance as I see this as integrally involved in my training as a clinical doctoral student. For this particular study, I see pinpointing any "heavy hitting" symptoms as a potential way of better identifying athletes who may be most at risk for other negative outcomes such as cognitive dysfunction. This could then inform treatment recommendations as well as academic accommodations that may be necessary for student-athletes who need to be back in playing shape both in the field and in the classroom.

Working in a sports concussion lab has provided me with a unique experience that integrates both clinical skill and research. My interaction with the athletes is often in a clinical role, providing evaluation and recommendations after injury. I then can use the data that are collected to answer questions that will further clarify how we assess and treat individuals with these neuropsychological difficulties. I view my work on sports concussion as a focus that highlights a strength of clinical psychology, particularly how our clinical practice and research work in tandem to advance science.

Erin Guty is currently a 3rd year doctoral student in The Pennsylvania State University's clinical psychology program. She is interested in cognitive and emotional functioning following damage to the brain and how research can allow neuropsychologists to better utilize assessments for informing interventions and treatment. She is currently involved in projects focused on assessments for both sports-related concussion and multiple sclerosis populations.

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2. Merritt, V. C., & Arnett, P. A. (2014). Premorbid predictors of postconcussion symptoms in collegiate athletes. *Journal of Clinical and Experimental Neuropsychology*.

2017 Student Poster Award Recipients

Ted Blau Student Poster Award ($500)
Amy Werry
Normal Neuropsychological Test Performance for Spanish Speaking Hispanic and Matched White Older Adults

Student Poster Awards ($100)
Madison Niermeyer
Reported Expressive Suppression in Daily Life is Related to Lower Executive Functioning and Slower Action Planning Among Older Adults

Jessica Saurman
Reliable Change on the RBANS: A Meta-Analysis

Emily Smith
Detection of MCI in African Americans Using the Montreal Cognitive Assessment (MoCA)

Rosemary Valdivia
Cortical Thickness Changes Associated with Failure to Recover from Proactive Semantic Interference as a Prognostic Factor of Mild Cognitive Impairment

Brittni Morgan
The Relationship of Urgency to Impulsive Decision-Making During Heightened Affective States in Problem Drinkers

Student Diversity Poster Award ($100)
Alejandra Morlett Paredes
Rey-Osterrieth Complex Figure: Normative Data for an Illiterate Adult Population from 5 Latin American Countries
Symbol Digit Modalities Test: Normative Data for an Illiterate Adult Population from 5 Latin American Countries
Brief Test of Attention: Normative Data for an Illiterate Adult Population from 5 Latin American Countries

Journal Section

Synopsis and review of: Higgins, Denny, & Maerlender (2017). Sandbagging on the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) in a high school athlete population. Archives of Clinical Neuropsychology, 32, 259-266.

Review by John Randolph, Ph.D., ABPP
Geisel School of Medicine at Dartmouth

Study Rationale:

Neuropsychologists working with athletes at any level have likely had considerable exposure to the computerized ImPACT measure. A common concern when interpreting ImPACT scores is whether an athlete has "sandbagged" their baseline evaluation, i.e., intentionally put forth insufficient effort. Such a strategy may increase the likelihood of clearing an athlete to return to play, even if he/she has not shown full cognitive and neurological recovery, given that a reduced post-concussion ImPACT score could still look stronger than a sandbagged baseline score. Since athletes are typically compared to their own baselines rather than normative standards, there is significant risk of misinterpreting ImPACT findings if sandbagging is not taken into account. A related concern, as Higgins et al. note, is that many athletic trainers do not assess the validity of baseline ImPACT scores. Further, prior work has found that some students who have previously taken the ImPACT can effectively sandbag their scores without being detected by built-in validity indicators.

Overarching Goal:

The authors sought to expand prior work by examining the issue of baseline ImPACT score validity in a sample of high school athletes. In their simulation paradigm, they asked athletes to engage in two forms of effort: 1) intentionally sandbagging their baseline scores, and 2) putting forth their best effort. The authors posited that performance across conditions would differ significantly, some ImPACT subtest scores would demonstrate higher classification accuracy than others, and a composite validity score would show the highest classification accuracy.

Methods:

54 high school athlete participants were retained for study analyses; 12 athletes were excluded for various reasons (including being ImPACT naïve and showing poor effort in the "best effort" condition). Participants were almost exclusively white, and a majority were male high school sophomores or juniors. Participants were from high schools in the rural Midwest. 50% of athletes were football players, followed by basketball, volleyball, and softball players. Participants were administered the ImPACT in a group setting under two counterbalanced conditions, corresponding to instructions to put forth their best effort and to provide suboptimal effort.

Results:

Significant differences were found between all ImPACT composite scores, with participant scores from the high effort condition being better than those in the simulated poor effort condition. Subtest scores generally followed the same pattern, with the exception of a few indicators from the Symbol Match subtest. The authors then created a logistic regression equation that comprised four ImPACT variables (Word Memory Learning and Delayed Memory; Design Memory Total; X's and O's Total Correct), which accurately classified 99.7% of participants' level of effort.

Conclusions:

In this simulation study, the authors derived a regression equation that successfully predicted poor effort on the ImPACT in high school athletes previously exposed to this test. They noted that their equation needs to be independently cross-validated before applying it clinically, particularly given that their sample was restricted to mostly white athletes from small towns in the Midwest without a diagnosed cognitive disorder. They also qualified their findings by indicating that generalizability to student athletes with learning or attentional disorders may not be appropriate. While this research is at an early stage, it shows promising potential future applications in high school and perhaps other athletes who undergo computerized neurocognitive testing as part of their athletic programs.

Dr. John Randolph is a board-certified clinical neuropsychologist in independent practice and Adjunct Assistant Professor of Psychiatry at the Geisel School of Medicine at Dartmouth. He earned his Ph.D. in Clinical Psychology (Neuropsychology specialization) from Washington State University, and completed clinical and research fellowships in Neuropsychology and Neuroimaging at the Geisel School of Medicine at Dartmouth. His research has focused on metacognition, executive functioning, cognitive and neuroimaging aspects of multiple sclerosis, and contributors to cognitive health, and he has received grant funding from the National MS Society and NIH. He is Past President of the New Hampshire Psychological Association, a National Academy of Neuropsychology Fellow, past recipient of the NAN Early Career Service Award, and editor of the recent book, *Positive Neuropsychology: Evidence-Based Perspectives on Promoting Cognitive Health.*

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- Neuroimaging for Neuropsychologists
- Neuropsychological Assessment of Hispanics Residing in the US: Ingles, Español o dos? (English, Spanish or both?)
- Sleep, Cognition and Affect: Sleep Disorders for the Neuropsychologist
- Memory Loss, Alzheimer's Disease, & Dementia: Update 2013
- Introduction to Sports Neuropsychology

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Professional Issues

Sex Differences in Sports-Related Concussion: A Brief Review

Tracey Covassin, Kyle M. Petit, Jennifer L. Savage, Abigail C. Bretzin, Morgan N. Anderson
Michigan State University, Department of Kinesiology

