Investigating the Assessment of Sport-Related Concussion in Youth Using Brain and Behavior

by

Justin R. Moody

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Approved by

Dr. Melissa Pangelinan, Ph.D., Chair, Assistant Professor
Dr. Matthew Miller, Ph.D., Associate Professor
Dr. Jennifer Robinson, Ph.D., Associate Professor
Dr. Wendi Weimar, Ph.D., Full Professor

Abstract

Concussions affect between 1.6 and 3.8 million people in sports and recreation annually (Langlois et al., 2006). The impact of sports-related concussion and participation in contact sports on the brain and behavior in pediatric populations is not well established. The purpose of this dissertation is to evaluate the immediate behavioral effects of concussion and establish effects of contact sports participation on behavioral and neurological trajectories in youth athletes.

Study 1 investigated the different acute concussion assessments currently employed in research for children and adults. This systematic review included a total of 28 studies that showed six assessments used in at least three studies. These six "common" assessments were evaluated with respect to their use by sex, age, and domain. Only 12% of the study populations evaluated by these assessments were female. The age range of participants evaluated was 9-67 years. Many common domains were evaluated. This first study suggests that that there is a need for a "gold standard" assessment.

Study 2 examined the effects of contact sport participation on brain and behavior in children and adolescents via a secondary data analysis longitudinal database acquired from the NIH Study of Normal Brain Development, which collected structural MRI, a parent questionnaire, and behavioral and neurological assessments. 306 participants were included in the analysis. Controls were matched to individuals that participated in three common contact

sports associated with sports-related concussion based on previous epidemiological studies based on age, sex, race, and total household income. Age and sex main effects were observed in many areas of interest. An Age x Number of Seasons in Contact Sports interactions were observed for a number of areas and behavioral assessments. These results suggest perhaps that participation in contact sports may lead to divergent developmental trajectories in both brain and behavior in healthy children and adolescents.

These studies suggest that behavioral and neurological assessments need to be consistently applied across research and clinical domains, before a concussion. Physical and neurological assessment utilized in Study 2 may be more sensitive to subtle neurological changes. Determining the most appropriate assessments is critical for safe sport participation in youth.

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List of Abbreviations

ADHD	Attention Deficit Hyperactive Disorder
ANAM	Automated Neuropsychological Assessment Metrics
ANTs	Automatic Normalization Tools
BRIEF	Behavioral Rating Inventory of Executive Function
CRI	Concussion Resolution Index
CTSIB	Clinical Test of Sensory Integration of Balance
DHI	Dizziness Handicap Inventory
DSST	Digit Symbol Substitution Test
DV	Dependent Variable
GEC	Global Executive Composite
GPA	Grade Point Average
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing
IQ	Intelligence Quotient
K-D Test	King-Devick Test
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
NIMH	National Institutes of Mental Health

PANESS	Physical and Neurological Examination of Soft Signs
PCS	Post-Concussion Syndrome
PCSS	Post-Concussion Symptom Scale
PD	Proton Density
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
R-PSQ	Rivermead Post-Concussion Symptoms Questionnaire
SCAT	Sport Concussion Assessment Tool
SOT	Sensory Organization Test (SOT)
SRC	Sport-Related Concussion
TMT-B	Trail Making Test – Part B
WASI	Wechsler Abbreviated Scale of Intelligence
WC-III	Woodcock Johnson 3rd Edition

Chapter 1: General Introduction

A concussion is defined as "a complex pathophysiological process affecting the brain, induced by biomechanical forces" (McCrory et al., 2017). Concussions affect between 1.6 and 3.8 million people in sports and recreation annually (Langlois et al., 2006). In recent years the number of studies examining the impact of sports-related concussion on brain and behavior have grown tremendously. However, the heterogeneity in the assessments (neuroimaging or behavioral), timing of the assessment (e.g., pre-season, acute, long-term), and the populations evaluated (e.g., pediatric, high school, collegiate, professional) has led to inconsistent effect sizes and conclusions.

The signs and symptoms of sports-related concussion are heterogeneous and as such, are difficult to reliably diagnose and track. Several research consortia (e.g. CARE, B-TEC) have been established to resolve this issue and several position statements and protocols have been established However, substantial variation in the assessments used for these protocols and assessments employed by different research labs have obfuscated the characterization of concussion symptoms and impact on cognitive and neurological function. Researchers and healthcare professionals alike face the challenge of choosing the most appropriate tool amongst many options to aid in their decisions in assessing concussion across different phases of injury (i.e., acute, sub-acute, chronic).

In order to identify the different concussion assessments that have been used in a research context during the acute phase, we conducted a systematic review (Chapter 2). We highlight the differences and similarities of the most widely used assessments with the goal of

aiding researchers and clinicians in identifying which of these assessment may be most appropriate for their population and the assessment domains of interest. Across 32 studies that met inclusion for this review, data were evaluated from a total of 3821 participants that ranged in age from 9 – 67 years. We found that a total of 22 different assessments were employed in the studies, but six of those assessments appear to be the most commonly used (i.e., used in at least 3 or more studies). These assessments were: the Immediate Post-Concussion and Cognitive Testing (ImPACT) battery (Schatz et al., 2006), CogState (Collie et al., 2003), Trail Making Test, Part B (TMT-B) (Tombaugh, 2004), Digit Symbol Substitution Test (DSST) (Wechsler, 1939), the Sport Concussion Assessment Tool (SCAT), and King-Devick Test (K-D Test). Considerable overlap in the cognitive constructs examined by these assessments was found, including: concentration, visual processing, signs/symptoms, memory, and speed. Few assessments examined oculomotor function (only the K-D) and balance (SCAT). We also found a large sex disparity in the athletes evaluated, in which males greatly outnumbered female athletes. We also found that very few studies have examined youth athletes. Taken together, future studies are needed to evaluate the use of these assessments across different phases of injury, across different populations/demographics, and across age in order to improve the selection of appropriate assessment for research and clinical purposes. In addition, incorporation of common clinical assessments (e.g., neurological assessments) used by emergency department physicians and neurologists may be useful to examine in the context of research and may provide insights to overt and subtle changes in neurological function following a concussion.

The systematic review highlighted the need to specifically assess the relationship between sports-related concussion on behavioral and neurological function in pediatric populations. Since childhood and adolescence are periods of rapid development, longitudinal assessments across a broad age range are necessary to appropriately assess divergent trajectories of brain and neurocognitive function in those that have sustained a concussion. However, the evaluation of structural MRI, functional MRI, and/or neurocognitive assessments for a large longitudinal study are both costly in terms of human and financial resources. However, secondary data analyses of extant data sets may provide insights regarding the relationship between sports participation and developmental trajectories of brain and neurological function.

To this end, we examined the effect of contact sport participation on developmental trajectories of brain and neurocognitive function in healthy children and adolescents that participate in contact sports compared to those that do not participate in contact sports (Chapter 3). We acquired structural magnetic resonance images and behavioral measures from the National Institutes of Health MRI Study of Normal Brain Development (Evans & Brain Development Cooperative, 2006). This database was formed from a longitudinal, multi-site study including six participating sites with children including structural MRI, physical and neurological examination for soft sign (PANESS), and anthropometric information. Participants in the study provided one, two, or three time points. We used a subset of the database, which included those ages 4 - 22 years. Contact sports were defined as basketball, football, and soccer based on data from an epidemiological study that determined that these sports had the greatest prevalence of sports-related head injury (Graham et al., 2014). We hypothesized that

those that participate in contact sports would have atypical neurological developmental trajectories. We also hypothesized that those participating in contact sports would show a reduction in motor, cognitive, and intelligence scores compared to their peers that did not play sports.

Study 2 included a total of 306 participants (152 contact sports and 152 no-contact sport controls); 65 participants provided a single data point, 130 provided two data points, and 111 provided three data points. Beyond the expected Age and Sex effects, interactions between Age and contact sport exposure were observed for several brain regions and behavioral measures. These results suggest that participation in contact sports may lead to divergent developmental trajectories in brain development for cortical and subcortical brain regions; where grey matter development is more rapid, white matter and cerebellar development is more protracted for those participating in contact sports. With respect to the neurocognitive measures, greater participation in contact sports was associated with improved motor performance for the Timed Repetitive and Timed Patterned subtests of the neurological assessment and Purdue Pegboard Performance, particularly for older participants. In addition, the calculation portion of the Woodcock Johnson (WJ-III) also exhibited an interaction between age x contact sport exposure interaction suggests that younger participants with high contact sport participation showed greater performance on the WJ-III calculation test, compared to younger participants with less contact sport participation. However, the performance difference is attenuated for older participants.

Study 2 replicates and extends previous studies examining developmental trajectories in brain volume (Barnea-Goraly et al., 2005; Eminian et al., 2018; Giedd et al., 1999; Paus, 2005;

Sowell et al., 2002) and studies examining experience dependent plasticity related to environmental enrichment such as musical training and exercise (Basterfield et al., 2015; Gaser & Schlaug, 2003). This is the first study to report that participtionin contact sport may lead to divergent trajectories in brain and behavioral development. Moreover, this is the first study to go beyond generic sport participation and focus on sports that are associated with the highest risk for sports-related concussion in youth. Contrary to our intial hypotheses, participation in contact sports may lead to enhanced behavioral performance and neurological development, such that greater performance is associated with contact sports participation. It is possible that these results are due to the exclusion of participants that sustained a concussion (i.e., those participants were not included in the original database). Thus,
while our findings are consistent with previous research has classified sport participation as generally healthy, yielding positive physical, social, and emotional benefits, it is important for future studies to determine the effects of potentially harmful continued exposure to contact sports.

Taken together, this research provides important information to both the clinician and researcher on the current and potential future directions of neurological and behavioral assessments with regard to developmental changes in youth athletes participating in contact sports.

Chapter 2: A Systematic Review of Acute Sports-Related Concussion Assessments

Abstract

The purpose of this study was to systematically review the current assessments selected for acute sports-related concussion. Acquisition of the studies were from Electronic databases: Academic Search Premier, CINHAL, MEDLINE, PsycINFO, and SPORTDiscus. English-language, peer-review published studies of acute (<72 hours) concussion assessments were included. The studies included those involved in recreation, sport, or military activity at the time of injury. 32 studies met inclusion criteria (of 291 evaluated); 28 studies provided sufficient data to be included in the descriptive statistics of the assessments. These studies were organized by assessment name, studies employing the assessment, age, and sex of the participants. A total of 11 different acute assessments were used. Six of these assessments were used in at least 3. These assessments had many common features (e.g., concentration, visual processing, sign/symptoms), while other domains were not consistently evaluated (e.g., balance, language, eye movements). Only 12% of the population studied was female. The age range for these assessments was 9-67 years, although the majority of participants ranged in age between 18-35 years. Given the large number of assessments available, many of which assess overlapping domains, there is a need for a "gold" standard concussion assessment to enable consistency across research and clinical outcomes. In addition, we found a large discrepancy between the number of males and females assessed, suggesting that future studies are needed to determine if these current assessments identify concussion symptomology unique to females as well as

males. Further studies are needed to determine which assessments are appropriate and valid for youth athletes.

Introduction

A concussion is defined as "a complex pathophysiological process affecting the brain, induced by biomechanical forces"(McCrory et al., 2013). The clinical and behavioral manifestations of concussion are highly heterogeneous and as such, reliable, objective measurements and protocols are needed to accurately identify and track concussion symptomology. To address this, many organizations, including the National Athletic Trainers' Association and the American Medical Society for Sports Medicine, have developed position statements and specific protocols for evaluation (Broglio et al., 2014; Harmon et al., 2013; Marshall & Spencer, 2001), however, these position statements and protocols also differ. In an effort to standardize the definition and evaluation of suspected concussions, the International Conference for Concussion in Sport gathered experts from several international organizations to review and improve standard procedures for initial and follow-up evaluations with those that sustain a concussion (Aubry et al., 2002; McCrory et al., 2005; McCrory et al., 2017; McCrory et al., 2009; McCrory et al., 2013). Despite these efforts, healthcare professionals face the challenge of choosing the most appropriate tool amongst many options to aid in their decisions in diagnosing concussion and determining the impact of the injury across different domains (e.g., neurological, psychological, cognitive, motor, etc.) during the acute phase.

Researchers also need to identify which assessments should be used in the study of the acute and long-term impacts of concussion. Several concussion research consortia (e.g., CARE Consortium, Brain Concussion Neuroimaging Consortium, Concussion Research Consortium) have been developed to collect multi-site longitudinal data and curate repositories to

consolidate data for secondary analyses. Yet, heterogeneity of the assessment used vary amongst the sites within a consortium. For example, the CARE Consortium, the largest multi-site research effort to investigate concussion allows individual researchers to employ assessments of their choice. Thus, amongst the 28+ sites a number of different assessments were employed including but not limited to: ImPACT, Automated Neuropsychological Assessment Metrics, the Cogstate Computerized Cognitive Assessment Tool, the Standardized Assessment of Concussion, the Balance Error Scoring System, Sports Concussion Assessment Tool 3rd Edition (SCAT-3), and Brief Symptom Inventory (Broglio et al., 2017).

The aims of this systematic review were to identify the different acute concussion assessments that have been used in a research context and highlight the differences and similarities of the most widely used assessments. The goal was to aid researchers and clinicians in identifying which of these assessment may be most appropriate for their population and evaluate the assessment domains of interest.

Methods

Search strategy

An electronic search was conducted on March 01, 2017 and included full-text, articles from 2001 until the search date. We selected a start year of 2001 as the First International Conference on Concussion in Sport took place in 2001. The following electronic databases were queried: Academic Search Premier (EBSCOhost), CINHAL (EBSCOhost), PsychINFO (OVID), MEDLINE (OVID), and SPORTDiscus (EBSCOhost). The search terms included: human AND (head injury OR brain injury OR concuss* OR “mild traumatic brain injury” OR mTBI) AND (sport* OR athlet* OR military OR blast) AND (assess* OR immediate OR sideline OR acute) NOT (stroke or

cerebrovascular accident or cva or cerebral vascular event or cve or transient ischaemic attack or tia).

Study selection

Articles met inclusion based on the following criteria: original experimental studies (e.g., randomized controlled trials, case control, case-cross-overs, quasi-experimental), published in peer reviewed journals, participants were involved in sport, recreational activity, or military duties at the time of injury, and the assessment was administered acutely (here, we define acute as <72 hours). All articles were evaluated with respect to these inclusion criteria based on the title and abstract (step 1) and full-text review (step 2) by the author. The authors of articles that met inclusion at the full-text review that lacked key information (e.g., what assessments were used, number of participants evaluated, and the timing of the assessment) were contacted to clarify the methods and results for those studies (N=5) (see below for details).

Results

Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram for the search based on the PRISMA Guidelines (Moher et al., 2009). The initial query resulted in 3,023 articles. Once duplications were removed, 2,474 articles were assessed for inclusion for title and abstract review. A total of 321 were then considered for full-text review. The final number of studies that met inclusion was 32. Of these, the authors of 5 articles were contacted for additional information; data from 4 of these articles were not provided. Thus, this review assessed 28 articles.

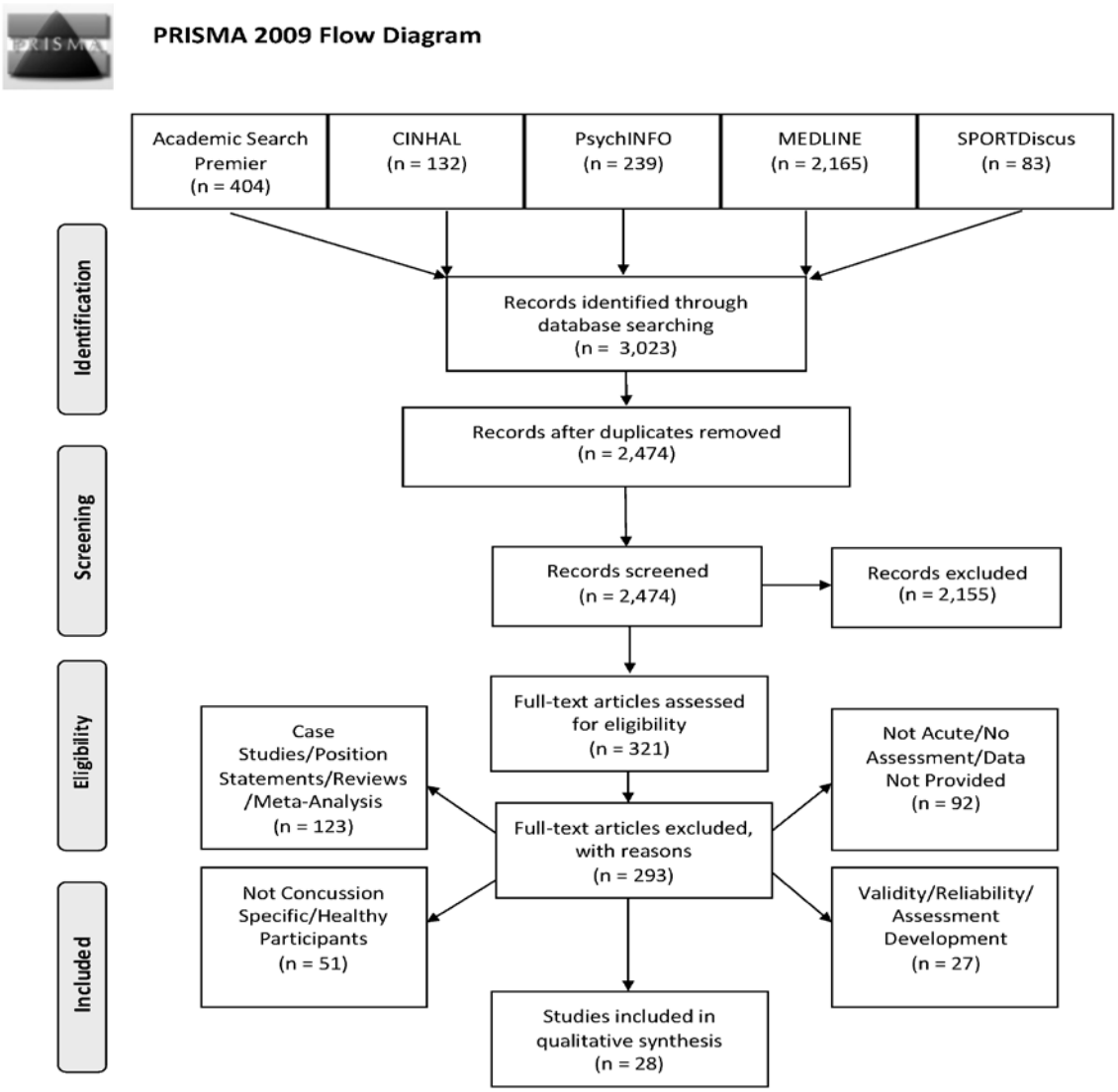

Figure 1. PRISMA Flow Diagram.