Epidemiology of Sports-Related Concussion

In 1972, the United States implemented Title IX as part of the Equality in Education Act. As a result, female sports participation increased dramatically, as did sports-related concussions (SRC). Numerous studies have suggested that female high school and collegiate athletes participating in comparable sports have a higher injury rate than their male counterparts.[13, 17] Specifically, female SRC injury rates are higher in soccer, basketball and softball compared to male athletes participating in the same sports. Female soccer and basketball athletes at both the high school and collegiate levels are over 1.5 times more likely to sustain a SRC compared to male soccer and basketball athletes (see Table 1). Softball high school and collegiate athletes are almost 4 times more likely to incur a SRC compared to baseball athletes. Lacrosse, on the other hand, has shown mixed results in terms of risk for SRC. Male high school lacrosse athletes are at a greater risk for a SRC compared to female high school lacrosse athletes;[13] however, female collegiate athletes are at an increased risk for a SRC when compared male collegiate lacrosse athletes.[17]

Female athletes may be at greater risk for a SRC due to having less neck strength and smaller girth, which possibly results in female athletes having increased angular acceleration at the head.[2] This increase in angular acceleration is what researchers believe may be a predisposing factor for greater SRC.[2] Due to the majority of females participating in non-contact sports, female athletes tend to incur their SRC with surface or ball contact, while male athletes tend to sustain their SRC from contact with another player.[4] Finally, we cannot overlook the fact that males may just "play through pain" and hide their symptoms. Former collegiate male athletes were 3 times more likely to not disclose their SRC compared to female collegiate athletes.[9] Therefore, this increase in female athletes risk for SRC may also be due to an increase in disclosure to a healthcare provider.

Sports-Related Concussion Outcomes

It is not unusual for male and female athletes to present with different signs and symptoms following a SRC. Female athletes have an increase in drowsiness, sensitivity to noise, pressure in the head, feeling slowed down, difficulty concentrating, feeling more emotional and irritable; while males tend to report a greater frequency in confusion, disorientation and amnesia.[7,1] Overall female concussed athletes report more total symptoms and increased severity of symptoms compared to male concussed athletes.[16] In addition, sex differences have also been demonstrated in vestibular ocular motor tasks, where female concussed athletes exhibit worse horizontal vestibular ocular reflex and greater provocation of symptoms following the vestibular and ocular motor screening (VOMS) test than males.8 As a result, neuropsychologists should be aware of these sex differences in self-reported concussion symptoms and vestibular and ocular motor impairments when examining concussed athletes.

TABLE 1.
Reported Concussion Rates by Sport, Sex, and Competition Level (High School and College) (Rates per 10,000 AEs)

Sport	Male Injury Rate with 95% Confidence Interval (lower, upper)	Female Injury Rate with 95% Confidence Interval (lower, upper)
Football		
College[a]	6.71 (6.17, 7.24)	-
High School[b]	9.21 (8.64, 9.78)	-
Ice Hockey		
College	7.91 (6.87, 8.95)	7.50 (5.91, 9.10)
High School	-	-
Wrestling		
College	10.92 (8.62, 13.23)	-
High School	5.76 (4.80, 6.73)	-
Basketball		
College	3.89 (3.06, 4.72)	5.95 (4.87, 7.04)
High School	2.52 (2.01, 3.04)	4.44 (3.67, 5.20)
Soccer		
College	3.44 (2.53, 4.35)	6.31 (5.25, 7.37)
High School	3.98 (3.12, 4.83)	6.11 (4.94, 7.27)
Lacrosse		
College	3.18 (2.31, 4.05)	5.21 (3.84, 6.59)
High School	6.65 (5.41, 7.89)	5.54 (4.09, 6.99)
Baseball / Softball		
College	0.90 (0.46, 1.34)	3.28 (2.40, 4.17)
High School	0.86 (0.46, 1.26)	3.57 (2.58, 4.56)
Swimming & Diving		
College	0.52 (0.06, 0.97)	0.33 (0.01, 0.65)
High School	0.00	0.92 (0.02, 1.82)
Volleyball		
College	-	3.57 (2.64, 4.51)
High School	-	2.50 (1.93, 3.06)

[a]O'Connor et al. (2017) for all high school data, [b]Zuckerman et al. (2015) for all college data

In addition to sex differences in SRC symptoms, researchers have also reported differences between male and female neurocognitive function post-concussion. Following a SRC, female athletes demonstrated cognitive impairment 1.7 times greater than male athletes.[3] Recently, researchers reported female athletes had cognitive declines in verbal and visual memory, visual motor speed and slower reaction time.[14] In addition, 74% of females compared to 59% of males demonstrated at least 1 reliable change index following a SRC.[14] Females may demonstrate greater neurocognitive declines due to an increase in cerebral blood flow,[6] which may exacerbate the neuro-metabolic cascade following SRC. The female sex hormone estrogen may also contribute to this greater decrease in neurocognitive functioning in female athletes.[5] As a result of these sex differences in neurocognitive function and symptoms, neuropsychologists should be aware of these different patterns in clinical outcomes among female athletes.

Recovery and Treatment

Approximately 80-85% of concussed athletes recover within 14 days,[12] however, female concussed athletes may take longer to recover than males.[15] Recently, researchers have suggested that female athletes may take as long as 30 days to recover from their SRC while males take approximately 14 days.[8, 15] The increased number and severity of symptoms, greater neurocognitive deficits, and worse vestibular ocular reflexes experienced by females following a SRC my contribute to this protracted recovery. Regardless of the cause, an individualized, multifaceted treatment approach should be taken when treating those suffering from a SRC.

Researchers have suggested that sex-differences exist in prescribed treatment interventions, in that females are prescribed nearly twice the amount of treatment interventions (2.2 treatment interventions) compared to males (1.3 treatment interventions).[10] Interventions used to treat these athletes include rest, academic accommodations, vestibular therapy, and medications.[10] Furthermore, females have been found to be prescribed vestibular therapy eight times more than males, rest seven times more often, medications four times, and academic accommodations three times more often than males.[10] However, recent research suggests rest may not be the best treatment for a SRC.[12] A potential explanation for the increase in prescribed medication may be due to females having a greater prevalence of migraines[11] and anxiety compared to males. Therefore, medications could alleviate these symptoms following a SRC. It should be noted that concussed athletes should not return to athletic participation while still on medication for their SRC.[18] Finally, in regards to academic accommodations, concussed athletes who are struggling with their symptoms and cognitive function should be prescribed an increased time for assignments, quizzes or tests, a note taker when absent from the classroom, and modifications to reduced light and noise.[10]

Clinical Take Home Points:

1. Female athletes are at a 1.5-4 times greater risk for SRC in sex-comparable sports (i.e. soccer, basketball, softball/baseball).
2. Following a SRC, females present with greater neurocognitive deficits and report more symptoms than males.
3. Males typically recover from a SRC within 14 days, whereas females may require up to 30 days to recover.
4. Females are often prescribed more treatment interventions compared to male athletes following SRC. However, all athletes who suffer a SRC should receive individualized treatment interventions that may include medication, physical and cognitive rest, vestibular therapy or academic accommodation.

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The Role of Genetic Factors in Recovery & Outcome Following Sports-Related Concussion

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VA San Diego Healthcare System/University of California, San Diego

Sports-related concussions have garnered widespread attention in recent decades from the scientific community, the media, and among those directly involved in sport—athletes, parents, and coaches. As a result of this increased awareness, innumerable questions and concerns have been raised pertaining to the risks associated with sustaining a concussion and the consequences of injury. *Who is most at risk for experiencing a concussion? What is the expected recovery time frame? What are risk factors for prolonged recovery?* Clinicians and researchers engaged in sports-related concussion efforts have begun exploring these questions by examining athletes at various levels of competition (i.e., high school, college, and professional), across sex, and even in specific sports such as football or soccer. While ongoing research and inquiry have resulted in increased knowledge regarding the consequences of injury and the nature and course of recovery following concussion, many important questions remain unanswered.