We evaluated 28 studies based on the assessment used, type of assessment (i.e., cognitive, motor, etc.), and participant demographics (i.e., age, sex). If portions of any assessment were included in a larger assessment battery (i.e., Standardized Assessment of Concussion (SAC) is part of the Sport Concussion Assessment Tool (SCAT)), then this was counted as use of the full assessment. Table 1 presents the details for all of the studies that met inclusion for the study.

Table 1 All studies included in the review.

Study	Assessment	N	Sex (N)	Age
(Baillargeon et al., 2012)	PCSS/NHL Battery	96	M (96)	9-24
(Benedict et al., 2015)	K-D/SCAT	80	Unreported	10-77
(Bock et al., 2015)	ImPACT	361	M(238) F(123)	11-39
(Broglio et al., 2011)	ImPACT	20	M(20)	15-18
(Collie et al., 2006)	DSST/TMT-B/ CogState	61	M(61)	18-28
(Covassin et al., 2013a)	ImPACT	165	M(111) F(54)	14-19
(Graves, 2016)	SCAT	15	M(15)	18-20
(Henry et al., 2016)	ImPACT	66	M(42) F(24)	14-22
(King et al., 2013)	K-D/SCAT	22	M(22)	18-26
(King et al., 2015)	K-D	19	M(14) F (5)	9-11
(Kontos et al., 2012)	ImPACT	75	M(51) F(24)	18-21
(Kontos et al., 2015)	ImPACT	19	M(19)	22-35
(Lau et al., 2011)	ImPACT	107	M(107)	13-19
(Lau et al., 2012)	ImPACT	108	M(108)	14-17
(Leong et al., 2014)	K-D	127	M(119) F(8)	18-20
(Makdissi et al., 2001)	DSST/TMT-B/CogState	6	M(6)	17-26
(Makdissi et al., 2009)	DSST/TMT-B	138	M(138)	24-25
(Makdissi et al., 2010)	DSST/TMT-B/CogState	88	M(88)	16-35

(McCrea et al., 2002)	SCAT	91	M(91)	15-20
(Mihalik et al., 2007)	ImPACT	180	M(152) F(28)	13-19
(Mihalik et al., 2013)	SCAT	296	M(241) F(55)	14-18
(Nance et al., 2009)	ImPACT	116	M(81) F(85)	11-17
(Norris et al., 2014)	ANAM4	210	Unreported	18-50
(Ono et al., 2016)	ImPACT	276	M(135) F(41)	10-18
(Pedersen et al., 2014)	ImPACT	14	M(14)	19-24
(Preiss-Farzanegan et al., 2009)	Rivermead PCS	215	M(144) F(71)	4-56
(Silverberg et al., 2014)	K-D/SCAT	26	M(19) F(7)	18-60
(Sosnoff et al., 2008)	ImPACT/Headminder/SOT	20	Unreported	19-22

Six assessments were included three or more times in the 28 articles reviewed (Figure 2). Thirteen studies used the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT Applications, San Diego, CA), 8 studies used the SCAT, 5 studies used the King-Devick (K-D), 4 studies each used the Digit Symbol Substitution Test (DSST) or Trail Making Test Part B (TMT-B), and 3 studies used the CogSport. In addition, five assessments were used in one or two studies (not shown in Figure 2) including: Headminder, Rivermead Post Concussion Symptoms Questionnaire, Automated Neuropsychological Metrics 4, Sensory Organization Test (SOT), and a derivative of the NHL concussion battery. For details for the 6 primary assessments that were included in this review, please see the supplementary materials (Appendix A).

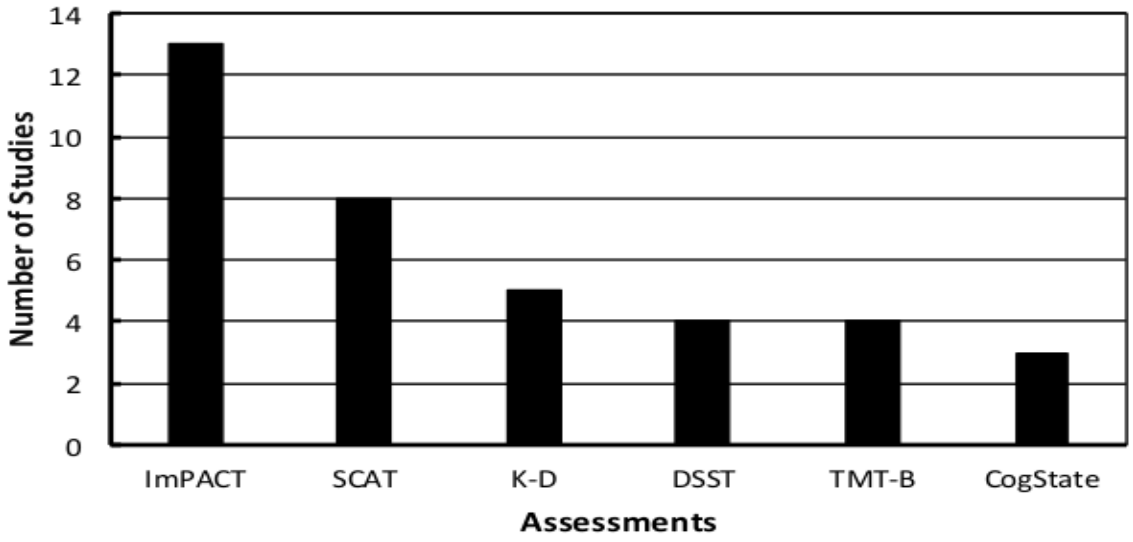

Figure 2. Number of studies employing each assessment.

Several of the domains overlap across the assessments (Table 2). Concentration and visual processing are included in 4 of the 6 assessments. Memory, processing speed, and symptoms are included in 3 of the 6 assessments. Balance, however, is only measure in the SCAT and eye movements and language are only assessed by the K-D Test.

Table 2 Assessments used 3 or more times, their cost and delivery method, and the domains they assess.

Assessment	Cost	Method	Domain(s)
ImPACT	$10.00-$20.00/Exam	Computer	Concentration, Visual Processing, Symptom, Memory, Processing Speed, Reaction Time,
SCAT	Free	Paper	Concentration, Symptom, Memory, Orientation, Balance, Physical

K-D	$20.00/Exam	Both	Visual Processing, Eye Movement, Language, Processing Speed
DSST	Free	Both	Concentration, Visual Processing
TMT-B	Free	Paper	Concentration, Visual Processing, Task Switching
CogState	License	Computer	Symptom, Memory, Attention, Processing Speed, Learning

There are other assessment features that are worth considering. The ImPACT battery and CogState are computerized tests. These tests cost more than the others, with the CogState battery offering a license for testing, and the ImPACT battery allowing either licensing or pay-by-test. If a comparison with baseline performance (i.e., pre-season) is of interest, the ImPACT battery has unique capabilities to determine if a participant is purposefully attempting to artificially score poorly on the baseline test. While the SCAT, TMT-B, and DSST are all paper-based assessments, these assessments are either freely available or low-cost.

A total of 3,601 participants were assessed across all included studies (Figure 3). Three studies did not specify sex (Benedict et al., 2015; Norris et al., 2014; Sosnoff et al., 2008). Of the studies that specified the number of participants by sex, 2,651 males and 479 females were included, with 471 participants' sex not reported (Figure 3). The disparity between the number of studies that have investigated male athletes and those that investigated female athletes is clear. Several of these commonly used assessments were not used to evaluate female participants (e.g., DSST, TMT-B, and CogSport).

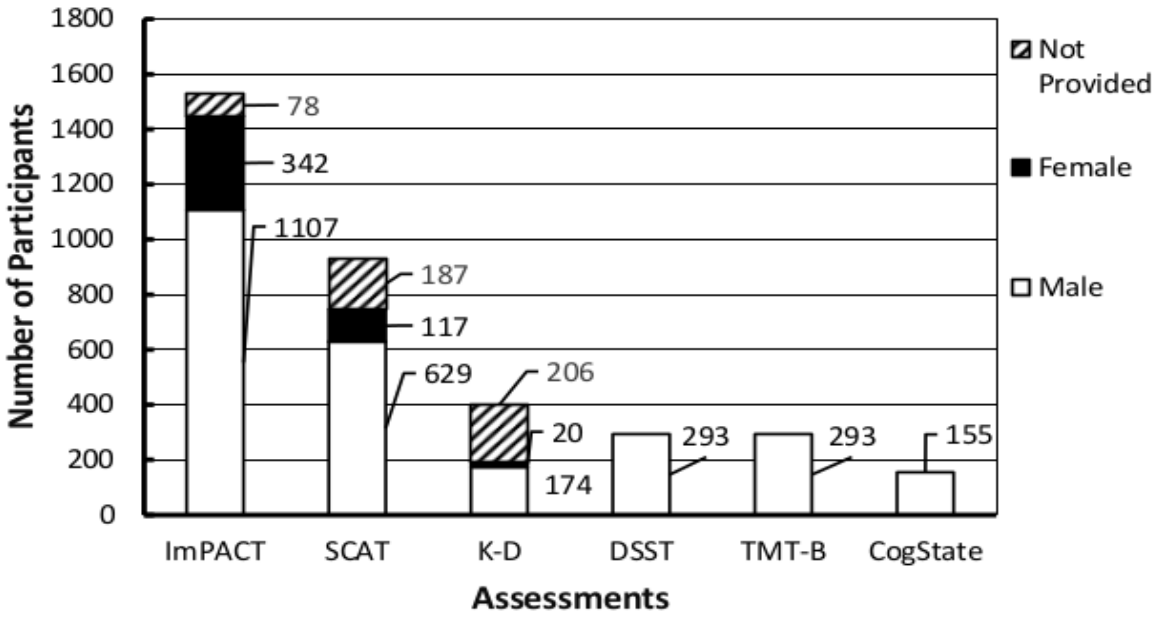

Figure 3. Number of participants by sex using each assessment.

The age range across all studies was 9-67 years. Figure 4 presents the age range of participant evaluated for each assessment. Although the ImPACT test has been used with the largest number of participants, a relatively restricted age range of participants (10-35 years) were tested in the studies included in this review. In contrast, a much broader age range of participants is found for the SCAT and K-D Test (i.e., 14-67 years and 9-67 years, respectively). The DSST, TMT-B, and CogState were used to evaluate a much smaller age range of participants (16-35 years).

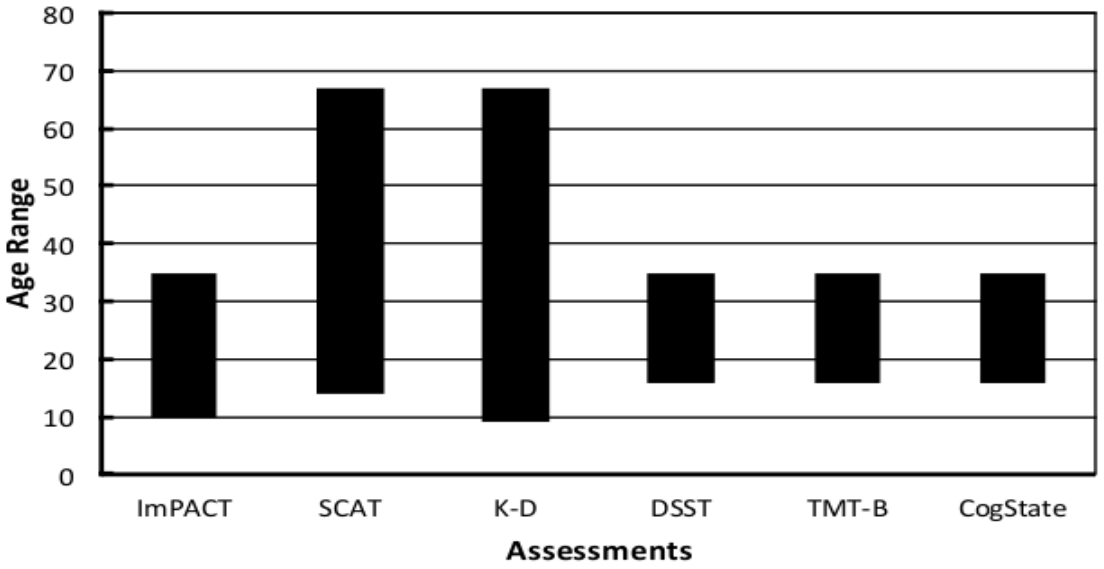

Figure 4. Age range of each assessment.

Discussion

This systematic review examined assessments used during the acute phase following a concussion. Findings from 28 studies were reported, in which a total of 3,821 participants, ranging in age from 9-67 were evaluated. A total of 11 assessments were employed in the studies, but six of those assessments appear to be the most commonly used (i.e., used in at least 3 or more studies). However, it is important to note that an additional 5 assessments were used, albeit to a lesser degree. Based on the current review, the latter assessments are used more often in other setting (e.g., military deployment, emergency rooms, etc.).

The need in research and the clinic for a gold-standard assessment is evident. This review highlights the largely homogenous domains assessed among the most prevalent sport-related concussion assessments in research (Table 2). Such a number of overlapping domains increases the difficulty of selecting the best method of concussion evaluation. Broglio et al. (Broglio et al., 2017) describes the evolution and current needs of a well-rounded, objective,

concussion assessment. Several of the assessments in this review measure several of the recommended domains, yet no single assessment objectively measures all (Van Kampen et al., 2006).

A large number of participants have been assessed in the context of research using these instruments. Information about the use of these instruments in clinical practice would be valuable in the future. For example, which instruments are being used in a clinical setting? What factors may influence the use of these instruments in the clinic or on the sideline (e.g., cost, administration time, logistical considerations)?

There is a large disparity between the number of male athletes evaluated using these assessments compared to female athletes. Females represent only 12.5 percent of the population in this review, whereas females represent 28 percent of the population of high school and college athletes (Senne, 2016). The disproportionate number of males could be due, in part, to the focus on American football in concussion research. Nevertheless, females have a higher incidence rate of concussion(Black et al., 2017; Covassin et al., 2016), and report more concussion symptoms and longer recovery times(Covassin et al., 2013b). As such, future research should evaluate the efficacy of these assessments in female athletes.

The majority of studies included in this review have examined adults, with some studies including participants as old as 67. A growing number of studies have begun to investigate the effects of concussion in youth and the potential long-term impact on cognitive and neurological development. However, of the assessments evaluated in the present study, only 3 of the 6 commonly used assessments included participants as young at 10 years of age. There are several possible explanations for a lack of youth athletes evaluated. First, only 4 out of the 6

assessments are validated for younger participants. Second, the level of cognitive function changes considerably during childhood and adolescence. Studies may have included a smaller age range for sample consistency. Further studies are needed to determine which assessments are appropriate and valid for youth athletes. In addition, it is imperative that normative data be established for sensitive periods of development.

The purpose of the present study was to examine the assessments that are utilized most commonly during the acute phase of concussive injury. However, vast majority of studies have evaluated sub-acute and chronic injury. Validation of these assessments across all phases of injury (i.e., acute, sub-acute, chronic), across different populations (i.e., male and female athletes) and developmental levels (i.e., children, adolescents, and adults) are currently lacking. These knowledge gaps should be addressed in future studies.

Chapter 3: Longitudinal Assessment of the Effects of Contact Sport Participation on Brain Structure and Behavior in Children and Adolescents

Abstract

The typically developing brain undergoes considerable structural changes that result in measurable difference in cortical and subcortical grey and white matter volumes across childhood and adolescence. These changes are related to age and sex, but have yet to be related to contact sport participation. Thus, the current study aimed to determine the longitudinal effects of single and multiple contact sports participation, compared to a control group, on brain structure during childhood and adolescence, as well as the effects of cumulative contact seasons. We hypothesized a dose effect of contact sports participation such that those that participating in multiple contact sports would exhibit different developmental trajectories in brain and neurocognitive function compare to single contact sport or no contact sport participation.