When examining a complex topic such as sports-related concussion, or traumatic brain injury (TBI) more generally, applying a biopsychosocial perspective[1, 2] is often advantageous to more fully understand the nuances associated with outcome and recovery. However, past research has primarily focused on the "psychosocial" aspect of the model, examining how factors such as age, sex, personality, and pre-morbid psychiatric functioning relate to outcome and recovery following sports-related concussion.[3-5] More recently, though, investigators have started to incorporate the "bio" aspect of the model into research programs, with an emphasis on better understanding the role of genetic factors on concussion outcome.[6] Although still a relatively new area of investigation within the sports concussion literature, the larger TBI literature suggests that genetic factors may at least partially contribute to the recovery process and clinical outcomes that are observed in the aftermath of TBI.[7-10]

Within the context of sports-related concussion, the apolipoprotein E (APOE) gene has received the greatest attention, and will be the focus of this review. The APOE gene serves multiple functions within the central nervous system (CNS), including maintenance of neuronal membranes, as well as regulating the transportation and distribution of lipid molecules such as cholesterol.[11, 12] Following neurotrauma, APOE is involved in neuronal repair and synaptogenesis.[12] The APOE gene is comprised of three primary alleles— ϵ2, ϵ3, and ϵ4; the polymorphic nature of the gene results in 6 possible genotypes: 3 heterozygous (ϵ2/ϵ3, ϵ2/ϵ4, and ϵ3/ϵ4) and 3 homozygous (ϵ2/ϵ2, ϵ3/ϵ3, ϵ4/ϵ4). The ϵ3 allele is most prevalent in humans (60-70%), followed by the ϵ4 (15-20%) and ϵ2 (5-10%) alleles.[12] Interestingly, the alleles have been found to differentially affect the neural restoration process after CNS insult; compared to the ϵ2 and ϵ3 alleles, the ϵ4 allele inhibits neurite outgrowth and exerts additional pathological functions on the CNS.[13, 14] Consequently, the ϵ4 allele has been considered a risk factor for neuropathology following brain injury.

At present, studies examining the relationship between the APOE gene and clinical outcome following sports-related concussion are limited, but available evidence suggests that the ϵ4 allele is indeed deleterious—at least in the acute to subacute phase of injury. Merritt & Arnett[15] reported that among college athletes who had sustained concussions and were evaluated within three months post-injury, athletes with at least one copy of the ϵ4 allele endorsed greater overall symptoms than ϵ4- athletes. When examining the specific types of symptoms responsible for the group differences, physical and cognitive-related symptoms appeared to be driving the differences. In a follow-up study, Merritt et al.[16] examined whether the ϵ4 allele specifically influences the presence and severity of post-injury headache—the most commonly endorsed post-concussion symptom. Findings from this study revealed that ϵ4+ athletes were more likely to experience headache, and endorse more severe headaches, than ϵ4- athletes. Remarkably, the ϵ4 allele had no effect on the presence or severity of headache in non-concussed athletes, suggesting that a synergistic relationship may exist between the ϵ4 allele and neurotrauma. In other words, these findings suggest that the presence of the ϵ4 allele appears to only be detrimental to the development of headache in the setting of neurotrauma, but otherwise does not influence headache symptoms in non-concussed athletes.

With respect to the ϵ4 allele and neuropsychological functioning, Kutner and colleagues[17] assessed professional football players and reported that athletes with an ϵ4 allele exhibited worse cognitive performance than ϵ4- athletes. Additionally, the authors showed that older ϵ4+ athletes performed worse on the cognitive measures than younger players of any genotype.[17] More recently, Merritt et al.[18] examined whether the ϵ4 allele of the APOE gene influences various aspects of neurocognitive outcome following sports-related concussion. Concussed college athletes with and without the ϵ4 allele were evaluated to determine whether there were differences in neurocognitive performance with respect to (1) mean performance on neurocognitive composite variables, (2) the number of impaired scores obtained following concussion, and (3) neurocognitive performance variability. The authors found no significant differences between ϵ4+ and ϵ4- athletes when examining mean neurocognitive performance; however, athletes with an ϵ4 allele were more likely to show neurocognitive impairments post-injury compared to athletes without an ϵ4 allele. Furthermore, athletes with an ϵ4 allele demonstrated greater neurocognitive performance variability than athletes without an ϵ4 allele. Taken together, these findings suggest that rather than influencing a specific aspect of cognitive functioning, the ϵ4 allele may universally affect CNS functioning and interrupt efficient cognitive processing.

In addition to examining the relationship between the APOE gene and clinical outcomes following sports-related concussion, investigators have also attempted to determine whether possession of an ϵ4 allele is related to increased *susceptibility* to concussion. Kristman et al.[19] assessed whether ϵ4-positivity predisposes athletes to concussion, but found no association between the ϵ4 allele and the development of concussion. Terrell et al.[20] examined the relationship between the ϵ4 allele and *history* of concussion, and similarly found no connection between having an ϵ4 allele and increased risk of prior concussion. However, the authors also examined polymorphisms in the APOE promoter region (G-219T polymorphisms) and reported that athletes with the G-219T TT polymorphism were at increased for having a history of concussion, relative to the G-219T GG polymorphism. In another study, Tierney et al.[21] examined polymorphisms in the APOE gene and APOE promoter region, and reported that athletes with an ϵ2 *and* ϵ4 allele, along with the APOE promoter G-219T G/T polymorphism, were at increased risk for having sustained a previous concussion. Thus, at present, the current data suggest that while there is not a strong relationship between the ϵ4 allele and susceptibility to concussion, the APOE promoter region may influence risk for concussion.

Even though the APOE gene has been the most frequently studied gene within sports-concussion, additional genetic factors beyond APOE have been examined within the broader TBI literature. For example, other potentially relevant genes include catechol-o-methyltransferase (COMT), brain-derived neurotrophic factor (BDNF), serotonin transporter gene (5-HTT), dopamine D2 receptor (DRD2), dopamine transporter gene (DAT), norepinephrine transporter gene (NET), and dopamine beta hydroxylase (DBH).[7-10] While these genes have not yet been extensively studied within the context of sports-related concussion, each has been proposed as a promising candidate gene to further understand the relationship between genetic factors and TBI.

Identifying a link between genetic factors and outcome from sports-related concussion has several important clinical implications. First, if genetic factors are associated with clinical outcomes following concussion, this could impact return to play decisions in sports. This research could also facilitate the development of individually targeted treatments for athletes with certain genotypes. Additionally, there are many ethical questions that will need to be considered as this research continues, especially issues related to who should have access to athletes' genetic information. As a field, we are only in the beginning stages of understanding what genes may be involved in recovery and outcome following sports-related concussion, but this area of investigation promises to expand our current knowledge base and raise additional, important questions for scientific exploration.

Clinical Take Home Points:

1. Genetic factors may influence recovery following TBI. Specifically, presence of certain genes may serve as important markers of symptom severity and neurocognitive impairment after concussion.
2. The ϵ4 allele of the APOE gene has been associated with greater symptom severity and worse cognitive outcome following sports-related concussion.
3. Assessing impaired scores and performance variability may be a more sensitive method for detecting genetic influences on neurocognitive functioning in concussed athletes who are in the acute to subacute phase of injury.
4. The influence of genetic factors other than APOE on recovery and clinical outcome should also be examined within the context of head injury.