Using a database of pediatric neuroimaging and physical and neurological assessments developed by the National Institutes of Health (NIH) MRI Study of Normal Brain Development. We used a subset of healthy children and adolescents that played contact sports with no history of head injury and matched them by sex, age, and income with those that did not play sports.

Several significant volumetric differences were discovered in the brain. Specific areas that exhibited an age by cumulative contact sport participation were frontal and temporal grey

matter in addition to total grey matter. Moreover, frontal and temporal white matter also show the similar, but opposite interactions. Behaviorally, a difference was seen in timed repetitive and patterned as well as the Woodcock Johnson (WC-III) calculation subtest.

These differences highlight an effect of contact sport participation and solidify the need for further research. Future research is needed to determine the deviations from these patterns following concussive and subconcussive impacts and other potential head injuries.

Introduction

The typically developing brain undergoes considerable structural changes that result in measurable differences in cortical and subcortical grey and white matter volumes across childhood and adolescence (Barnea-Goraly et al., 2005; Eminian et al., 2018; Giedd et al., 1999; Paus, 2005; Sowell et al., 2002). Recent longitudinal studies have reported that although regional/lobar differences in the developmental trajectory of brain development are observed, overall, cortical grey matter volume increases through childhood, peaks around puberty, and decreases across adolescence (Brain Development Cooperative Group, 2012; Mills et al., 2016). In contrast, peak white matter volumes are not achieved until late adolescence and then begin to decline in early adulthood (Brain Development Cooperative Group, 2012; Mills et al., 2016). The developmental trajectory of subcortical structures also exhibited a protracted development with peak volumes achieved in adolescence (Wiergenga, 2014).

Beyond these age-related (maturational) changes in brain volumes, childhood and adolescence represent periods of brain development particularly sensitive to environmental factors. Research has shown that an enriched environment can lead to increase in cortical and subcortical plasticity (Hirase & Shinohara, 2014; Sale et al., 2009). Extracurricular activities can be considered environmental enrichment and would likely impact the trajectory of brain development, particularly if started early during childhood when the brain is sensitive to experience-dependent plasticity. The few studies have examined the relationship between structural brain development and extracurricular activities have predominantly focused on second language learning (Bartolotti et al., 2017; Stein et al., 2012; White et al., 2013) and musical training (Gaser & Schlaug, 2003; Hyde et al., 2009; Munte et al., 2002). For example,

compared to non-musicians, adult musicians exhibit greater grey matter volume in primary motor cortex, primary auditory cortex, and superior parietal cortex brain volume (Gaser & Schlaug, 2003) and cerebellum (Hutchinson et al., 2003). Interestingly, in a follow-up study, Hyde et al. (2009) reported that 15 months of musical training during early childhood (~ages 5-7 years) resulted in greater volume of similar brain regions (e.g., primary motor cortex, primary auditory cortex) as well as additional regions in the frontal cortex. Similar results were reported by Hudziak et al. (2014), who examined longitudinal trajectories of cortical thickness with respect to years of musical (instrumental) experience. In this study, age interacted with years playing a musical instrument, such that musical training was associated with an increased rate of cortical maturation of several motor-related brain regions as well as prefrontal and parietal regions.

Similar to musical training, sport and exercise participation enhanced motor and cognitive functions as well as promote physical fitness and physical activity levels (Hopkins et al., 2012). For example, greater motor performance and fitness were observed for children and adolescents with a higher number of sports and greater number of hours participating in sports (Fransen et al., 2012; Vandorpe et al., 2012). Sports participation is associated with reduced adiposity and greater physical activity levels (Basterfield et al., 2015). Moreover, greater participation in sports is positively associated with high school GPA, independent of overall physical activity levels (Fox et al., 2009).

Only recently has any study examined the effect of sports participation on brain development. López-Vincent et al. (2017) examined the relationship between sports participation and brain structure in children (ages 6-10 years). This large, cross-sectional study

found a positive relationship between cortical thickness in motor and premotor regions, but did not find any relationship with grey matter volume. Thus, it would be reasonable to hypothesize that sports participation would likely yield similar, if not greater, neuroplastic effect when examined over the course of childhood and adolescence. Indeed, sports participation may enhance a broad network of cortical and subcortical brain regions. Yet, few studies have examined changes in subcortical structures, such as the cerebellum, related to extracurricular activities despite the central role of the cerebellum in motor and cognitive aspects of skill acquisition.

Although youth sports participation may promote brain development, the relationship is muddled by a lack of research and the growing body of literature regarding youth sport concussion. Recent studies have suggested that youth sport concussion is on the rise with more than 250,000 children and adolescents admitted to emergency departments yearly with concussion related injuries (McCrory et al., 2004). Indeed, children are more likely to have a longer recovery from youth sport concussions, compared to adolescents or adults suggesting that children's brains may be at greater risk for long-term changes in neurological development following a concussion (Field et al., 2003). Moreover, subconcussive injuries may be incurred during participation in contact sports, which may result in microtrauma that may cause additional neurological impairments over time (Baugh et al., 2012). Therefore, it is worthwhile to determine whether or not participation in sports, particularly contact sports, leads to different developmental trajectories in healthy children and adolescents.

Thus, the current study aimed to determine the longitudinal effects of contact sports participation on brain structure and neurocognitive outcomes in children and adolescents. To

do this, we examined volumetric brain measures, a sports participation questionnaire, and neurocognitive assessments from the MRI Study of Normal Brain Development, a multi-site, pediatric neuroimaging and behavioral database developed by the National Institutes of Health (Evans & Brain Development Cooperative, 2006). A total of 306 healthy participants ages 5 to 22 years provided one (N=65), two (N=130), or three (N=111) data points acquired roughly 2 years apart. We hypothesized a dose effect of contact sports participation such that those with greater participation in contact sports would exhibit different developmental trajectories in brain and neurocognitive function compared to those with less or no contact sport participation.

Methods

Data Acquisition and Analysis

Data were obtained from the National Institutes of Health Study of Normal Brain Development (Evans & Brain Development Cooperative, 2006; Waber et al., 2007; Waber et al., 2012) through the National Institutes of Mental Health (NIMH) Data Archive (https://data-archive.nimh.nih.gov/). This is a multisite, longitudinal study of typically developing children from ages newborn through young adulthood conducted by the Brain Development Cooperative Group and supported by the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke (Contract #s N01-HD02-3343, N01-MH9-0002, and N01-NS-9-2314, -2315, -2316, -2317, -2319 and -2320). A listing of the participating sites and a complete listing of the study investigators can be found at: http://pediatricmri.nih.gov/nihpd/info/participating_centers.html. This manuscript reflects the

views of the authors and may not reflect the opinions or views of the NIH.

Participant Selection and Definition of Contact Sports Participation

Parents completed an MRI Child History Questionnaire that asked about participation in sports (baseball, basketball, boxing, football, hockey, lacrosse, soccer, and "other sports"), incidence of head injuries, and exposure to potential environmental enrichment (e.g., breastfeeding or musical training) or environmental impacts (e.g., anesthesia, lead, steroids). Participants were selected based on their participation in basketball, football, soccer, or a combination of these sports (i.e., multisport) for the current study. These sports were selected based on epidemiological studies suggesting a high incidence of youth sport-related concussions from these sports (Gessel et al., 2007; Lincoln et al., 2011; Marar et al., 2012). The years of participation in basketball, football, and soccer was summed to provide an index of the number of seasons participating in contact sports. Each individual identified as participating in basketball, football, and soccer was matched to a control based on age, sex, total household income, and race. A participant was considered a control if they had less than 2 seasons of contact sports over the previous two years (e.g., played one year of basketball at age 7 and one year of soccer at age 8, but was tested at age 9).

A total of 306 healthy participants ages 5 to 22 years provided one (N=65), two (N=130), or three data points (N=111) acquired roughly 2 years apart. Table 3 presents the number of participants, mean age and standard deviation, and mean income level and standard deviation for the controls and contact sport participants.

Table 3. Participant demographics including number of participants total and by sex, mean age and standard deviation, mean income level and the standard deviation, and mean number of seasons in contact sports and standard deviation. * indicates a significant difference between the controls and contact sport group at the $p < 0.001$ level.

Group	N (Male/Female)	Mean Age (SD)	Mean Income Level (SD)	Mean Number of Seasons In Contact Sports (SD)
Controls	153 (74/79)	12.67 (3.95)	6.16 (1.31)	0.65 (1.29)
Contact Sports	153 (74/79)	12.65 (3.84)	6.71 (1.16)*	6.02 (4.98)*

Structural MRI

The MRI volumetric analysis pipeline has been described previously by Evans and colleagues (Evans & Brain Development Cooperative, 2006). Briefly, brain extraction was performed on the average of T1, T2, and proton density (PD) images. Linear and non-linear registrations were used to transform raw MRI into MNI stereotaxic space. Images were then segmented and labeled using Automatic Nonlinear Image Matching and Anatomic Labeling. All volumetric data passed quality inspection. Volumetric measurements for total grey and white matter volume, lobar grey and white matter volume (Left + Right Frontal, Left + Right Parietal, Left + Right Occipital, Left + Right Temporal) and Cerebellum (Left + Right) volumes were computed.

Neurological Examination

A neurological examination was administered to preclude any participants that exhibited overt neurological problems; none of the participants were excluded based on this assessment. The full procedures for this assessment may be found in the procedure manual for Objective 1 of

the NIH Study of Normal Brain Development (https://pediatricmri.nih.gov/nihpd/info/Documents/Objective1_procedure_manual.pdf). Of the 111 items evaluated, the following component scores were computed consistent with the Physical and Neurological Assessment of Soft Signs (PANESS; (Trudler et al., 2015)): Gaits, Stations, Overflow, Timed Repetitive, and Timed Patterned. The Gaits score was the total errors for the lower extremities (e.g., not striking on heel during the heel walking task) and degree abnormal upper extremity movements (e.g., changes in arm postures to dystonia-like positions) during normal, heel, side of feet, and tandem walking. The lower extremity movements for the left and right limbs were each scored as 0 = no errors, 1 = 1-2 errors, and 2 = 3 or more errors for each of the gaits. The upper extremity movements for the left and right limbs were scored as 0 = absence of abnormal movements or 1 = presence of abnormal movements. The Stations score included Romberg Sign and single-leg hopping ten times in place on the left and right legs. Romberg Sign was scored as 1 = stable and eyed closed for 20 seconds, 2 = completed the task with eyes closed by body wavered, 3 = lost balance and stepped out of position, and 4 = opened eyes during the task. The single-leg hopping was scored for each leg as 0 = successful on all 10 hops, 1 = not successful on all 10 hops, and 2 = unable to get balanced on one foot. The Overflow score was based on a sum of the upper extremity movement scores during the gait tasks described above. The Timed Repetitive score was the total time needed to complete 20 repetitions of the following movements: thumb and forefinger opposition for the left and right hands, palm tapping on the thigh for the right and left sides, and heel tapping for the left and right feet. The Timed Patterned score was the total time needed to complete the following movements: thumb-finger sequential opposition (index-middle-ring-little; 5 sets) for the left

and right hands, alternating palm and dorsum pat on the thigh (20 times), and heel-toe tapping (20 times).

Other Behavioral Assessments:

In addition to the Neurological Assessment, we examined the Behavioral Rating Inventory of Executive Function (BRIEF) Global Executive Composite (GEC) score, the Purdue Pegboard for both hands, and IQ (a full scale, performance, and verbal) from the Wechsler Abbreviated Scale of Intelligence (WASI). The GEC score is a composite score derived from the 86-items of the BRIEF parent questionnaire that assesses executive functioning at school and home. The Purdue Pegboard measures coordination and manual dexterity, for the current analysis the total number of pegs placed with both hands was assessed. The full scale, performance, and verbal IQ scores were obtained from the WASI. Performance IQ measures non-verbal skills, such as placing objects in a specific order. Verbal IQ measures problem-solving using language-based reasoning. Full-scale IQ is a combination of the performance and verbal measurements.

Statistical Analysis

All statistical analyses were performed using R/RStudio (3.3.0/1.0.136). Linear mixed-effects models were used to evaluate the following base model for each brain region. For example:

$$Y_{ij} = \beta_0 + \beta_1 X_{Age} + \beta_1 X_{Age\text{^}2} + \beta_2 X_{Age\text{^}3} + \beta_3 X_{Sex} + \beta_4 X_{Age\ x\ Sex} + \beta_5 X_{Sport} + \gamma_i + \varepsilon_{ij}$$

where: Y_{ij} = observed MRI volume or behavioral variable for individual i at time j, β_0, β_1, β_2, β_3, β_4, β_5 = regression coefficients, and γ_{ij} is the random intercept for subject *i* and slope across time. Time was measured as the age interval between repeated measures.

The linear mixed effects modeling approach accounts for correlations amongst repeated measures for both the dependent and covariates. Using this model, subject specific age-based

slopes and intercepts were computed to control for repeated measures. Time was measured as the age interval between repeated measures for each subject.

Results

The statistical results are represented in Table 4 for the brain volumes and Table 5 for the behavioral measures. As expected, several MRI volumes and behavioral measure exhibited main effects of age and/or sex. **I**nterestingly, a main effect of Number of Seasons in Contact Sports and an interaction between Age and Age x Number of Seasons in Contact Sports were revealed for several of the brain regions and behavioral measures. These effects will be discussed with respect to differences in grey matter volumes, white matter volumes, cerebellum, and neurocognitive assessments below.

Table 4. Statistical output for all MRI measures, including the regression coefficients (β), standard errors (SE) for each coefficient, the degrees of freedom, the T-values, and p-values. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Brain Region	**β**	**SE**	**df**	**t-value**	**p**
Total Grey Matter					
Intercept	8.12e5	5.34e3	331	152	<0.001***
Age	-6.66e3	790	245	-8.44	<0.001***
Sex	7.18e4	7.31e3	296	9.82	<0.001***
Contact Seasons	1.93e3	632	588	3.05	0.002**
Age*Contact	-303	132	411	-2.29	0.022*
Total White Matter					

Intercept	4.14e5	4.15e3	338	99.8	<0.001***
Age	6.39e3	610	621	10.5	<0.001***
Sex	4.67e4	5.68e3	299	8.22	<0.001***
Contact Seasons	1.15e3	501	587	2.29	0.022*
Age*Contact	-184	104	493	-1.77	0.078
Frontal Grey					
Intercept	2.79e5	2.01e3	325	139	<0.001***
Age	-2.25e3	274	266	-8.20	<0.001***
Sex	2.31e5	2.77e3	294	8.35	<0.001***
Contact Seasons	783	209	540	3.75	<0.001***
Age*Contact	-139	43.5	415	-3.20	<0.001***
Frontal White					
Intercept	1.54e5	1.50e3	331	102	<0.001***
Age	2.42e3	190	581	12.7	<0.001***
Sex	1.70e5	2.08e3	299	8.18	<0.001***
Contact Seasons	343	151	520	2.26	0.024*
Age*Contact	-65.1	31.0	459	- 2.10	0.036*
Occipital Grey					
Intercept	6.88e5	737	332	93.4	<0.001***
Age	-866	102	251	-8.51	<0.001***
Sex	7.20e3	1.02e3	300	7.07	<0.001***

Contact Seasons	78.6	81.2	550	0.980	0.334
Age*Contact	7.03	16.8	376	0.420	0.675
Occipital White					
Intercept	3.38e5	570	337	59.3	<0.001***
Age	558	84.3	612	6.63	<0.001***
Sex	5.61e3	779	295	7.21	<0.001***
Contact Seasons	123	69.2	591	1.77	0.077
Age*Contact	-13.3	14.4	496	- 0.926	0.355
Parietal Grey					
Intercept	1.37e5	1.13e3	330	122	<0.001***
Age	-2.02e3	158	624	-12.8	<0.001***
Sex	1.4e5	1.55e3	297	9.03	<0.001***
Contact Seasons	239	129	566	1.86	0.064
Age*Contact	-32.4	26.4	484	-1.23	0.221
Parietal White					
Intercept	8.13e5	880	334	92.4	<0.001***
Age	1.28e3	117	600	10.9	<0.001***
Sex	1.03e4	1.22e3	300	8.40	<0.001***
Contact Seasons	159	94.1	533	1.69	0.0921
Age*Contact	-32.8	19.3	460	-1.70	0.0897
Temporal Grey					

Intercept	1.70e5	1.22e3	328	140	<0.001***
Age	-1.11e3	172	240	-6.45	<0.001***
Sex	1.62e4	1.68e3	292	9.69	<0.001***
Contact Seasons	423	137	561	3.10	0.002**
Age*Contact	-72.2	28.4	406	-2.54	0.011*
Temporal White					
Intercept	7.64e4	850	340	89.9	<0.001***
Age	1.16e3	125	209	9.23	<0.001***
Sex	8.13e3	1.16e3	304	6.98	<0.001***
Contact Seasons	241	103	578	2.34	0.020*
Age*Contact	-53.7	21.3	294	-2.53	0.012*
Cerebellum					
Intercept	1.30e5	909	315	142	<0.001***
Age	806	85.5	222	9.43	<0.001***
Sex	9.53e3	1.28e3	300	7.44	<0.001***
Contact Seasons	241	59.7	432	4.04	<0.001***
Age*Contact	-63.8	12.1	387	-5.27	<0.001***

Grey Matter Volumes

With respect to grey matter volume, total grey matter (Figure 5), frontal grey matter (Figure 6), and temporal grey matter (Figure 7) all exhibited significant main effects for Number of Seasons in Contact Sports and interactions between Age and Number of Seasons in Contact Sports.

Overall, greater participation in contact sports is associated with greater volumes of these structures. In addition, the age-related decrease in grey matter (from 5 – 22 years) is greater (i.e., more negative slope) for the participants with greater participation in contact sports, compared to those with less participation in contact sports.

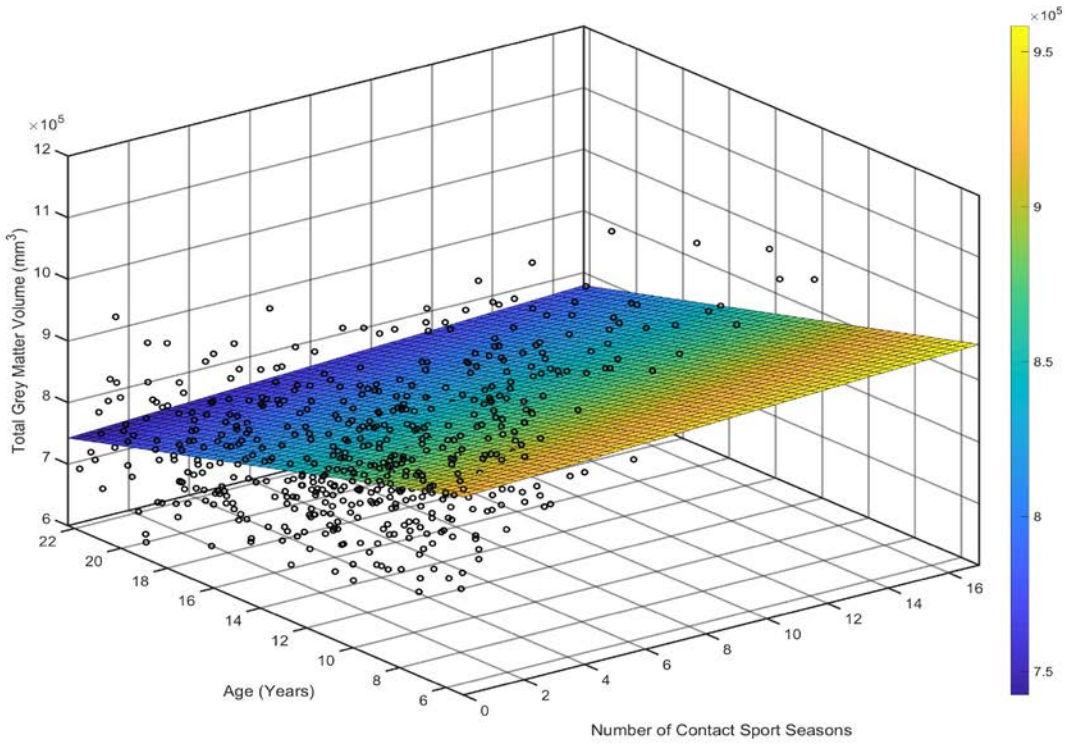

Figure 5. Total grey matter volume by age and contact sport seasons.

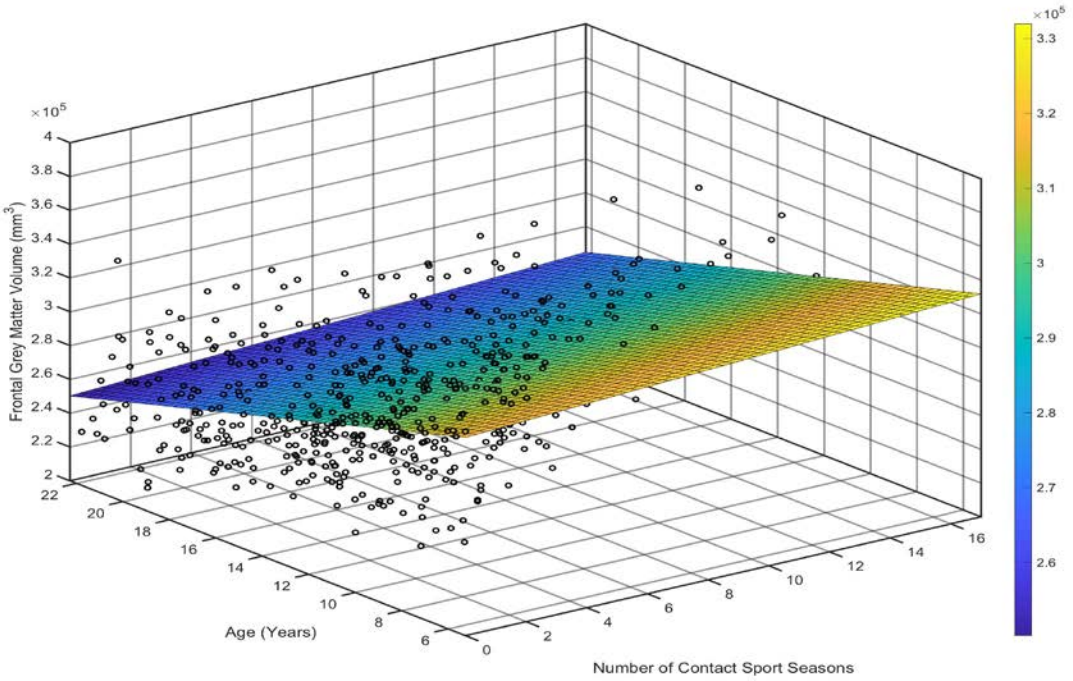

Figure 6. Frontal grey matter volume by age and contact sport seasons.

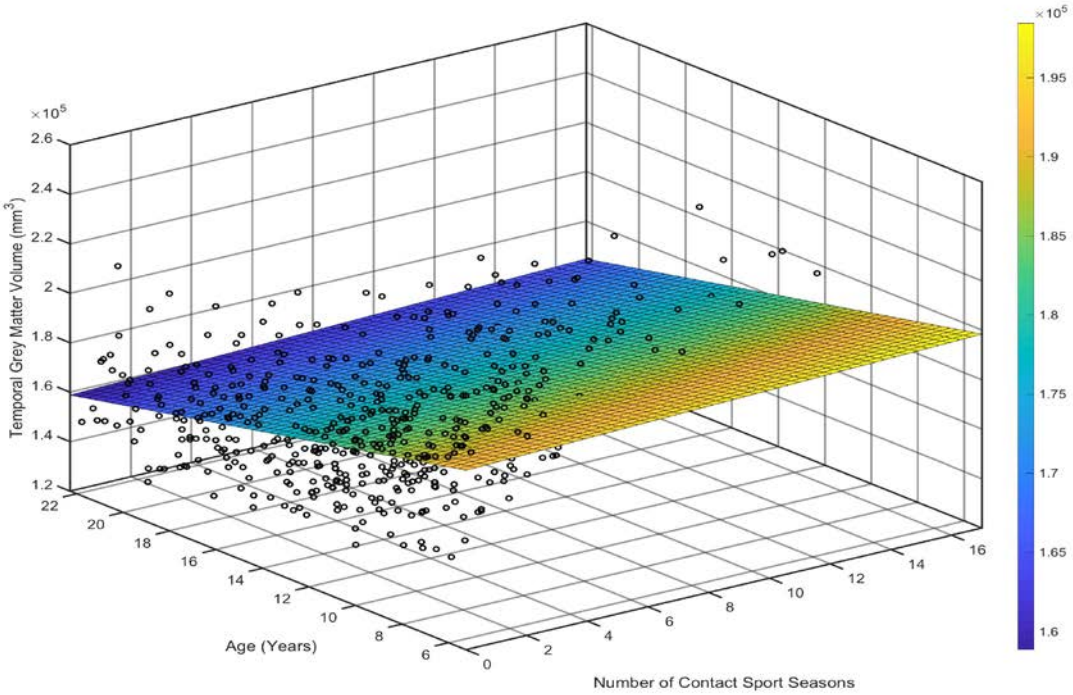

Figure 7. Temporal grey matter volume by age and contact sport seasons.

White Matter Volumes

Again, significant main effects for Number of Seasons in Contact Sports were observed for total white matter, frontal white matter, and temporal white matter. Overall, greater participation in contact sports is associated with greater volumes of these structures. Interactions between Age and Number of Seasons in Contact Sports were observed for frontal white matter (Figure 8) and temporal white matter (Figure 9); the interaction for total white matter approached conventional significance (see Table 4). Interestingly, age-related increase in white matter volume (from 5 – 22 years) was reduced in participants with greater participation in contact sports, compared to those with less participation in contact sports.

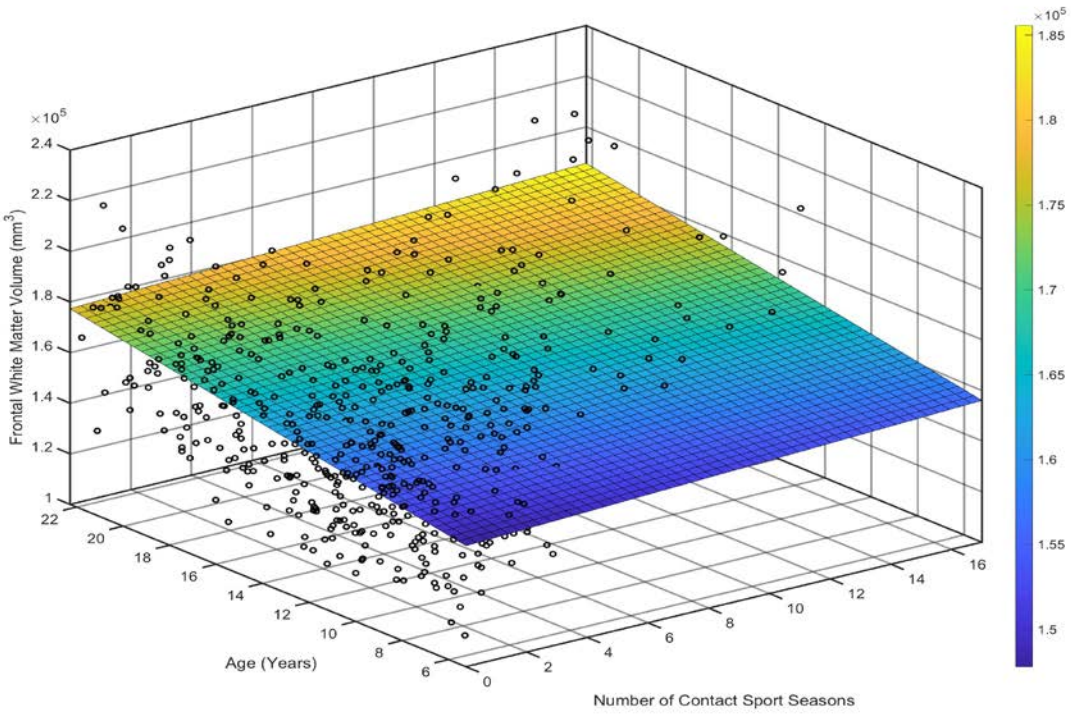

Figure 8. Frontal white matter volume by age and contact sport seasons.

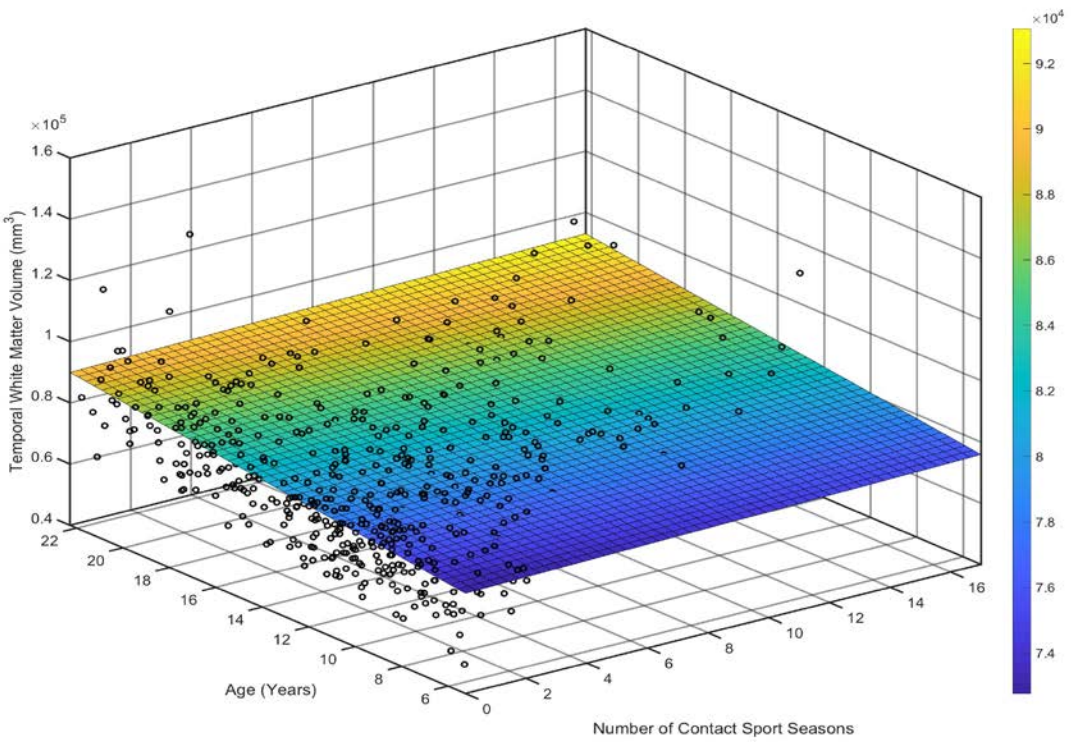

Figure 9. Temporal white matter volume by age and contact sport seasons.

Cerebellum Volume

The main effect for Number of Seasons in Contact Sports was striking for cerebellum volume (Figure 10). Greater participation in contact sports was associated with a greater volume of the cerebellum, compared with those with less participation across all ages. The Age x Number of Seasons in Contact Sports relationship for the cerebellum was similar to that observed for white matter. Age-related increases in cerebellum volume (from 5 – 22 years) was reduced for the participants with greater participation in contact sports, compared to those with less participation in contact sports.

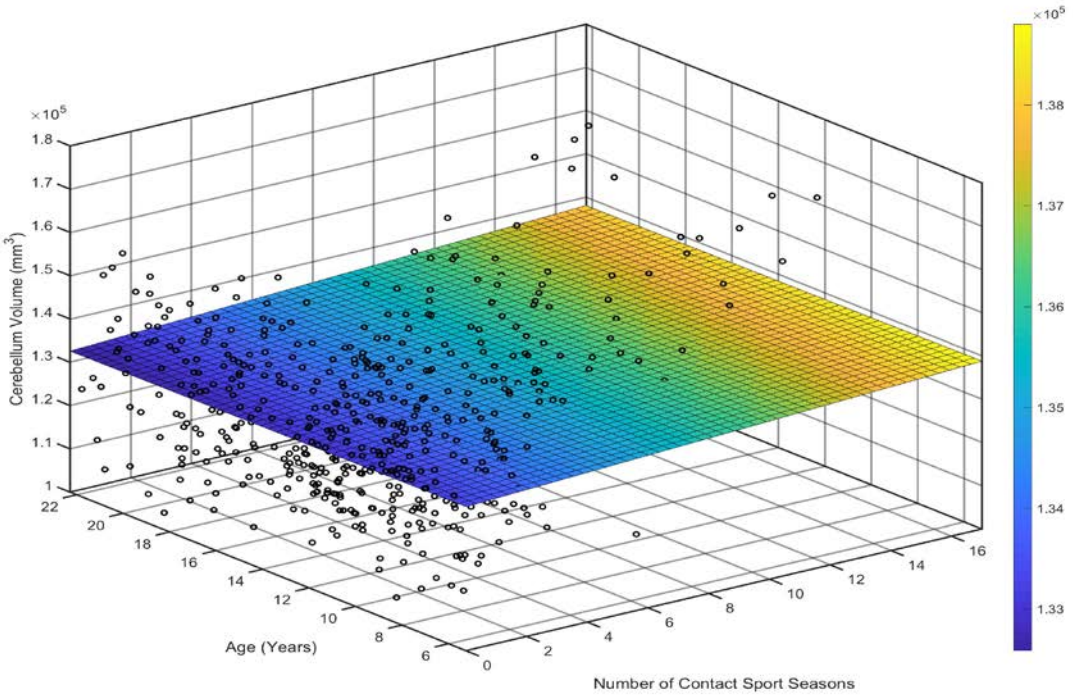

Figure 10. Cerebellum volume by age and contact sport seasons.

Taken together, the volumetric results suggest perhaps that although those participating in contact sports may exhibit greater brain volumes overall, participation in contact sports may lead to divergent developmental trajectories in brain development for cortical and subcortical brain regions. Grey matter development is more rapid, while white matter and cerebellar development is more protracted for those participating in contact sports compared to those with less contact sport participation.

Behavioral Assessments

With respect to the neurocognitive measures (Table 5), main effects for Number of Seasons in Contact Sports were observed for the timed repetitive subtest of the Physical and Neurological Examination for Soft Signs (PANESS), Purdue Pegboard, and Woodcock-Johnson III calculation

subtest. Across all ages, participants with greater participation in contact sports exhibited better performance, compared to those with less participation in contact sports.