Dr. Victoria Merritt earned her Ph.D. in Clinical Psychology from The Pennsylvania State University and completed her internship at the VA San Diego Healthcare System/University of California, San Diego. She is currently a postdoctoral fellow in clinical neuropsychology at the VA San Diego Healthcare System. Dr. Merritt's research interests include examining predictors of recovery and outcome following traumatic brain injury in military and civilian populations, including sports-related concussion. She also has an interest in exploring the relationship between genetic factors and outcome after brain injury. Dr. Merritt previously was the Volunteer Coordinator for NAN's Annual Conference and served on NAN's Program Committee as a student member. She currently is serving on NAN's Student Committee and is the recipient of NAN's 2017 Outstanding Dissertation Award.

Ms. Nicole Evangelista received her B.S. in Physiology and Neuroscience from the University of California, San Diego (UCSD). She is currently a Research Assistant at the VA San Diego Healthcare System and UCSD. She is interested in pursuing a degree in Clinical Psychology, with an emphasis in neuropsychology. Her research interests focus on the neuropathological mechanisms and genetic factors involved in cognitive decline following head injury and in aging.

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Assessment and Impact of Depression in Sports Concussion Evaluations

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Although there are some studies on the long-term effects of concussion on mood functioning more generally, this piece will mostly focus on the relatively acute period post-concussion.

Prevalence

Depression is relatively common following concussion. We recently examined depression at baseline and post-concussion in a sample of collegiate athletes.[1] We assessed 84 athletes at baseline and then again post-concussion on the Beck Depression Inventory-Fast Screen (BDI-FS). We compared this athlete group to a control group of 42 athletically active undergraduates who were also tested at two time points. Whereas we found that 11% of athletes at baseline scored above the cutoff for depression on the BDI-FS, about twice that many (23%) were above this cutoff post-concussion. Whereas 7% of the control group were depressed when they were initially tested, only 10% were depressed 6-7 weeks later. We also assessed reliable change in BDI-FS scores. Significantly more athletes (20%) compared with controls (5%) displayed a reliable increase in BDI-FS scores between the two time points. Thus, our study showed that the prevalence of depression post-concussion is substantially elevated over what it is at baseline. Other studies have generally been consistent with these findings.

What causes higher depression rates post-concussion is unclear. In our study, we found that those individuals at greatest risk for post-concussion depression had higher baseline BDI-FS scores and higher baseline post-concussion symptoms, as well as lower estimated FSIQ.

Mainwaring and colleagues[2] assessed emotional functioning in a group of athletes post-concussion and those with ACL injuries and compared both to a non-injured control group. Compared to the control group, both injured groups had significantly higher depression scores, as well as a significant increase in depression from baseline to the first time point post-injury. The depression scores of the concussed group also returned to baseline levels by the second time point post-injury (7 days).

Given that both the concussed and ACL groups in Mainwaring and colleagues' (2010) study displayed increased depression and mood disturbance post-injury, it may be that simply being injured caused the athletes to become depressed, regardless of the nature of that injury. Mainwaring et al.'s study provides a good methodological template for other studies to follow by including another type of injured athlete group for comparison to make it possible to tease out the specific emotional effects of concussion versus more general effects of simply being injured more generally.

Roiger and colleagues[3] conducted a study mirroring the methodology of investigations by the Mainwaring et al.'s (2010) study in a Division I NCAA sample using a longitudinal design. Their study included 7 participants in each of the groups, with one group having sport-related concussions, another group with injuries other than concussion, and a third group of sport-matched healthy controls.

These investigators found that the three groups did not differ at baseline on their depression measure (CES-D); however, both of the injured groups displayed comparable significant increases from baseline to the one-week post-injury time point. The non-concussed injured group also showed a significant increase from baseline at the one-month post-injury time point, indicating that it took them longer to get back to baseline than the concussed injury group. Both groups were back to their baseline depression scores at three months post-injury.

Meier et al.[4] compared 17 concussed football players and 27 non-injured football team controls on the Hamilton Depression (HAM-D) rating scale. These investigators found that the concussed athletes had significantly higher depression scores at one day post-concussion. The concussed athletes were also higher than healthy athletes at one week and one month post-concussion. These researchers also found that the depression scores were significantly improved at one month compared with both one day and one week post-concussion.

Common Strategies for Measuring Depression Post-Concussion

In the most recent consensus statement on concussion in sport[5], recognition of depression as a post-concussion symptom is recognized. Also, the importance of assessing and treating depression is mentioned and some appreciation for its possible moderating effect on concussion outcomes is discussed. However, no specific measurement tools are discussed, and no particular guidelines for assessing depression post-concussion are mentioned. In the prior consensus statement[6], the authors noted that, "Although such mental health issues may be multifactorial in nature, it is recommended that the treating physician consider these issues in the management of concussed patients." However, no such passage appears in the updated statement. Surprisingly, even though both of these articles also highlight the potential importance of neuropsychologists in the sports concussion context more generally, no mention is made of the role that clinical neuropsychologists might play in diagnosing and managing depression in these individuals. This is despite the fact that clinical neuropsychologists, by virtue of their usual training in clinical psychology and treatment approaches for a variety of psychiatric conditions, would seem to be ideally suited for this role. Moving forward, this is an area within the sports concussion context where clinical neuropsychologists could play a greater role, and would generally have much more experience in addressing such issues than "the treating physician," whose focus and training are more likely to center around diagnosing and treating the neurological and physical sequelae of concussion than addressing psychiatric issues.

As noted, the recent consensus statements on sports concussion (McCrory et al., 2013; 2017) offer no suggestion of a formal measure to assess depression post-concussion. A number of studies have used some variant of the Beck Depression Inventory (e.g., BDI-II, BDI-FS), and they appear to have some validity in this context. Vargas et al. (2015) used the BDI-FS, and there is much to recommend its use. First, it is brief, including only 7 items that can be completed in a couple of minutes. Second, it has been widely used and a number of published studies have demonstrated that it has good psychometric properties, including good reliability and validity (Beck et al., 2000). Third, it has a well-established cutoff (>= 4) that has been validated in a number of different contexts. With that said, to our knowledge, there has been no full validation study of the BDI-FS published in the sports concussion literature that provides specificity and sensitivity values. Still, the cutoff of >= 4 has been replicated in other neurological populations.[7, 8]

At present, the BDI-FS seems most practical for measuring depression. It is brief, has well-established reliability and validity, has been used in the sports concussion context, and can be used for individuals as young as age 13.

Association of Depression with Cognitive Functioning

Given the well-established association between depression and anxiety with cognitive functioning in the broader literature outside of sports-related concussion[9, 10], combined with the fact that depression and anxiety appear to be fairly common post-concussion, it is surprising that there have been relatively few studies examining this issue in the sports concussion literature. Kontos and colleagues[11] found that worse visual memory and reaction time at two and seven days post-concussion were associated with higher depression scores in a sample of high school and collegiate athletes. We examined this issue in a recent study assessing 29 depressed and 103 non-depressed collegiate athletes at baseline and post-concussion using the BDI-FS.[12] The depressed athletes performed significantly worse on both the Hopkins Verbal Learning Test – Revised Total Recall and the ImPACT Visual Memory Composite score. Reliable change on the cognitive test indices was also examined between groups, and we found that compared with non-depressed athletes (8%), significantly higher proportions of depressed athletes (25%) showed reliable declines on the ImPACT Verbal Memory Composite Score and the SDMT.