Table 5. Statistical output for all MRI measures, including the regression coefficients (β), standard errors (SE) for each coefficient, the degrees of freedom, the T-values, and p-values. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Behavioral Measures	**β**	**SE**	**df**	**t-value**	**p**
Gait					
Intercept	6.22e-1	9.02e-2	4.31e2	6.90	<0.001***
Age	-9.58e-2	1.82e-2	3.55e2	-5.27	<0.001***
Sex	6.79e-3	1.09e-1	6.12e2	0.062	0.950
Contact Seasons	6.83e-3	1.41e-2	6.19e2	0.484	0.628
Age*Contact	7.82e-4	3.14e-3	4.49e+2	0.249	0.804
Stations					
Intercept	1.02	1.93e-2	5.33e2	53.15	<0.001***
Age	-1.64e-2	4.28e-3	3.05e2	-3.82	<0.001***
Sex	3.90e-2	2.55e-2	6.19e2	1.53	0.126
Contact Seasons	-1.74e-3	3.31e-3	5.74e2	-0.524	0.601
Age*Contact	4.89e-4	8.03e-4	4.40e2	0.609	0.543
Overflow					
Intercept	5.10e-1	8.06e-2	3.53e2	6.32	<0.001***
Age	-6.70e-2	1.60e-2	3.25e2	-4.19	<0.001***
Sex	6.60e-3	9.88e-2	2.062e2	0.067	0.947
Contact Seasons	1.07e-2	1.26e-2	6.15e2	0.849	0.396

Age*Contact	-4.60e-4	2.78e-3	4.15e2	-0.165	0.869
Timed Patterned					
Intercept	208	6.49	564	32.04	<0.001***
Age	-5.77	1.48	185	-3.89	<0.001***
Sex	10.1	8.69	585	1.16	0.245
Contact Seasons	1.02	1.13	531	0.902	0.367
Age*Contact	-0.596	0.28	333	-2.13	0.034*
Timed Repetitive					
Intercept	186	5.34	321	34.8	<0.001***
Age	-14.9	1.04	213	-14.3	<0.001***
Sex	-7.19	6.96	293	-1.03	0.302
Contact Seasons	-4.01	0.823	570	-4.87	<0.001***
Age*Contact	0.723	0.190	472	3.80	<0.001***
Purdue Pegboard					
Intercept	10.6	0.121	314	87.2	<0.001***
Age	0.282	0.023	227	12.2	<0.001***
Sex	-0.416	0.162	288	-2.56	0.011*
Contact Seasons	0.077	0.019	586	4.08	<0.001***
Age*Contact	-0.016	0.004	370	-3.91	<0.001***
WJ-III Calculation					
Intercept	110	0.889	318	123	<0.001***
Age	-0.057	0.167	263	-0.343	0.732
Sex	-0.426	1.19	285	-0.358	0.721

Contact Seasons	0.552	0.122	601	4.52	<0.001***
Age*Contact	-0.093	0.028	493	-3.33	<0.001***
WJ-III Comprehension					
Intercept	108	0.752	319	143	<0.001***
Age	0.289	0.132	255	2.18	0.030*
Sex	0.563	1.01	293	0.556	0.579
Contact Seasons	0.028	0.112	611	0.250	0.802
Age*Contact	-0.011	0.024	340	-0.479	0.632
Full-Scale IQ					
Intercept	111	0.937	320	119	<0.001***
Age	0.132	0.134	218	0.987	0.325
Sex	2.89	1.29	279	2.23	0.026*
Contact Seasons	0.010	0.100	520	0.100	0.920
Age*Contact	-0.014	0.021	312	-0.683	0.495
Performance IQ					
Intercept	109	0.962	326	114	<0.001***
Age	0.304	0.142	624	2.14	0.033*
Sex	3.68	1.30	261	2.83	0.005**
Contact Seasons	0.058	0.114	548	0.506	0.613
Age*Contact	-0.006	0.023	446	-0.280	0.780
Verbal IQ					
Intercept	110	0.982	329	112	<0.001***
Age	-0.106	0.156	218	-0.677	0.499

Sex	0.981	1.35	293	0.728	0.467
Contact Seasons	0.050	0.122	586	0.413	0.679
Age*Contact	-0.031	0.026	329	- 1.21	0.227
BRIEF:GEC					
Intercept	45.6	0.643	324	70.9	<0.001***
Age	-0.067	0.114	237	-0.589	0.556
Sex	0.772	0.867	293	0.891	0.374
Contact Seasons	0.007	0.085	574	0.084	0.933
Age*Contact	0.027	0.022	409	1.26	0.207
BMI					
Intercept	21.6	0.54	445	40.1	<0.001***
Age	0.816	0.121	403	6.77	<0.001***
Sex	-0.945	0.659	641	-1.43	0.152
Contact Seasons	-0.043	0.087	584	-0.498	0.618
Age*Contact	0.003	0.022	610	0.117	0.907

In addition, the timed repetitive and patterned subtests from the PANESS both showed interactions between Age x Number of Seasons in Contact Sports. For the timed repetitive task (Figure 11), the age-related decrease in time to complete the task is reduced (i.e., less negative slope) for the participants with greater participation in contact sports, compared to those with less participation in contact sports.

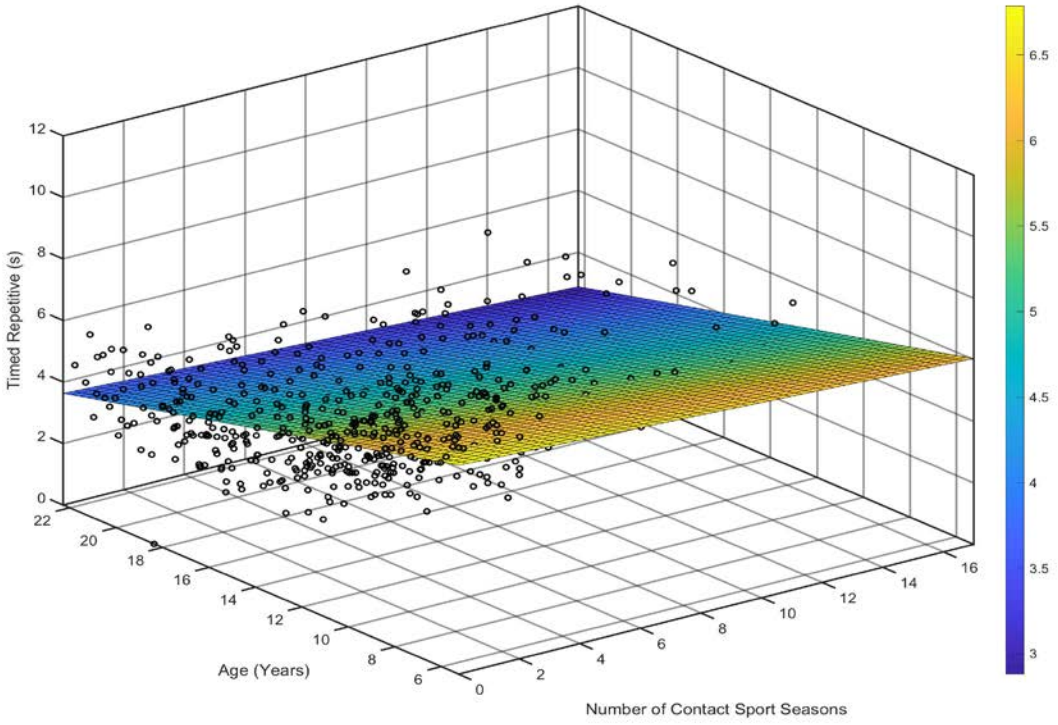

Figure 11. Timed repetitive by age and contact sport seasons.

For the timed patterned task (Figure 12), the age-related decrease in time to complete the task is greater (i.e., more negative slope) for the participants with greater participation in contact sports, compared to those with less participation in contact sports.

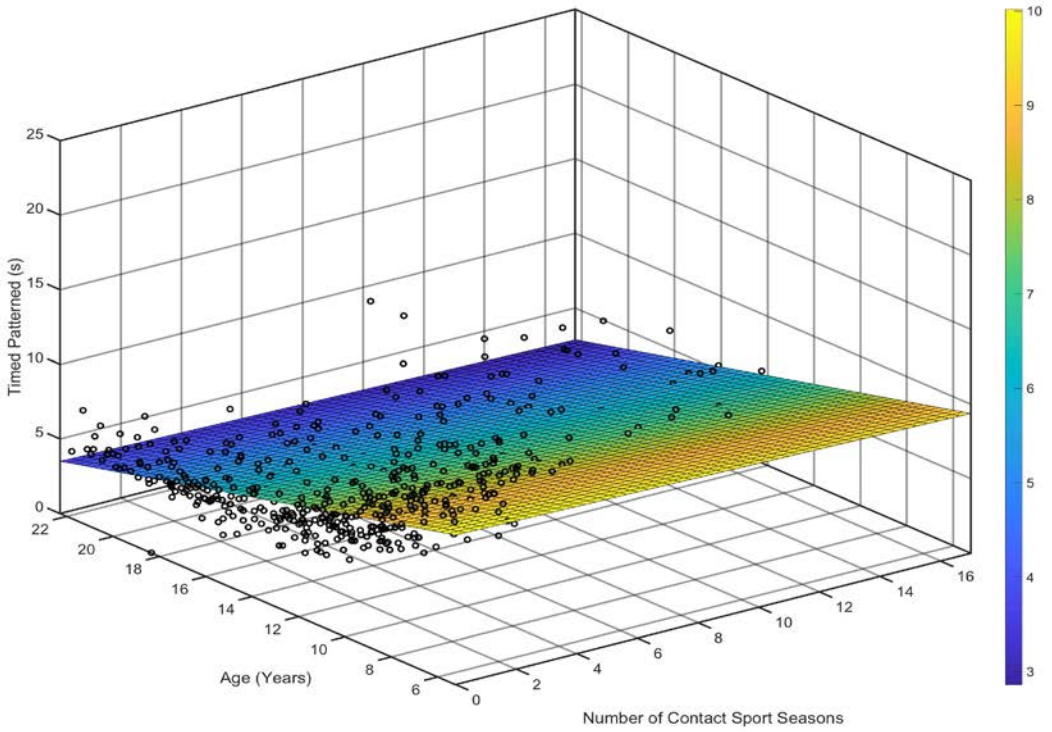

Figure 12. Timed patterned by age and contact sport seasons.

For the Purdue Pegboard test (Figure 13) the age-related increase in the number of pegs placed with both hands was reduced greater in those with more participation in contact sports, compared to those with less participation in contact sports.

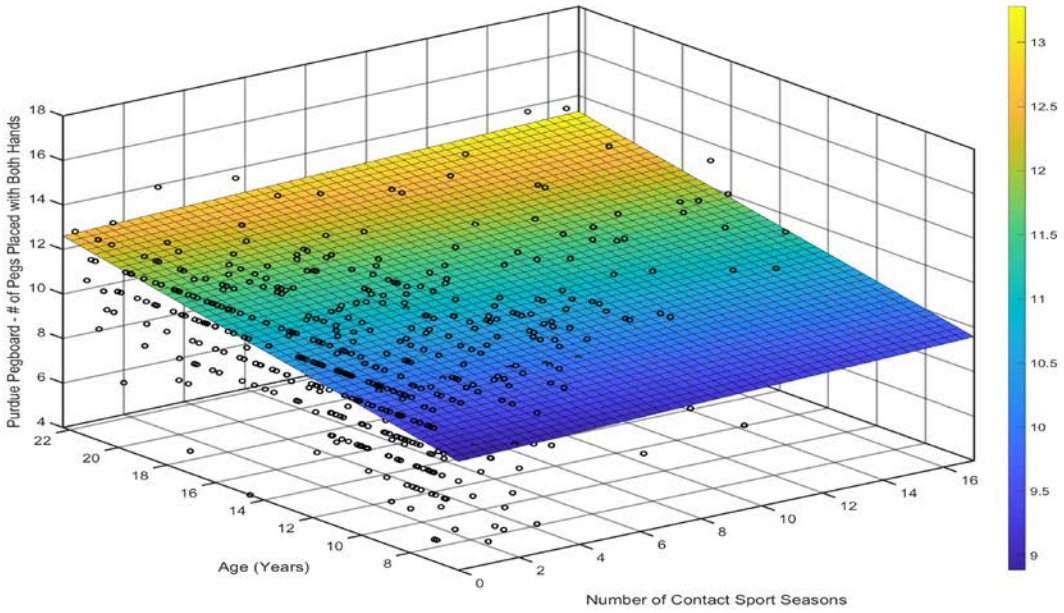

Figure 13. Purdue Pegboard by age and contact sport seasons.

Thus, across these three timed fine motor tasks (timed repetitive, timed patterned, and Purdue Pegboard), greater participation in contact sports is associated with improved motor performance, particularly for older participants.

In addition to the timed motor tasks, the results for the calculation portion of the Woodcock Johnson (WJ-III) examination also exhibited an Age x Number of Seasons in Contact Sports interaction. However, the pattern differed slightly from the other behavioral measures. Specifically, since age-standardized scores were used for this assessment, as expected no Age main effect was observed. However, the Age x Number of Seasons in Contact Sports interaction suggests that younger participants with high contact sport participation showed greater performance on the WJ-III calculation test, compared to younger participants with less contact sport participation (Figure 14). The performance difference is attenuated for amongst older participants. Such that older individuals that played in more contact seasons, albeit scoring

higher than those that played in fewer, differed less than younger participants across the spectrum.

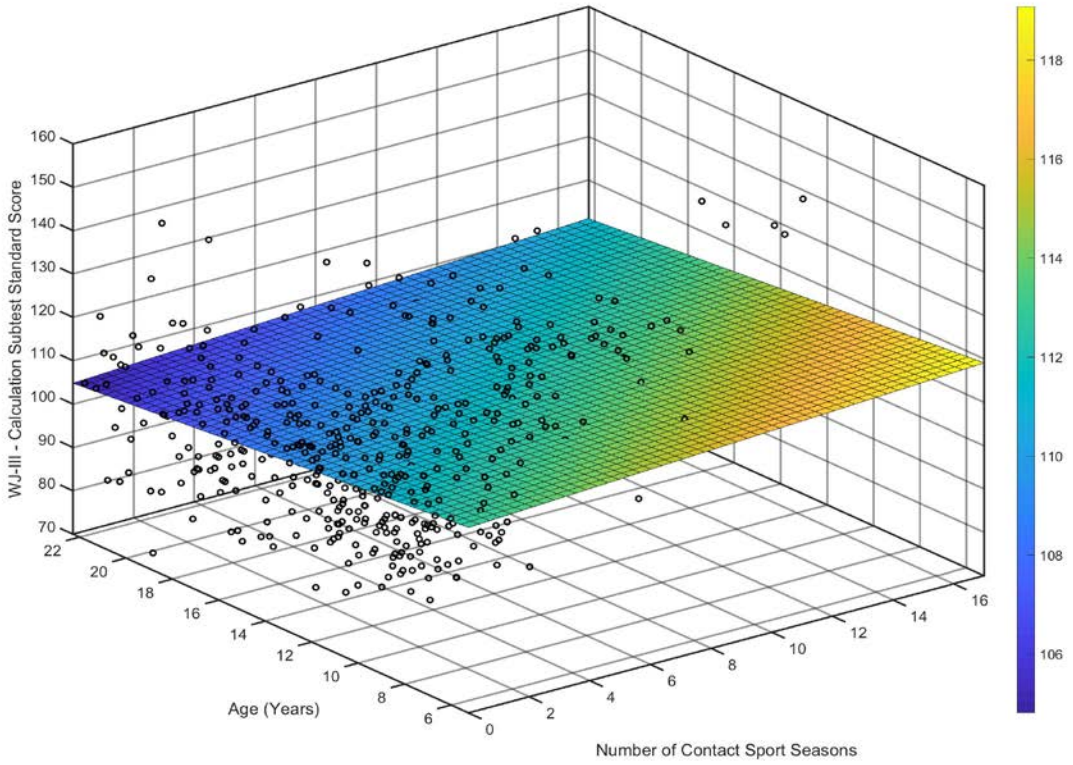

Figure 14. Timed patterned by age and contact sport seasons.

Discussion

The present study is the first to examine the longitudinal impact of contact sport participation on brain and behavioral measures in children and adolescents. As expected, significant age and/or sex main effects were exhibited for several brain volumes and behavioral assessments. Beyond these expected developmental patterns, significant interactions between age and cumulative contact sport participation were revealed for several brain volumes and behavioral assessments. The effects observed were opposite to our hypotheses, such that it appears that

greater participation in contact sports may be beneficial for brain development and behavioral performance for “healthy” children and adolescents (i.e., those that have not sustained a sports-related concussion).

Brain Volume

Cross-sectional and longitudinal characterizations of the trajectory of structural brain development have been reported over the last 20 years. A recent study by Mills et al. (2016) examined the longitudinal trajectory of brain volumes in four large longitudinal datasets and found that cortical grey matter volume is greatest during childhood and decreases throughout adolescence into adulthood. In contrast, white matter trajectories are somewhat protracted such that peak white matter volumes are not achieved until late adolescence and then begin to decline in early adulthood. Similar results were reported in a previous analysis of the NIH Study of Normal Brain Development (Brain Development Cooperative, 2012) which was used for the present analyses. Longitudinal analyses of subcortical volumes, including that of the cerebellum, also revealed a protracted development such that peak volumes were observed in mid- to late-adolescence (Habibi et al., 2017; Lopez-Vicente et al., 2017; Wierenga et al., 2014). In addition to developmental patterns with respect to age, sexual dimorphisms in brain volume have also been consistently reported such that generally males exhibited greater volumes across cortical regions (white and grey matter) as well as at the whole brain level (Ruigrok et al., 2014). The current results are consistent with previous reports; age and sex main effects were observed for all brain volumes.

Beyond the expected patterns observed for age and sex, the overall impact of cumulative contact sport participation has only been previously reported in children (Habibi et

al., 2017; Lopez-Vicente et al., 2017). Although López-Vicente et al. (2017) found a positive relationship between sports participation and cortical thickness in children, they did not find any differences in grey matter. Since grey matter continues to develop beyond the age range examined by López-Vicente et al. (2017), it is possible that the continued impact of sports participation on volumetric measures of grey matter (e.g., total and regional grey matter volume) we not captured. In the present longitudinal study, a positive relationship was observed between cumulative contact sport participation and grey and white matter volumes of the frontal and temporal cortices as well as overall grey and white matter in children and adolescents ages 5-22 years after accounting for age and sex differences. The present results are consistent with previous longitudinal studies suggesting that experience playing music impacts the development of grey matter structures such as the motor, prefrontal, and temporal cortices (Hudziak et al., 2014; Hyde et al., 2009). Therefore, the current findings represent an important addition to the literature, because of the number of participants, large age range of participants, and continuous nature of the sports participation measure. As such, these results have broad generalizability.

In addition to the overall effect of cumulative contact sport participation, we also observed that cumulative contact sport participation modified the age-related trajectories of brain development (i.e., the interaction between Age and Number of Seasons in Contact Sports). The developmental changes in the frontal and temporal grey matter and total grey matter were much steeper for those that had greater participation in contact sports, while the opposite pattern was observed for white matter and cerebellum volume. The divergent effects on different neural components (e.g., white matter, grey matter, and cerebellum) may be due

to the seemingly earlier maturational changes in grey matter, compared with more protracted development of white matter (Brain Development Cooperative, 2012; Wierenga et al., 2014) and the cerebellum (Brain Development Cooperative, 2012; Tiemeier et al., 2010). Interestingly, differences in the age-related slope of grey matter across childhood and adolescence has been reported with respect to intelligence (Shaw et al., 2006). Children with superior intelligence exhibit greater cortical thickness in the frontal and, to a lesser extent, temporal regions. However, individuals with superior intelligence exhibited an accelerated rate of cortical thinning compared with those with high or average intelligence. Using the same dataset as the present study, Hudziak et al. (2014) also showed that the rate of cortical thickness maturation differed by years of playing a musical instrument. Individuals that played an instrument for more than 2 years showed a steeper developmental trajectory for cortical thickness in the motor, pre-motor, supplementary motor regions, as well as the prefrontal and parietal cortices. The present study adds to this line of research in that age-related changes in grey matter volume (total, frontal, and temporal) were steeper for those with greater contact sport participation. The similarities between the results of previous studies and those presently reported with respect to the pattern of maturation and the regions affected suggest that greater participation in contact sports may actually be beneficial to brain development.

Few studies have examined the impact of musical training or sports participation with respect to white matter volumes. Instead, much of the evidence regarding experiential changes in white matter is based on diffusion tensor imaging (DTI). Interestingly, there has been divergence in the literature regarding the impact of musical training on fractional anisotropy (FA), a common measure of “white matter integrity”. For example some studies have reported

greater FA in the corpus callosum (Bengtsson et al., 2005; Schmithorst & Wilke, 2002) and corticospinal tract (Bengtsson et al., 2005) of musically-trained adults compared to controls. Other studies have reported reduced FA in the corticospinal tract (Giacosa et al., 2016; Imfeld et al., 2009; Schmithorst & Wilke, 2002) and corpus callosum (Giacosa et al., 2016) in musically-trained adults compared to controls. It is important to note that all of the aforementioned studies were cross-sectional evaluations of adult musicians with retrospective analyses of musical training onset, practice time during childhood or adolescence, or cumulative music experience.

Only one longitudinal study has examined differences in white matter in musically-trained 6-7 year old children (Habibi et al., 2017) and found greater FA in the corpus callosum for those that were musically-trained, compared to a sport-trained (soccer and swimming) or controls. In this study, it is important to note that the dose of training differed between the musically-trained children (6-7 hours weekly) compared with the sport trained group (3-4x weekly). Although the present study was unable to examine developmental and experiential differences in white matter volume of specific tracts, and white matter volume is not comparable to diffusion indices directly, we did observe that children and adolescents that had a greater cumulative contact sports participation exhibited overall greater white matter volume in the frontal and temporal cortices, and to a lesser extent total white matter volume. Given that motor skill learning requires interactions between the two hemispheres (via the corpus callosum) and corticospinal pathways, it is reasonable to hypothesize that experiential changes in these tracts would influence total and regional white matter. In addition to the main effect of cumulative contact sports participation, similar to what was observed for grey matter, the age-

related trajectories of white matter in these regions was modified by cumulative contact sports participation (i.e., Age x Number of Seasons in Contact Sports). Children and adolescents with greater cumulative contact sports participation exhibited a protracted development of white matter (i.e., reduced slope) compared to those with less cumulative contact sports participation. It is possible that white matter development may continue into adulthood for those with greater cumulative sports participation (e.g., outside of the age ranged examined here) and may suggest a widening of the developmental period for white matter. Future studies are necessary to determine if this is indeed the case and what the behavioral implications are for continued development of white matter in to adulthood.

In addition to examining grey and white matter volumes, the present study also examined the cerebellum, as it is a key structure in motor and cognitive skill acquisition. Indeed, studies of musically-trained adults have reported differences in the volume of the cerebellum (Hutchinson et al., 2003) and individual lobules of the cerebellum (Baer et al., 2015) compared to non-musicians. However, the results are mixed regarding the impact of musical experience on cerebellar volume. For example, Hutchinson et al. (2003) reported greater total cerebellar volumes in male musicians compared to controls (no difference for females), while Baer et al. (2015) reported no difference in total and lobar cerebellar volumes between musicians and controls. No longitudinal or developmental studies have examined the impact of experiential factors or the volume of the cerebellum. The present findings that the cerebellar volume is greater for those with high cumulative experience in contact sports (compared to those with less experience) and the modifying effect of cumulative experience on the age-related increases in cerebellar volume are indeed novel. If participation in sports may serve as a

proxy for motor learning, based on the animal literature (Greenough et al., 1987), it is reasonable to hypothesize that greater cumulative experience would lead to synaptogenesis of the cerebellum, thus increasing the its total volume. However, future studies are needed to segment differences in grey and white matter compartments of the cerebellum and the effect of cumulative experience participating in contact sports.

Taken together, the present study provides novel insights to the potential beneficial and long-term impact of participation in contact sports on brain development in healthy children and adolescents. With this said, the present study is limited to healthy participants without a history of concussion or head trauma and further study is needed to examine the effects of contact sports participation for youth that have sustained sports-related concussion. Indeed, the positive benefit of sports participation may not generalize for those that have sustained an injury especially during sensitive developmental periods and non-strategy involved sports.

Behavioral

Several previous studies have characterized the effects of youth sport participation on academic performance (Fox et al., 2010) and motor function (Fransen et al., 2012; Vandorpe et al., 2012). The present study replicates and extends this line of work in that we observed better performance on math calculation and three timed motor tasks. Moreover, across the three timed fine motor tasks (timed repetitive, timed patterned, and Purdue Pegboard), greater participation in contact sports is associated with improved motor performance, particularly for older participants.

Although these motor tasks, in addition to the WJ-III, are common neurological and neurocognitive assessments, they are not currently assessed with the available concussion

assessments (e.g., Sport Concussion Assessment Tool, 5th edition). Given that these assessments were sensitive to age and sex differences as well as participation in contact sports, these assessments may be very useful in differentiating those that participate in contact sports with and without sports-related concussion across childhood and adolescence.

Limitations

There are several limitations to consider. First, the cumulative contact sport measure was derived from a lengthy parent reported questionnaire that not only asked about contact sport participation, but many other environmental and experiential factors. Errors in reporting and coding may lead to variability in this measure.

Second, given the nature of the contact sport measure, higher cumulative contact sports participation was only reported for adolescents (i.e., few young children are participating in a high volume of contact sports). Thus, the present findings may be skewed by the large number of adolescents reporting high cumulative contact sports. With this said, the previous study examining sports participation on brain development in children ages 6 – 10 years split sports participation into three categories (no participation, less than 1 hour per week, or greater than 1 hour per week) and found that sports participation was positively associated with cortical thickness in the motor and premotor cortices (López-Vicente et al., 2015). Therefore, the present study replicates and extends these findings across a much larger population and with a longitudinal design.

Unfortunately, the present results are not generalizable to all contact sport participants. As mentioned, the population assessed in this study have not sustained a concussion or other acquired brain injury. Thus, the present study cannot address any potential negative

consequences of contact sports participation due to concussion or other brain-related injury. This limitation suggests that additional research is needed using similar outcome measures as those currently reported in contact sports participants that have sustained a sport-related concussion. The Federal Interagency Traumatic Brain Injury Research (FITBIR) is a joint effort to standardize and centralize data from studies examining concussion. Some of the studies that will provide data to this repository are focused on youth sport concussion and would be appropriate for secondary data analyses to investigate differences in brain and neurocognitive outcomes in youth athletes that have or have not sustained a concussion.

Conclusions

The results of the present study suggest that participation in contact sports affect the trajectories of brain and neurocognitive development in children and adolescents. Additional studies are needed to determine more granular (e.g., tract- or area-specific) effects of contact sports participation. Yet, these results are promising in that sports participation may confer a benefit similar to that of musical training or other enriched experiences during development. Moreover, these results suggest that youth athletes should complete baseline neuroimaging or neurocognitive assessments prior to sport participation to better assess changes across a season or from one season to the next to identify divergence from positive developmental trajectories (i.e., negative impact of contact sports) even prior to the onset of overt brain injury or concussion.

CHAPTER 4. GENERAL DISCUSSION

The purpose of study 1 was to examine the assessments that are utilized most commonly during the acute phase of concussive injury. However, a vast majority of studies have evaluated sub-acute and chronic injury. Validation of these assessments across all phases of injury (i.e., acute, sub-acute, chronic), across different populations (i.e., male and female athletes) and developmental levels (i.e., children, adolescents, and adults) are currently lacking. These knowledge gaps should be addressed in future studies to aid clinicians and researchers in selecting the best assessment for acute concussions.

Study 2 suggests that the developmental trajectory of neural and behavioral measures is (positively) affected by contact sports participation in healthy children and adolescents. This is the first longitudinal study across a large age range of children and adults to report such a finding. And, the present findings are consistent with other studies examining other enriched environmental experiences (e.g., musical training). These results call into question the pervasive concern regarding the negative impact of contact sports participation in youth athletes. With that said, these results suggest that youth athletes should complete baseline neuroimaging and/or neurocognitive testing prior to sport participation. This would help better assess changes across a season or from one season to the next to identify divergence from positive developmental trajectories (i.e., negative impact of contact sports) even prior to the onset of overt brain injury or concussion.

While Study 1 was a direct measurement of analysis in acute sport-related concussions, Study 2 explored the changes in developmental trajectories of the sports most associated with

head injuries in youth sport. Indeed, the number of head injuries in youth sport are alarming, with over 250,000 admitted to the hospital each year (McCrory et al., 2004). Thus, it is even more important to determine the most effective measurement of these injuries. In order to do so, the effects of these sports, outside of the injury, is vital to determining the best path to precise and accurate diagnoses. Measuring the consequences, both positive and negative, that contact sport participation has on brain and behavior, is vital to determine the effects such brain injuries have. Moreover, with the growing knowledge that neurodegenerative diseases, such as Chronic Traumatic Encephalopathy (CTE), are associated with a history of concussions and repetitive head trauma (Stein et al., 2015). Thus, head injuries particularly during youth sport participation should be properly diagnosed and managed to reduce the potential long-term impact of contact sports participation. In order to properly balance the potential benefits and risks of participation in youth contact sports, more research is critical.

Future directions for these studies include additional analyses of extant databases to better characterize brain and neurocognitive development in those that have sustained a head injury or concussion. The Federal Interagency Traumatic Brain Injury Research (FITBIR) is a data repository for all funded studies examining traumatic brain injury, including sports-related concussion. This joint effort between the Department of Defense (DoD), National Collegiate Athletic Association (NCAA), and the National Institutes of Health (NIH) provides a unique opportunity for researchers to deposit and compile data from several sites allowing for better powered studies and secondary data analyses of funded projects. Databases like FITBIR and the NIH Study of Normal Brain Development (Chapter 3) provide data necessary for novel data

analytic approaches and identification of useful independent and dependent measures for future study design and hypothesis generation.

In addition, there is a growing number of functional MRI studies that have examined differences in task performance between youth athletes that have or have not sustained a concussion. The systematic review of this literature and the development of activation likelihood estimates (ALE) based on all available fMRI studies will allow consistent regions of interest to be identified without the bias of small samples from single studies.

Based on the information gathered from the studies presented in Chapter 2 and 3, future projects should include assessments of neurological and neurocognitive measures to determine the acute and long-term effects of concussions in youth athletes. For example, the physical and neurological assessment presented in Chapter 3 may provide critical information and be more sensitive to subtle neurologic changes especially in children and adolescents. Moreover, the combination of structural and functional neuroimaging analyses will facilitate a better understanding between the present result and those reported using fMRI in youth athletes that have or have not sustained a concussion. These future studies are necessary for determining the most appropriate assessments for both general examinations and post-injury evaluations to ensure safe and enriching participation of youth in sport.

References

Aubry, M., Cantu, R., Dvorak, J., Graf-Baumann, T., Johnston, K. M., Kelly, J., Lovell, M., McCrory, P., Meeuwisse, W. H., Schamasch, P., & Concussion in Sport, G. (2002). Summary and agreement statement of the 1st International Symposium on Concussion in Sport, Vienna 2001. *Clin J Sport Med, 12*(1), 6-11.

Baer, L. H., Park, M. T., Bailey, J. A., Chakravarty, M. M., Li, K. Z., & Penhune, V. B. (2015). Regional cerebellar volumes are related to early musical training and finger tapping performance. *Neuroimage, 109*, 130-139.

Baillargeon, A., Lassonde, M., Leclerc, S., & Ellemberg, D. (2012). Neuropsychological and neurophysiological assessment of sport concussion in children, adolescents and adults. *Brain Inj, 26*(3), 211-220.

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Dant, C. C., & Reiss, A. L. (2005). White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cereb Cortex, 15*(12), 1848-1854.

Bartolotti, J., Bradley, K., Hernandez, A. E., & Marian, V. (2017). Neural signatures of second language learning and control. *Neuropsychologia, 98*, 130-138.

Basterfield, L., Reilly, J. K., Pearce, M. S., Parkinson, K. N., Adamson, A. J., Reilly, J. J., & Vella, S. A. (2015). Longitudinal associations between sports participation, body composition and physical activity from childhood to adolescence. *J Sci Med Sport, 18*(2), 178-182.

Baugh, C. M., Stamm, J. M., Riley, D. O., Gavett, B. E., Shenton, M. E., Lin, A., Nowinski, C. J., Cantu, R. C., McKee, A. C., & Stern, R. A. (2012). Chronic traumatic encephalopathy:

neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging Behav, 6*(2), 244-254.

Benedict, P. A., Baner, N. V., Harrold, G. K., Moehringer, N., Hasanaj, L., Serrano, L. P., Sproul, M., Pagnotta, G., Cardone, D. A., Flanagan, S. R., Rucker, J., Galetta, S. L., & Balcer, L. J. (2015). Gender and age predict outcomes of cognitive, balance and vision testing in a multidisciplinary concussion center. *J Neurol Sci, 353*(1-2), 111-115.

Bengtsson, S. L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H., & Ullen, F. (2005). Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci, 8*(9), 1148-1150.

Black, A. M., Sergio, L. E., & Macpherson, A. K. (2017). The epidemiology of concussions: number and nature of concussions and time to recovery among female and male Canadian varsity athletes 2008 to 2011. *Clin J Sport Med, 27*(1).

Bock, S., Grim, R., Barron, T. F., Wagenheim, A., Hu, Y. E., Hendell, M., Deitch, J., & Deibert, E. (2015). Factors associated with delayed recovery in athletes with concussion treated at a pediatric neurology concussion clinic. *Childs Nerv Syst, 31*(11), 2111-2116.

Brain Development Cooperative, G. (2012). Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI Study of Normal Brain Development. *Cereb Cortex, 22*(1), 1-12.

Broglio, S. P., Cantu, R. C., Gioia, G. A., Guskiewicz, K. M., Kutcher, J., Palm, M., Valovich McLeod, T. C., & National Athletic Trainer's, A. (2014). National Athletic Trainers' Association position statement: management of sport concussion. *J Athl Train, 49*(2), 245-265.