In a study of collegiate athletes at baseline, Bailey and colleagues[13] examined cognitive functioning and depression in 47 collegiate football players at baseline. They measured emotional/personality functioning using the PAI, a broad-based measure consisting of 344 items and 22 distinct subscales, 11 of which are clinical in nature. They measured cognitive functioning with the computerized Cognitive Resolution Index (CRI). The CRI includes three composite indices including simple reaction time (SRT), complex reaction time (CRT), and processing speed (PS).

Bailey et al. (2010) found significant correlations for the Anxiety scale of the PAI with the CRI – SRT and CRI – CRT composites, with effect sizes in the medium range. No significant correlations were found between the Depression scale from the PAI and any of the CRI composite indices. However, when the authors divided their sample up into those with high scores on the Suicidal Ideation Scale (SUI) of the PAI, they found that it was significantly correlated with both the CRI – SRT and CRI – CRT composites.

Bailey and colleagues' (2010) results are important, because they show that, even at baseline, collegiate athletes' neurocognitive difficulties are associated with increased distress. This suggests that athletes who are significantly distressed at baseline may under-perform cognitively. As such, if they do not show similar levels of distress post-concussion, their scores at this post-injury time point may not provide an accurate comparison with their baseline scores. In this case, post-concussion scores could be equivalent to baseline scores because the athlete is no longer distressed, and obscure declines actually associated with their concussion. In these instances, it may be worthwhile to compare such athletes' post-concussion scores to available norms, as a way of double-checking whether they are, in fact, impaired. This study underscores the importance not only of assessing athletes' psychological distress post-concussion, but also at baseline.

Clinical Take Home Points:

It is critical for clinicians to be aware of risk for affective problems and anxiety post-concussion. What follows are a few clinical take home points in relation to this.

1. **Clinicians should routinely screen for depression post-concussion. Although the state of our empirical knowledge about how best to screen for depression in concussion is not well-developed, we recommend the use of the BDI-FS**. It only includes 7 items, and can thus be completed quickly. Any athlete scoring 4 or above on this measure should be referred for further evaluation and possible pharmacologic and/or psychotherapeutic treatment.
2. **There is an extensive literature demonstrating that depression is associated with cognitive impairments**. Though the specific literature in relation to concussion on this topic is limited, the few studies that have addressed these issues have been consistent with the broader depression literature. As such, clinicians should be aware that when depression is co-morbid with cognitive impairments post-concussion, it may mediate some of the cognitive problems that are seen. As such, successful resolution of the depression may result in improved cognitive functioning. Knowledge of this relationship helps to underscore the importance of correctly assessing and treating post-concussion depression, because failure to treat it may result in the delayed resolution of cognitive problems.

Dr. Arnett received his Ph.D. in Psychology (Clinical) from the University of Wisconsin – Madison, and completed a post-doctoral fellowship in Clinical Neuropsychology at the Medical College of Wisconsin under the direction of Drs. Stephen Rao and Thomas Hammeke. He is currently a Psychology Professor and Director of the Neuropsychology of Sports Concussion and multiple sclerosis (MS) Programs at Penn State University. Dr. Arnett's research has focused on clinical neuropsychology, with an emphasis on studying secondary influences on cognitive functioning in persons with MS and sports-related mild traumatic brain injury (concussion). He is a fellow of the NAN, past winner of NAN's Nelson Butters Award for Research Contributions to Clinical Neuropsychology, and past winner of the Herndon Award for the Outstanding *International Journal of MS Care* for the 2013 year. Dr. Arnett was the Program Co-Chair for the 2010 Mid-Year Meeting of the International Neuropsychological Society (INS), and is a past board member of the INS. Dr. Arnett is the author of over 130 research articles and book chapters, and has edited a book entitled, *Secondary Influences on Neuropsychological Test Performance*. Dr. Arnett is also currently working on an edited book entitled, *Neuropsychological Perspectives on Sports-Related Concussion* that will be published by the American Psychological Association in 2018. He is an editorial board member of several journals, and has received grant funding from the National MS Society, NIH, and NIMH.

Erin Guty is currently a 3rd year doctoral student in The Pennsylvania State University's clinical psychology program. She is interested in cognitive and emotional functioning following damage to the brain and how research can allow neuropsychologists to better utilize assessments for informing interventions and treatment. She is currently involved in projects focused on assessments for both sports-related concussion and multiple sclerosis populations.

Megan Bradson is currently a senior Psychology (B.S.) major at The Pennsylvania State University, expecting to graduate from the Schreyer Honors College in Spring 2018. As an undergraduate, she is highly involved as a research assistant in PSU's Sports Concussion Lab in addition to assisting with projects in PSU's Neuropsychology of Multiple Sclerosis (MS) Lab. She is currently examining the relationship between genetic factors and functional connectivity in patients with MS for her honors thesis. In the future, she hopes to receive her Ph.D. in Clinical Psychology with a concentration in neuropsychology.

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Post-Traumatic Migraine Following Concussion: The Benefit of Regulation versus Rest

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Clinicians and researchers have identified concussion clinical profiles to help guide individualized versus generic management and treatment recommendations[1,2]. Six clinical profiles of concussion have been proposed, including post-traumatic migraine (PTM). Post-traumatic headache (PTH) was defined by the International Headache Society (2013) as a headache developing within seven days of injury that generally occurs acutely, but can be persistent[3,4]. PTH can be classified into different types, with tension and migraine headaches reported most frequently[3,5]. Migraine has been defined to include at least several of the following characteristics: unilateral location, pulsating quality, moderate/severe pain, aggravation with activity, nausea and/or vomiting, and light/noise sensitivity[4]. Research has identified strong correlations among migraine symptoms in concussed youth and clustering of these symptoms in youth with/without a migraine history, suggestive of PTM being a distinct clinical entity versus chance occurrence[3]. Estimates of PTM occurrence remain unknown, though headaches have been identified to occur in approximately 70% of concussion cases[3].

Effects of PTM on Recovery and Neurocognitive Functioning

Patients with PTM are at risk for experiencing prolonged recoveries when compared to concussed individuals experiencing non-migraine headaches (2.6x) or no headaches (7.3x), likely due to experiencing more symptoms and greater neurocognitive declines[6]. Specifically, athletes with PTM demonstrated worse performance on the verbal memory, visual memory, visual motor speed, and reaction time composites of the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) acutely when compared to concussed non-migraine headache and no headache groups[7]. Significant differences between baseline and post-injury scores were also identified for athletes with PTM across all ImPACT composites[7]. Beyond the acute period, research demonstrated worse cognitive performance for athletes with PTM 8-14 days post-injury for visual memory, reaction time and symptom scores than concussed non-migraine headache or no headache groups and for verbal memory when compared to a concussed non-migraine headache group[6]. Research has also found patients with PTM to demonstrate reduced brain network activation for Go/NoGo tasks 3 weeks and NoGo tasks 4 weeks post-injury when compared to a concussed no headache group and controls[8]. Thus, PTM has been found to be associated with prolonged recovery as well as greater cognitive difficulties and symptoms acutely and across recovery when compared to concussed individuals with non-migraine headaches or no headaches and control groups[9].