Broglio, S. P., Eckner, J. T., Surma, T., & Kutcher, J. S. (2011). Post-concussion cognitive declines and symptomatology are not related to concussion biomechanics in high school football players. *J Neurotrauma, 28*(10), 2061-2068.

Broglio, S. P., Guskiewicz, K. M., & Norwig, J. (2017). If You're Not Measuring, You're Guessing: The Advent of Objective Concussion Assessments. *J Athl Train, 52*(3), 160-166.

Collie, A., Makdissi, M., Maruff, P., Bennell, K., & McCrory, P. (2006). Cognition in the days following concussion: comparison of symptomatic versus asymptomatic athletes. *J Neurol Neurosurg Psychiatry, 77*(2), 241-245.

Collie, A., Maruff, P., Makdissi, M., McCrory, P., McStephen, M., & Darby, D. (2003). CogSport: reliability and correlation with conventional cognitive tests used in postconcussion medical evaluations. *Clin J Sport Med, 13*(1), 28-32.

Covassin, T., Crutcher, B., & Wallace, J. (2013a). Does a 20 minute cognitive task increase concussion symptoms in concussed athletes? *Brain Inj, 27*(13-14), 1589-1594.

Covassin, T., Elbin, R. J., Bleecker, A., Lipchik, A., & Kontos, A. P. (2013b). Are there differences in neurocognitive function and symptoms between male and female soccer players after concussions? *Am J Sports Med, 41*(12), 2890-2895.

Covassin, T., Moran, R., & Elbin, R. J. (2016). Sex differences in reported concussion injury rates and time loss from participation: an update of the National Collegiate Athletic Association injury surveillance program from 2004-2005 through 2008-2009. *J Athl Train, 51*(3), 189-194.

Eminian, S., Hajdu, S. D., Meuli, R. A., Maeder, P., & Hagmann, P. (2018). Rapid high resolution T1 mapping as a marker of brain development: Normative ranges in key regions of interest. *PLoS One, 13*(6), e0198250.

Evans, A. C., & Brain Development Cooperative, G. (2006). The NIH MRI study of normal brain development. *Neuroimage, 30*(1), 184-202.

Field, M., Collins, M. W., Lovell, M. R., & Maroon, J. (2003). Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. *J Pediatr, 142*(5), 546-553.

Fox, C. K., Barr-Anderson, D., Neumark-Sztainer, D., & Wall, M. (2010). Physical activity and sports team participation: associations with academic outcomes in middle school and high school students. *J Sch Health, 80*(1), 31-37.

Fransen, J., Pion, J., Vandendriessche, J., Vandorpe, B., Vaeyens, R., Lenoir, M., & Philippaerts, R. M. (2012). Differences in physical fitness and gross motor coordination in boys aged 6-12 years specializing in one versus sampling more than one sport. *J Sports Sci, 30*(4), 379-386.

Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. *J Neurosci, 23*(27), 9240-9245.

Gessel, L. M., Fields, S. K., Collins, C. L., Dick, R. W., & Comstock, R. D. (2007). Concussions among United States high school and collegiate athletes. *J Athl Train, 42*(4), 495-503.

Giacosa, C., Karpati, F. J., Foster, N. E., Penhune, V. B., & Hyde, K. L. (2016). Dance and music training have different effects on white matter diffusivity in sensorimotor pathways. *Neuroimage, 135*, 273-286.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience, 2*, 861.

Graham, R., Rivara, F. P., Ford, M., & Spicer, C. (2014). Sports-Related Concussion in Youth *National Research Council and Institute of Medicine Sports-Related Concussions in Youth: Improving the Science, Changing the Culture* (pp. 309-330): The National Academies Press, Washington, DC.

Graves, B. S. (2016). University football players, postural stability, and concussions. *J Strength Cond Res, 30*(2), 579-583.

Greenough, W. T., Black, J. E., & Wallace, C. S. (1987). Experience and brain development. *Child Dev, 58*(3), 539-559.

Habibi, A., Damasio, A., Ilari, B., Veiga, R., Joshi, A. A., Leahy, R. M., Haldar, J. P., Varadarajan, D., Bhushan, C., & Damasio, H. (2017). Childhood Music Training Induces Change in Micro and Macroscopic Brain Structure: Results from a Longitudinal Study. *Cereb Cortex*, 1-12.

Harmon, K. G., Drezner, J. A., Gammons, M., Guskiewicz, K. M., Halstead, M., Herring, S. A., Kutcher, J. S., Pana, A., Putukian, M., & Roberts, W. O. (2013). American Medical Society for Sports Medicine position statement: concussion in sport. *Br J Sports Med, 47*(1), 15-26.

Henry, L. C., Elbin, R. J., Collins, M. W., Marchetti, G., & Kontos, A. P. (2016). Examining recovery trajectories after sport-related concussion with a multimodal clinical assessment approach. *Neurosurgery, 78*(2), 232-241.

Hirase, H., & Shinohara, Y. (2014). Transformation of cortical and hippocampal neural circuit by environmental enrichment. *Neuroscience, 280*, 282-298.

Hopkins, M. E., Davis, F. C., VanTieghem, M. R., Whalen, P. J., & Bucci, D. J. (2012). Differential effects of acute and regular physical exercise on cognition and affect. *Neuroscience, 215*, 59-68.

Hudziak, J. J., Albaugh, M. D., Ducharme, S., Karama, S., Spottswood, M., Crehan, E., Evans, A. C., Botteron, K. N., & Brain Development Cooperative, G. (2014). Cortical thickness maturation and duration of music training: health-promoting activities shape brain development. *J Am Acad Child Adolesc Psychiatry, 53*(11), 1153-1161, 1161 e1151-1152.

Hutchinson, S., Lee, L. H., Gaab, N., & Schlaug, G. (2003). Cerebellar volume of musicians. *Cereb Cortex, 13*(9), 943-949.

Hyde, K. L., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A. C., & Schlaug, G. (2009). Musical training shapes structural brain development. *J Neurosci, 29*(10), 3019-3025.

Imfeld, A., Oechslin, M. S., Meyer, M., Loenneker, T., & Jancke, L. (2009). White matter plasticity in the corticospinal tract of musicians: a diffusion tensor imaging study. *Neuroimage, 46*(3), 600-607.

King, D., Brughelli, M., Hume, P., & Gissane, C. (2013). Concussions in amateur rugby union identified with the use of a rapid visual screening tool. *J Neurol Sci, 326*(1-2), 59-63.

King, D., Hume, P., Gissane, C., & Clark, T. (2015). Use of the King-Devick test for sideline concussion screening in junior rugby league. *J Neurol Sci, 357*(1-2), 75-79.

Kontos, A. P., Covassin, T., Elbin, R. J., & Parker, T. (2012). Depression and neurocognitive performance after concussion among male and female high school and collegiate athletes. *Arch Phys Med Rehabil, 93*(10), 1751-1756.

Kontos, A. P., Elbin, R. J., Kotwal, R. S., Lutz, R. H., Kane, S., Benson, P. J., Forsten, R. D., & Collins, M. W. (2015). The effects of combat-related mild traumatic brain injury (mTBI): Does blast mTBI history matter? *J Trauma Acute Care Surg, 79*(4 Suppl 2), S146-151.

Langlois, J. A., Rutland-Brown, W., & Wald, M. M. (2006). The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil, 21*(5), 375-378.

Lau, B. C., Collins, M. W., & Lovell, M. R. (2012). Cutoff scores in neurocognitive testing and symptom clusters that predict protracted recovery from concussions in high school athletes. *Neurosurgery, 70*(2), 371-379.

Lau, B. C., Kontos, A. P., Collins, M. W., Mucha, A., & Lovell, M. R. (2011). Which on-field signs/symptoms predict protracted recovery from sport-related concussion among high school football players? *Am J Sports Med, 39*(11), 2311-2318.

Leong, D. F., Balcer, L. J., Galetta, S. L., Liu, Z., & Master, C. L. (2014). The King-Devick test as a concussion screening tool administered by sports parents. *J Sports Med Phys Fitness, 54*(1), 70-77.

Lincoln, A. E., Caswell, S. V., Almquist, J. L., Dunn, R. E., Norris, J. B., & Hinton, R. Y. (2011). Trends in concussion incidence in high school sports: a prospective 11-year study. *Am J Sports Med, 39*(5), 958-963.

Lopez-Vicente, M., Tiemeier, H., Wildeboer, A., Muetzel, R. L., Verhulst, F. C., Jaddoe, V. W. V., Sunyer, J., & White, T. (2017). Cortical Structures Associated With Sports Participation in Children: A Population-Based Study. *Dev Neuropsychol, 42*(2), 58-69.

Makdissi, M., Collie, A., Maruff, P., Darby, D. G., Bush, A., McCrory, P., & Bennell, K. (2001). Computerised cognitive assessment of concussed Australian Rules footballers. *Br J Sports Med, 35*(5), 354-360.

Makdissi, M., Darby, D., Maruff, P., Ugoni, A., Brukner, P., & McCrory, P. R. (2010). Natural history of concussion in sport: markers of severity and implications for management. *Am J Sports Med, 38*(3), 464-471.

Makdissi, M., McCrory, P., Ugoni, A., Darby, D., & Brukner, P. (2009). A prospective study of postconcussive outcomes after return to play in Australian football. *Am J Sports Med, 37*(5), 877-883.

Marar, M., McIlvain, N. M., Fields, S. K., & Comstock, R. D. (2012). Epidemiology of concussions among United States high school athletes in 20 sports. *Am J Sports Med, 40*(4), 747-755.

Marshall, S. W., & Spencer, R. J. (2001). Concussion in Rugby: The Hidden Epidemic. *J Athl Train, 36*(3), 334-338.

McCrea, M., Kelly, J. P., Randolph, C., Cisler, R., & Berger, L. (2002). Immediate neurocognitive effects of concussion. *Neurosurgery, 50*(5), 1032-1040; discussion 1040-1032.

McCrory, P., Collie, A., Anderson, V., & Davis, G. (2004). Can we manage sport related concussion in children the same as in adults? *British Journal of Sports Medicine, 38*(5), 516.

McCrory, P., Johnston, K., Meeuwisse, W., Aubry, M., Cantu, R., Dvorak, J., Graf-Baumann, T., Kelly, J., Lovell, M., & Schamasch, P. (2005). Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med, 39*(4), 196-204.

McCrory, P., Meeuwisse, W., Dvorak, J., Aubry, M., Bailes, J., Broglio, S., Cantu, R. C., Cassidy, D., Echemendia, R. J., Castellani, R. J., Davis, G. A., Ellenbogen, R., Emery, C., Engebretsen, L., Feddermann-Demont, N., Giza, C. C., Guskiewicz, K. M., Herring, S., Iverson, G. L., Johnston, K. M., Kissick, J., Kutcher, J., Leddy, J. J., Maddocks, D., Makdissi, M., Manley, G. T., McCrea, M., Meehan, W. P., Nagahiro, S., Patricios, J., Putukian, M., Schneider, K. J., Sills, A., Tator, C. H., Turner, M., & Vos, P. E. (2017). Consensus statement on concussion in sport-the 5(th) international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med, 51*(11), 838-847.

McCrory, P., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M., & Cantu, R. (2009). Consensus statement on Concussion in Sport--the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *J Sci Med Sport, 12*(3), 340-351.

McCrory, P., Meeuwisse, W. H., Aubry, M., Cantu, B., Dvorak, J., Echemendia, R. J., Engebretsen, L., Johnston, K., Kutcher, J. S., Raftery, M., Sills, A., Benson, B. W., Davis, G. A., Ellenbogan, R., Guskiewicz, K., Herring, S. A., Iverson, G. L., Jordan, B. D., Kissick, J., McCrea, M., McIntosh, A. S., Maddocks, D., Makdissi, M., Purcell, L., Putukian, M., Schneider, K., Tator, C. H., & Turner, M. (2013). Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *J Am Coll Surg, 216*(5), e55-71.

Mihalik, J. P., McCaffrey, M. A., Rivera, E. M., Pardini, J. E., Guskiewicz, K. M., Collins, M. W., & Lovell, M. R. (2007). Effectiveness of mouthguards in reducing neurocognitive deficits following sports-related cerebral concussion. *Dent Traumatol, 23*(1), 14-20.

Mihalik, J. P., Register-Mihalik, J., Kerr, Z. Y., Marshall, S. W., McCrea, M. C., & Guskiewicz, K. M. (2013). Recovery of posttraumatic migraine characteristics in patients after mild traumatic brain injury. *Am J Sports Med, 41*(7), 1490-1496.

Mills, K. L., Goddings, A. L., Herting, M. M., Meuwese, R., Blakemore, S. J., Crone, E. A., Dahl, R. E., Guroglu, B., Raznahan, A., Sowell, E. R., & Tamnes, C. K. (2016). Structural brain development between childhood and adulthood: Convergence across four longitudinal samples. *Neuroimage, 141*, 273-281.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med, 6*(7), e1000097.

Munte, T. F., Altenmuller, E., & Jancke, L. (2002). The musician's brain as a model of neuroplasticity. *Nat Rev Neurosci, 3*(6), 473-478.

Nance, M. L., Polk-Williams, A., Collins, M. W., & Wiebe, D. J. (2009). Neurocognitive evaluation of mild traumatic brain injury in the hospitalized pediatric population. *Ann Surg, 249*(5), 859-863.

Norris, J. N., Sams, R., Lundblad, P., Frantz, E., & Harris, E. (2014). Blast-related mild traumatic brain injury in the acute phase: acute stress reactions partially mediate the relationship between loss of consciousness and symptoms. *Brain Inj, 28*(8), 1052-1062.

Ono, K. E., Burns, T. G., Bearden, D. J., McManus, S. M., King, H., & Reisner, A. (2016). Sex-based differences as a predictor of recovery trajectories in young athletes after a sports-related concussion. *Am J Sports Med, 44*(3), 748-752.

Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends Cogn Sci, 9*(2), 60-68.

Pedersen, H. A., Ferraro, F. R., Himle, M., Schultz, C., & Poolman, M. (2014). Neuropsychological factors related to college ice hockey concussions. *Am J Alzheimers Dis Other Demen, 29*(3), 201-204.

Preiss-Farzanegan, S. J., Chapman, B., Wong, T. M., Wu, J., & Bazarian, J. J. (2009). The relationship between gender and postconcussion symptoms after sport-related mild traumatic brain injury. *PM R, 1*(3), 245-253.

Ruigrok, A. N. V., Salimi-Khorshidi, G., Lai, M.-C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure(). *Neuroscience and Biobehavioral Reviews, 39*(100), 34-50.

Sale, A., Berardi, N., & Maffei, L. (2009). Enrich the environment to empower the brain. *Trends Neurosci, 32*(4), 233-239.

Schatz, P., Pardini, J. E., Lovell, M. R., Collins, M. W., & Podell, K. (2006). Sensitivity and specificity of the ImPACT Test Battery for concussion in athletes. *Arch Clin Neuropsychol, 21*(1), 91-99.

Schmithorst, V. J., & Wilke, M. (2002). Differences in white matter architecture between musicians and non-musicians: a diffusion tensor imaging study. *Neurosci Lett, 321*(1-2), 57-60.

Senne, J. A. (2016). Examination of gender equity and female participation in sport. *Sport J, 19*, 1-9.

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., Evans, A., Rapoport, J., & Giedd, J. (2006). Intellectual ability and cortical development in children and adolescents. *Nature, 440*(7084), 676-679.

Silverberg, N. D., Luoto, T. M., Ohman, J., & Iverson, G. L. (2014). Assessment of mild traumatic brain injury with the King-Devick Test in an emergency department sample. *Brain Inj, 28*(12), 1590-1593.

Sosnoff, J. J., Broglio, S. P., & Ferrara, M. S. (2008). Cognitive and motor function are associated following mild traumatic brain injury. *Exp Brain Res, 187*(4), 563-571.

Sowell, E. R., Trauner, D. A., Gamst, A., & Jernigan, T. L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Developmental Medicine and Child Neurology, 44*(1), 4-16.

Stein, M., Federspiel, A., Koenig, T., Wirth, M., Strik, W., Wiest, R., Brandeis, D., & Dierks, T. (2012). Structural plasticity in the language system related to increased second language proficiency. *Cortex, 48*(4), 458-465.

Stein, T. D., Alvarez, V. E., & McKee, A. C. (2015). Concussion in Chronic Traumatic Encephalopathy. *Current Pain and Headache Reports, 19*(10), 47.

Tiemeier, H., Lenroot, R. K., Greenstein, D. K., Tran, L., Pierson, R., & Giedd, J. N. (2010). Cerebellum development during childhood and adolescence: a longitudinal morphometric MRI study. *Neuroimage, 49*(1), 63-70.

Tombaugh, T. N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol, 19*(2), 203-214.

Trudler, D., Nash, Y., & Frenkel, D. (2015). New insights on Parkinson's disease genes: the link between mitochondria impairment and neuroinflammation. *J Neural Transm (Vienna), 122*(10), 1409-1419.

Van Kampen, D. A., Lovell, M. R., Pardini, J. E., Collins, M. W., & Fu, F. H. (2006). The "value added" of neurocognitive testing after sports-related concussion. *Am J Sports Med, 34*(10), 1630-1635.

Vandorpe, B., Vandendriessche, J., Vaeyens, R., Pion, J., Matthys, S., Lefevre, J., Philippaerts, R., & Lenoir, M. (2012). Relationship between sports participation and the level of motor coordination in childhood: a longitudinal approach. *J Sci Med Sport, 15*(3), 220-225.