Treatment and Management of PTM

With the increased risk for prolonged recovery, it is important to consider management and treatment. Research has consistently demonstrated that poor sleep habits, inadequate nutrition, dehydration, lack of physical activity, and stress can result in headaches and migraines[10]. Therefore, previous concussion recommendations including strict rest should be reconsidered when PTM symptoms are present and for individuals with a history of headaches and/or migraines as this leads to an altered schedule versus a regulated schedule including a normal sleep-wake cycle (i.e., obtaining 7-9 hours per night, limiting naps), regular meals (i.e., eating breakfast, lunch, and dinner), adequate hydration (i.e., obtaining at least half their body weight in ounces per day), regular physical activity (i.e., at least 30 minutes of non-contact activity) and stress management[11,12]. Reliance on over-the-counter medications must also be considered due to the risk for rebound headaches when using these medications greater than three times per week[13,14]. Research showed that up to 70% of adolescents receiving treatment in a headache clinic post-concussion met criterion for medication overuse headaches, with 68.5% meeting resolution or improvement after discontinuation[15]. These simple management techniques can improve symptoms, reduce the need for medication management, and subsequently reduce the length of recovery.

If PTM persists, it is important to determine if other treatments are needed. To avoid over treating, clinicians should be aware that patients may experience symptoms including anxiety, dizziness, and sensitivity to visual motion stimulation while experiencing migraine episodes[16]. With that said, some patients may experience additional symptoms associated with other concussion clinical profiles (e.g., vestibular-related dizziness) that may require concurrent treatment. In cases where multiple profiles are present, a multidisciplinary management/treatment approach is important[2].

Medication use for PTM utilizes a prophylaxis (i.e., preventing or reducing the frequency) and/or abortion (i.e., eliminating the pain if it occurs) approach. Due to typical improvement in symptoms and common medication side effects, prescription medications are generally not utilized acutely[17]. Medications are often considered when symptoms continue for an extended period or inhibit engagement in treatments. Medication options typically include analgesics, anticonvulsants, antidepressants, β-Adrenergic antagonists, benzodiazepines, neurostimulants, NSAIDs, and triptans[18]. Other naturopathic options include melatonin, magnesium, vitamin B, riboflavin, Coenzyme Q10 and fish oil[18,19].

Clinical Take Home Points:

1. PTM is common following concussion and can result in a prolonged recovery, which warrants close monitoring and comprehensive assessment of symptoms and neurocognitive functioning.
2. Immediate management should involve regulation of schedule, consistent with the headache and migraine literature to avoid prolonged recoveries.
3. When regulation of schedule, including non-contact physical activity, and controlled use of OTC medications is ineffective other treatments should be considered.

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Michael "Micky" Collins, Ph.D., is an internationally renowned expert in sports-related concussion. A leading clinician and researcher, Dr. Collins serves as director and a founding member of the UPMC Sports Medicine Concussion Program. Established in 2000, it was the first program of its kind; more than a decade later, it remains the largest research and clinical program focused on the assessment, treatment, rehabilitation, research and education of sports-related mild traumatic brain injury in athletes of all levels. Dr. Collins' expertise attracts elite and professional athletes from around the world seeking the comprehensive care he provides and the multidisciplinary approach he helped to introduce. The program has roughly 20,000 patient visits annually at six different locations across Pittsburgh. Dr. Collins and his UPMC program colleagues attract patients embodying youth, high-school, collegiate and pro athletes with concerns about safe return to play and clinical management and treatment of sports concussion.

Besides his extensive clinical experience, Dr. Collins also has been a lead author and investigator on numerous groundbreaking studies of high-school and college athletes published in JAMA, Neurosurgery, American Journal of Sports Medicine and Pediatrics, among many others. He has been the lead author or co-author on more than 90 peer-reviewed research articles, and has delivered more than 350 presentations at national and international scientific meetings. Dr. Collins currently has upward of $6 million in funding for his research efforts from entities including the NFL-GE Head Health Challenge, National Institute of Health, Major League Baseball, and the United State Army Special Operations Command. National and local media frequently interview him as an expert source.

Dr. Collins has been an instrumental source across the nation in developing concussion-management policy in youth sports, state legislation on youth safety, the Centers for Disease Control's concussion toolkit, and pioneering targeted treatment pathways for his patients. He is a co-founder of ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing), the most widely used computerized sports-concussion evaluation system that has become a standard of care in nearly all organized sports at all levels. As a result, he is a leader in educating and implementing the proper usage of such baseline and post-injury neurocognitive testing as one tool to help determine an injury's severity and recovery for safe return to play. More recently, Dr. Collins was the Meeting Chairman for the Targeted Evaluation and Active Management (TEAM) Approach to Treating Concussion. This meeting was held in Pittsburgh in October, 2015 and was the first focused meeting regarding treatment of sports-related concussion. Underwritten by the NFL, this meeting resulted in the first published white paper on treatment of concussion, published in Neurosurgery.

In addition to training thousands of physicians and certified athletic trainers in the diagnosis, management, and treatment of sports-related concussion, he advises and is a consultant to numerous athletic organizations and teams – including the NFL Steelers, the NHL Penguins, other NFL teams, numerous MLB clubs, several NCAA programs, USA Rugby and Cirque De Soleil. He serves as an Associate Editor of the Journal of Neurosurgery and the Journal of Sports Neurology. Dr. Collins is also on the editorial board of such publications as Brain Injury Professional and the Journal of Athletic Training.

A graduate of the University of Southern Maine with a bachelor's degree in psychology and biology in 1991, Dr. Collins earned a master's degree in psychology in 1995 and doctorate degree in clinical psychology in 1998 at Michigan State University.

Among numerous national and international honors over the past decade, Dr. Collins was named an Irish-America Healthcare and Life Sciences Top 50 Honoree in 2014. In 2010, he received the National Council on Brain Injury annual award for outstanding research and advocacy. In 2009, he was bestowed the Kenneth L. Knight Award for outstanding research. In 2007, the National Academy of Neuropsychology honored him with the Annual Butters Award. An athlete himself, Dr. Collins played in the 1989 NCAA Baseball College World Series.

Chronic Traumatic Encephalopathy: A Long-Term Consequence of Repetitive Head Impacts

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Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease that results in a progressive decline in clinical function,[1-3] and is believed to be a consequence of exposure to repetitive concussive and subconcussive head trauma, also referred to as repetitive head impacts (RHI).[4] CTE emerged at the forefront of lay attention and clinical research in 2005, following the publication of a case study of a former American professional football player who had progressive cognitive and behavioral/mood problems during life, as well as confirmed neuropathology of CTE.[5] Since 2005, CTE has been found in numerous former contact sport athletes (e.g., American football players, boxers, rugby players), military veterans, and other individuals with a history of RHI exposure whose brains were donated to research.[1] Most recently, neuropathological evidence of CTE was found in a convenience sample of 177/202 American football players, including 110 of the 111 former National Football League (NFL) players.[2] CTE is beginning to emerge as a potential public health concern and the purpose of this *Bulletin* article is to provide a brief overview on current knowledge of CTE in order to facilitate awareness of what CTE is and what it is not.

Neuropathology of CTE

McKee and colleagues at the Boston University (BU) Alzheimer's Disease Center, the BU CTE Center, and the Veterans Administration-BU-Concussion Legacy Foundation (VA-BU-CLF) brain bank have devoted their research to the refinement and validation of the neuropathology of CTE. As part of a National Institute of Neurological Disorders and Stroke (NINDS)-funded study, known as, "Understanding Neurologic Injury in Traumatic Encephalopathy (UNITE)" (PI: Ann McKee), McKee et al. proposed neuropathological diagnostic criteria for CTE.[1] A NINDS and National Institute of Biomedical Imaging and Bioengineering (NIBIB)-sponsored conference was convened among seven independent neuropathologists with expertise in neurodegenerative disease to evaluate McKee and colleagues' proposed diagnostic criteria. The panel evaluated 25 selected cases of various tauopathies, and there was strong agreement for the neuropathological diagnosis of CTE (kappa = 0.78). The panel agreed that CTE is a unique disease, is only is seen in individuals with a history of brain trauma, mostly repetitive, and that the pathognomonic lesion defined as an irregular perivascular deposition of hyperphosphorylated tau protein (ptau) at the depths of the cortical sulci. In the early stages of the disease, the ptau deposition is in multifocal frontotemporal brain regions. As the disease progresses, the ptau spreads to medial temporal lobes (MTLs), eventually becomes widespread, and results in neurodegeneration.

RHI Exposure and CTE

RHI appears to be a necessary risk factor for CTE, however, it is not a sufficient cause, given not all individuals exposed to RHI develop CTE. Other (unknown) risk factors are thought to interact with RHI to contribute to the development of CTE and clinical decline. A few potential factors include early age of first exposure,[6-8] presence of APOE genotype,[3] older age,[1,2] cognitive reserve,[9] and cerebrovascular health. More definitive research is needed to fully understand CTE risk. Recurrent subconcussive head trauma, in contrast to acute concussion, plays a prominent role in the development of CTE; CTE is not believed to be a consequence of a single or even multiple traumatic brain injuries. In neuropathologically-confirmed cases of CTE, 16% have only had a history of exposure to subconcussive head trauma,[10] and family estimated number of concussions has been shown to be unrelated to CTE neuropathological severity.[1] In a McKee et al. published case series of 68 cases with neuropathologically-diagnosed CTE, 64 were exposed to subconcussive head trauma through contact sport participation, namely American football (n = 50) where longer duration of play predicted worse severity of CTE.[1] CTE neuropathology was not present in 18 age- and gender-matched controls without a history of RHI exposure. Likewise, in the recent autopsy case series of American football players, neuropathological evidence of CTE was found in three of the 14 individuals who played tackle football only at the high school level, 48 of 53 who played college football, and 117 of 119 who played professional football (110/111 former NFL players and 7/8 who played in the Canadian Football League).[2] An important limitation to these findings and others from the VA-BU-CLF brain bank is that the generalizability is limited due to sample selection bias. These studies are not designed to answer questions about incidence and prevalence. That being said, research from the Mayo Clinic brain bank corroborates the relationship between RHI exposure and CTE.[11] The medical charts of over 1,700 brain donation cases from the Mayo Clinic brain bank were reviewed to ascertain history of contact sport participation. Sixty-six males that participated in contact sports at the amateur level (34 of which played American football) were identified. Following re-examination of the brain tissue, 21 of these 66 brain donation cases with a contact sport history had the diagnostic lesion of CTE. CTE neuropathology was not present in 198 age- and disease-matched men and women who did not have a history of contact sport participation. In a recent autopsy study from England, four out of six former soccer players who had dementia during life were found to have neuropathological evidence of CTE upon autopsy.[12] Only one of the four soccer players had a known history of concussion and therefore repeated subconcussive blows in soccer, such as those from heading, was believed to lead to CTE.

Clinical Presentation of CTE

Stern et al.[3] conducted retrospective clinical family telephone interviews and medical record reviews were performed for all subjects whose brains were in the BU-VA-CLF brain bank. The interviews and medical record reviews (and all summaries) were conducted blind to the results of the neuropathological examinations; the neuropathologists were likewise blind to the clinical history.

Thirty-six contact sport male athletes who were neuropathologically diagnosed with *only* CTE (i.e., there was no other neuropathological evidence of disease, such as AD) were included in the study. Of the 36 subjects, 22 exhibited initial declines in behavior and mood, at a mean age of 35, primarily characterized by explosivity, impulsivity, physical and verbal violence, in addition to depression and related symptoms (e.g., hopelessness, suicidality). Although this behavioral/mood subgroup eventually progressed to develop cognitive symptoms, there was a second distinct subgroup of 11 subjects who had cognitive difficulties as the initial symptom at a mean age of 60, especially in episodic memory and executive function. This cognitive subgroup tended to develop dementia, and had more advanced CTE neuropathology. There were three subjects that were asymptomatic: one was only 17 years old and had early stage CTE neuropathology (stage I) and the other two had advanced graduate degrees and high occupational achievement. Cognitive reserve has been supported as a potential modifier of cognitive and behavioral/mood decline in CTE.[9] Stern et al.'s description of the clinical presentation of CTE was corroborated by the clinical features reported in the recent autopsy case series of 177 American football players who had CTE.[2]

Clinical Research Diagnostic Criteria

At this time, CTE cannot be detected or diagnosed during life. Provisional research diagnostic criteria for the clinical syndrome associated with CTE and/or exposure to RHI have been proposed by previous authors. Our group has published criteria for what we refer to as, "Traumatic Encephalopathy Syndrome" (TES).[13] The objective of the TES criteria are to facilitate clinical research investigations on CTE and not to be used for clinical diagnostic or medico-legal purposes. TES is based on a comprehensive literature review of the clinical features of neuropathologically-confirmed cases of CTE. A TES diagnosis requires a history of multiple impacts to the head (e.g., from contact sport participation, military service, domestic violence), including concussions and subconcussive injuries, and/or moderate to severe traumatic brain injury (TBI). At least one of three core clinical features must be present, and are based on signs and symptoms found in a majority of neuropathologically-confirmed cases of CTE: 1) Behavioral disturbances (e.g., aggression, impulsivity); 2) Mood dysfunction (e.g., depression and related symptoms); and 3) Cognitive decline, particularly in executive function and episodic memory, that is corroborated by standardized testing. The TES diagnosis also requires the presence of at least two supportive features (impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor signs, documented decline, delayed onset), symptom duration of a minimum of 12 months, and no other neurological disorder that can fully account for the clinical features. The core features form four different TES diagnostic variants: cognitive, behavioral/mood, mixed, and dementia. TES dementia requires a progressive clinical course and functional impairment. For all variants, motor disturbances and the clinical course (i.e., 'stable,' 'progressive,' or 'unknown/inconsistent') must be indicated.

TES describes the clinical syndrome associated with exposure to RHI and is not intended to be specific to underlying CTE neuropathology. TES can be diagnosed in individuals with other neurological conditions and/or neurodegenerative diseases associated with exposure to head trauma. The behavioral, mood, and cognitive features included in the TES diagnosis are not at all specific to CTE. In addition, the specific criteria used for brain trauma exposure are not yet validated. Again, these criteria are meant to be provisional and subject to refinement and modification as new research is conducted. For now, based on the existing model, if an individual meets the TES diagnostic criteria, the next step is to indicate whether the etiology is 'Probable CTE,' 'Possible CTE,' or 'Unlikely CTE.' Similar to diagnostic criteria for Alzheimer's disease (AD) dementia, a 'Probable CTE' diagnosis requires an *in vivo* biomarker that supports the presence of underlying CTE neuropathology. Without a biomarker to support a 'Probable CTE' diagnosis, only a 'Possible CTE' diagnosis can be made.

Proposed *In Vivo* Biomarkers of CTE

Validated *in vivo* biomarkers of CTE are not yet available, but several have been proposed. Various magnetic resonance imaging (MRI) technologies have been examined in former professional American football players, and provide support for a range of non-specific structural, functional, and molecular biomarkers of CTE. Positron Emission Tomography (PET) tau imaging is anticipated to be the gold standard for the *in vivo* detection of underlying ptau pathology associated with CTE. The PET ptau ligand [(18) F]-AV1451 (also referred to as T807 or Flortaucipir) is the focus of current research due to its specificity to 3R and 4R paired helical filament tau (i.e., the tau species seen in both AD and CTE). Fluid biomarkers are more pragmatic than PET imaging and may also detect underlying neurodegenerative disease pathology. There is preliminary evidence for plasma exosomal tau[14] and plasma total tau[15] as candidate biomarkers for CTE. Cerebrospinal fluid (CSF) proteins of total tau, ptau, and beta-amyloid are of particular interest as potential fluid markers of CTE and analysis of CSF concentrations in former professional American football players is currently being conducted.

Conclusions and Future Directions

CTE may be a major public health concern given the millions of contact sport athletes and military personnel exposed to RHI each year, in addition to the many more living individuals with a history of RHI exposure. Despite what may be portrayed by the media, research on this disease is in its initial stages. Provisional clinical research diagnostic criteria for CTE (i.e., TES) have been proposed, but the reliability and validity of TES has yet to be determined. It is currently not possible to detect or diagnose CTE during life, partially because validated *in vivo* biomarkers for CTE do not yet exist, and the clinical presentation of CTE remains ill-defined. The ability to detect CTE during life using validated *in vivo* biomarkers is the essential next step in order to facilitate clinical research investigations on the risk factors and epidemiology of CTE, as well as testing of proposed theories for the pathophysiological mechanisms that underpin the association between RHI exposure and CTE, and, perhaps, most importantly, conducting clinical trials for the treatment and prevention of CTE. These knowledge gaps are being addressed through a NINDS-funded, seven-year multicenter study, referred to as, "Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) Research Project" (PIs: Robert A. Stern [Contact PI], Jeffrey Cummings from Cleveland Clinic, Eric Reiman from Banner Alzheimer's Institute, and Martha Shenton from Brigham and Women's Hospital and Harvard). DIAGNOSE CTE is a longitudinal examination (baseline and three-year follow-up) of 45-74 year old symptomatic and asymptomatic former NFL players, symptomatic and asymptomatic former college football players, and an asymptomatic control group without a history of head trauma or contact sport participation. The DIAGNOSE CTE Research Project involves approximately 50 co-investigators from nine different institutions. Participants are evaluated at one of four centers (in Boston, Las Vegas, Scottsdale/Phoenix, and New York City) and undergo clinical exams (neurological, motor, neuropsychological, neuropsychiatric, and daily functioning), neuroimaging (PET tau and amyloid, MRI, fMRI, DTI, MRS), lumbar puncture, and blood and saliva collection. The ultimate endpoint for the DIAGNOSE CTE Research Project is to develop methods and criteria to diagnose CTE during life in order to initiate clinical trials, and facilitate epidemiological studies on CTE.

Clinical Take Home Points:

1. Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disease that is associated with exposure to repetitive head impacts, predominantly recurrent subconcussive head impacts like those experienced in American tackle football, boxing, and other contact sports.
2. CTE is not a consequence of a single or even multiple symptomatic traumatic brain injuries, including concussion. However, although a history of repetitive head impacts is a necessary variable to develop CTE, it is not sufficient. Specific variables that increase or decrease risk for CTE are being studied.
3. A constellation of cognitive, behavioral, and mood symptoms have been described as the clinical manifestations of underlying CTE pathology. However, these symptoms are not specific to CTE, and occur in the general population without history of repetitive head impacts. The specific relationship between underlying CTE neuropathology and clinical presentation remains to be determined.
4. "Traumatic Encephalopathy Syndrome" has *provisional* clinical research diagnostic criteria that describe a clinical syndrome associated with exposure to repetitive head impacts and proposes biomarker criteria for determining CTE as the underlying etiology.
5. An *in vivo* diagnosis of CTE is not yet possible because validated biomarkers that can detect underlying CTE pathology with a high degree of certainty do not currently exist. Development and examination of potential biomarkers for CTE is a primary target of current research in this field.

Dr. Alosco completed his undergraduate studies at Providence College and he earned his doctoral degree in clinical psychology, with a focus in neuropsychology, in 2015 from Kent State University. He completed his clinical internship in neuropsychology at the VA Boston Healthcare System. In 2015, Dr. Alosco was awarded a post-doctoral fellowship at the Boston University (BU) Alzheimer's Disease (AD) and CTE Center through the NIA-funded Alzheimer's Disease Translational Research Training Program (T32-AG036697). In 2016, Dr. Alosco transitioned to a Ruth L. Kirschstein National Research Service Award (NRSA) F32 from the National Institute of Neurological Disorders and Stroke to continue his advanced clinical research training at the BU AD and CTE Center. Dr. Alosco's research focuses on risk factors and biomarkers of neurodegenerative conditions, with a focus on AD and CTE. Dr. Alosco is particularly interested in the contribution of cerebrovascular disease to the clinical and neuropathological presentation of AD and CTE. He is additionally involved in research examining the relationship between exposure to repetitive head impacts and long-term neurological consequences. Dr. Alosco plays a critical role in several large-scale in vivo and ex vivo studies on AD and CTE at the BU AD and CTE Center. Dr. Alosco has accumulated >100 peer-reviewed publications, has written numerous book chapters, serves as an ad-hoc reviewer for several journals, and has received several honors and awards.

Megan Mariani graduated from the University of Delaware in 2016 as a double major, with a B.S in Neuroscience and B.A in Psychology. She has had diverse research experience, allowing her to explore neurocognitive processes in both clinical and healthy populations. Currently, she is a clinical research assistant at the Boston University Alzheimer's Disease and CTE Center. Her specific focus is on The DIAGNOSE CTE Research Project, a 7-year multi-site project funded by the National Institutes of Health. The study is looking to develop methods of diagnosing Chronic Traumatic Encephalopathy during life and examine potential risk factors for developing the brain disease. She hopes to pursue a doctoral program in clinical psychology with a focus in neuropsychology.

Dr. Robert Stern received his PhD in Clinical Psychology from the University of Rhode Island. He completed his predoctoral internship training under Dr. Edith Kaplan at the Boston VA Medical Center and his post-doctoral fellowship at the University of North Carolina School of Medicine. He is currently Professor of Neurology, Neurosurgery, and Anatomy & Neurobiology at Boston University (BU) School of Medicine, where he is also Director of the Clinical Core of the NIH-funded BU Alzheimer's Disease Center, and Director of Clinical Research for the BU Chronic Traumatic Encephalopathy (CTE) Center. A major focus of his research involves the long-term effects of repetitive head impacts in athletes, including the neurodegenerative disease, CTE. He is the lead co-principal investigator of a $16 million NIH grant for a multi-center, longitudinal study to develop methods of diagnosing CTE during life as well as examining potential risk factors of the disease. Dr. Stern's other current major area of funded research involves the diagnosis and treatment of Alzheimer's disease. He has published on various aspects of cognitive assessment and is the senior author of the Neuropsychological Assessment Battery (NAB), as well as the Boston Qualitative Scoring System for the Rey-Osterreith Complex Figure. He has received numerous NIH and other national grants and he is a Fellow of both NAN and the American Neuropsychiatric Association. Dr. Stern has over 175 peer-reviewed publications, is on several journal editorial boards, and is the co-editor of two upcoming books: Sports Neurology (part of the Handbook in Clinical Neurology series published by Elsevier), and The Oxford Handbook of Adult Cognitive Disorders. He is a member of the medical advisory boards of several biotech/pharma companies as well as the Mackey-White Health and Safety Committee of the NFL Players Association and the Medical Scientific Committee for the NCAA Student-Athlete Concussion Injury Litigation.

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