Waber, D. P., De Moor, C., Forbes, P. W., Almli, C. R., Botteron, K., Leonard, G., Paus, T., & Rumsey, J. (2007). *The NIH MRI study of normal brain development: performance of a population based sample of healthy children aged 6 to 18 years* (Vol. 13).

Waber, D. P., Forbes, P. W., Almli, C. R., Blood, E. A., & Brain Development Cooperative, G. (2012). Four-year longitudinal performance of a population-based sample of healthy children on a neuropsychological battery: the NIH MRI study of normal brain development. *J Int Neuropsychol Soc, 18*(2), 179-190.

Wechsler, D. (1939). The measurement of adult intelligence.

White, E. J., Hutka, S. A., Williams, L. J., & Moreno, S. (2013). Learning, neural plasticity and sensitive periods: implications for language acquisition, music training and transfer across the lifespan. *Front Syst Neurosci, 7*, 90.

Wierenga, L., Langen, M., Ambrosino, S., van Dijk, S., Oranje, B., & Durston, S. (2014). Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24. *Neuroimage, 96*, 67-72.

Appendix A

Supplementary Material

Assessment Details

Immediate Post-Concussion Assessment and Cognitive Test (ImPACT)

The ImPACT battery is a computerized neurocognitive assessment that tests 6 cognitive domains. Upon completion of the battery, there are 5 composite scores computed. These scores are combinations of tests for verbal and visual memory, reaction time, visual motor processing speed, and impulse control. Additionally, the Post-Concussion Symptom Scale (PCSS) is also included. The PCSS is a 21-item symptom checklist that asks the participant to grade each symptom on a scale of 0 (not experiencing symptom) to 6 (severely experiencing symptom). The ImPACT battery was used in 13 out of 28 studies and covered 1,527 participants (1,107 males, 342 females, and 78 unspecified).

ImPACT is considered reliable, sensitive, and valid with normative data for ages 12-59. The test requires a computer and, preferably a quiet, dimly lit room. Although there are normative data for the test, it is recommended to perform baseline testing prior to participation in the season.

Sport Concussion Assessment Tool (SCAT)

The SCAT is a multifaceted paper test that was developed as part of the Second International Conference on Concussion in Sport. Currently, the most updated version of the SCAT is the fifth edition. The SCAT-5 includes an immediate or on-field evaluation determining signs and symptoms including: observable signs, Maddocks Score, the Glascow Coma Scale for

assessment of level of consciousness, and a cervical spine evaluation. There is also an off-the-field evaluation, including patient demographics, a 22-item symptom checklist, cognitive screening (immediate memory, orientation, and concentration task). There is a basic neurological screening and balance examination utilizing a Modified Balance Error Scoring System followed by a follow-up delayed recall memory test.

The SCAT-5 is freely available and may be considered more convenient than computerized neurocognitive assessments for "on the field" assessments or immediate assessments. Although the current version of the SCAT (version 5) does not have normative data available yet, previous versions do provide normative data for comparison. However, some of the normative data for components of the previous versions have been found to be less reliable. Specifically, the Modified Balance Error Scoring System (mBESS), a component of the SCAT, total score shows poor inter-rater and intra-rater reliability. The SCAT-5 may be used for participants ages 12 and older, with the Child SCAT-5 covering ages 5 to 12. The SCAT was included in 8 of the 28 studies and employed 933 participants (629 males, 117 females, and 187 unspecified).

King-Devick Test (K-D Test)

The K-D Test includes measurements of language, attention, eye-movements, and reading performance during a directional number reading task. This oculomotor test is able to detect and identify injuries in players that do not report any obvious signs or symptoms of a concussion. Participants are instructed to read increasingly difficult numbers in a directional sequence and the administrator notes any verbal or saccadic issues that the participant experiences.

The K-D Test is a simple-to-use sideline assessment that preliminary data shows high test-retest reliability with clinicians and parents. The K-D Test was included in 5 of the 28 studies and employed 400 participants (174 males, 20 females, and 206 unspecified).

Digit Symbol Substitution Test (DSST)

The DSST is a portion of the Wechsler-Bellevue Intelligence Scale. This test allocates specific symbols to certain numbers and requires the participant to recall which symbol corresponds to the given number. Normative data for ages 24-81 is available for several alternate forms of the DSST.

The DSST is a paper test that requires minimal equipment, utilizing only a score sheet, stopwatch, and pencil, but must be purchased. The administrator instructs the participant according to the guidelines, and records the amount of time taken to complete the task sheet. The participant is then given a score based on the number of correctly and incorrectly coded symbols. The DSST was included in 4 of the 28 studies and included 293 male participants.

Trail Making Test Part B (TMT-B)

TMT-B is an evaluation of a participants executive, speed, and visual function. This test requires individuals to draw lines connecting alternating letters and numbers in sequential form (i.e. A-1-B-2). This is a more difficult task than part A, which includes only numbers. Studies show a statistically significant decrease in performance (increase in time to complete the task) and increase in task difficulty of those with concussions.

The TMT-B has normative data for individuals 18-89 years. This assessment is free to use and requires only a pencil, paper, and stopwatch. Scoring is determined by the amount of time taken to correctly connect all letters and numbers. Participants completing the trail in 75

seconds or less are considered average and greater than 273 seconds is scored as deficient. This leaves a large margin without differentiating performance. The TMT-B was included in 4 of the 28 studies and included 293 male participants.

CogState (CogSport)

The CogState assessment is used more frequently outside the United States. This assessment was developed to be used in conjunction with other concussion-related assessments. CogState measures aspects of psychomotor function, decision making, working memory, and learning, all with speed and accuracy sub score. Some studies show that this test is reliable for multiple sessions while others find that there is a practice effect after the second assessment. The CogState was included in 3 of the 28 studies and included 155 male participants.

Additional Assessments

NHL Battery, Automated Neuropsychological Assessment Metrics (ANAM), Sensory Organization Test (SOT), Rivermead Post-Concussion Symptoms Questionnaire (R-PSQ), Headminder Concussion Resolution Index (CRI).

Appendix B

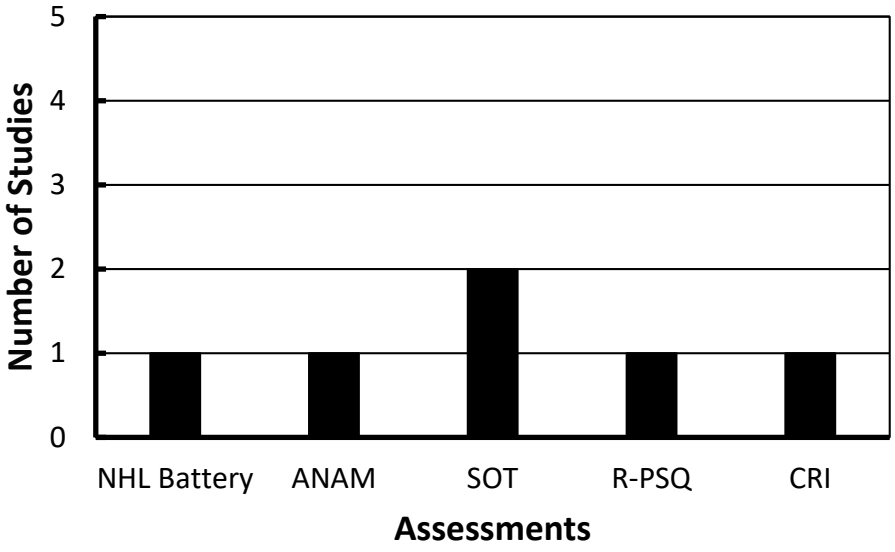

Figure 15. Number of studies employing each assessment.

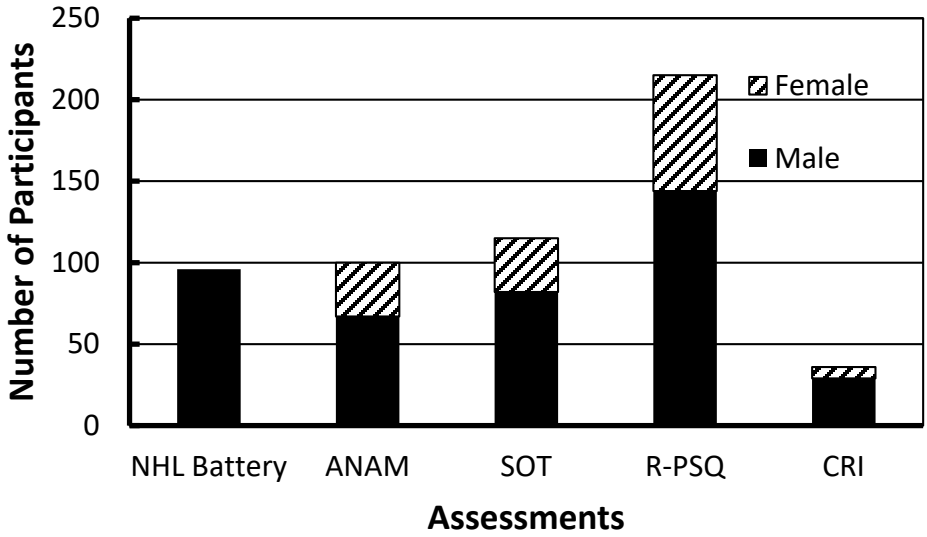

Figure 16. Number of participants by sex using each assessment.

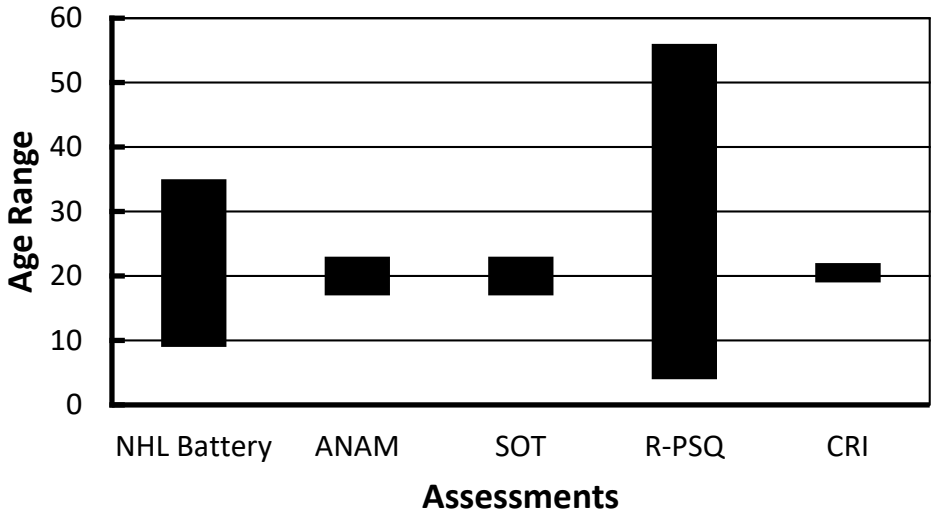

Figure 17. Age range of each assessment.

OMB Control Number: 0925-0667 Expiration Date: 02/28/2018

NIMH Data Archive

Data Use Certification

Last updated: July 17, 2017

Table of Contents

NIMH Data Archive Data Use Certification

I. Introduction

The National Institute of Mental Health (NIMH) Data Archive (NDA) are a group of Federal data repositories based on an informatics platform for research domains related to mental health, initially established as the National Database for Autism Research to support autism-related research. As of May 2017, the system has expanded to include the following domains:

- National Database for Autism Research (NDAR)—data submission and access
- National Database for Clinical Trials Related to Mental Illness (NDCT)—data submission and access
- Research Domain Criteria Database (RDoCdb)—data submission and access
- NIH Pediatric MRI Repository (PedsMRI)—data access only
- Adolescent Brain Cognitive Development (ABCD) Study—data submission and access

This form is for purposes of requesting permission to access data from the NDA. Recipients seeking access to data from any of the NDA domains must submit a Data Use Certification (DUC) certified and co-signed by the Principal Investigator and the designated Institutional Official(s). In order to submit data to the NDA, the NDA Data Submission Agreement (DSA) must be completed, which is a separate document.

The NIMH Data Archive (NDA)

The National Institutes of Health (NIH) and NIMH have developed a federation of data repositories to store the collection of data from participants in research studies related to mental health, regardless of the source of funding. The extensive information collected by these studies, and subsequently made available via the National Database for Autism Research (NDAR), the NIH Pediatric MRI Repository (PedsMRI), the National Database for Clinical Trials Related to Mental Illness (NDCT), the Research Domain Criteria Database (RDoCdb), and the Adolescent Brain Cognitive Development (ABCD) Study provides a rare and valuable scientific resource. The NIH and NIMH seek to encourage the use of these resources to achieve rapid scientific progress. In order to take full advantage of such resources and maximize their research value, it is important that data are **broadly** made **available**, on appropriate terms and conditions, to the largest possible number of qualified investigators in a timely manner. Data collected by the Submitters have been stripped of all individual identifiers, but the unique and intrinsically personal nature of genomics data, brain imaging, and other derivative data of which are included in these repositories, combined with the recent increase in the accessibility of conducting genotype and other sequence analyses (in terms of technological capacity and cost), has altered the framework through which "identify-ability" can be defined. To protect and assure the confidentiality and privacy of all participants, the Recipient who is granted access to these data is expected to adhere to the specifications of this DUC. Failure to do so could result in denial of further access to data.

National Database for Autism Research (NDAR)

The National Database for Autism Research (NDAR) is an NIH-funded research data repository that aims to accelerate progress in autism spectrum disorder (ASD) research through data sharing, data harmonization, and the reporting of research results. Raw genomics, clinical, imaging, and neurosignal recordings data and results are available.

National Database for Clinical Trials Related to Mental Illness (NDCT)

NIMH has made data sharing an expectation for all future clinical trials funded by the NIMH (see NOT-MH-14-015). Researchers are expected to submit both positive and negative data and results from NIMH-funded clinical trials to the National Database for Clinical Trials Related to Mental Illness (NDCT). NDCT will provide a system to support the submission, sharing and access of relevant data at all levels of biological and behavioral organization and for all data types. At present, data submitted to NDCT will be the result of grants funded through a series of NIMH funding opportunity announcements (FOAs).

Research Domain Criteria Database (RDoCdb)

The Research Domain Criteria (RDoC) initiative aligns research in neuroscience and behavioral science to develop a precision-medicine approach for classifying mental illnesses. In contrast to current symptom-based diagnostic systems for mental illnesses, precision medicine integrates many levels of information for each patient to define a precise diagnosis. Data submitted to the RDoC Database (RDoCdb) will include the results of grants funded through a series of NIMH FOAs in support of the RDoC project, as well as relevant data submitted by other interested investigators, regardless of funding source. More information on the RDoC project and related FOAs can be found at http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml. Omics data associated with these studies are found in the National Library of Medicine supported genomics repositories (dbGaP and SRA).

NIH Pediatric MRI Data Repository (PedsMRI)

The goal of the NIH MRI Study of Normal Brain Development and the resulting Pediatric MRI Data Repository (PedsMRI) is to generate data that can help foster a better understanding of normal brain maturation as a basis for understanding atypical brain development associated with a variety of developmental, neurological, and neuropsychiatric disorders affecting children and adults.

Adolescent Brain Cognitive Development Study (ABCD)

The ABCD Study is a long-term study of brain development and child health in the United States. Multiple NIH Institutes and Centers and additional federal partners are supporting this ambitious project. The ABCD Consortium consists of a Coordinating Center, a Data Analysis and Informatics Center, and 21 research sites across the country where investigators will perform regular, comprehensive biological and behavioral assessments on more than 10,000 children beginning when they are ages 9 or 10, continuing throughout adolescence into early adulthood. A more complete description of the study is available at https://abcdstudy.org.

II. Definitions

For purposes of this agreement, “data” refers to the information which have been collected and recorded from participants in any study, regardless of the source of funding. For human subjects, data include all research and clinical assessments and information obtained via interviews, direct observations, laboratory tasks and procedures, records reviews, genetic and genomic data (related to autism only), neuroimaging data, psychophysiological assessments, data from physical examinations, etc. The following are not included as data: laboratory notebooks, preliminary analyses, drafts of scientific papers, plans for future research, peer review reports, communications with colleagues, or physical objects, such as gels or laboratory specimens.

A "Submitter" is defined as a researcher with a past or current/active grant, contract, or consulting agreement with the NIH, one of its contractors, or any other funding source, who has submitted data to the NDA, according to the policies laid out in the NDA Submission Agreement.

The "Recipient" is a researcher at a non-profit or for-profit organization or corporation with an approved Federal Wide Assurance (FWA) from the Department of Health and Human Services Office for Human Research Protections (OHRP), as well as any collaborating organizational staff listed in the NDA DUC. The Recipient requests access to study data at his or her sole risk and at no expense to the study or the NIH.

III. Instructions

1. Read the DUC.
2. Complete Section VII. Recipient Information and Certifications. List all the collaborating investigators at your organization. By submitting an individual's name on the form, you and your Institutional Official affirm that the collaborators have read and agreed to the terms and conditions within the DUC. Collaborators at different organizations/institutions must complete separate requests for the data sponsored by their own organization/institution. Coordinated requests by collaborating organizations should all use the same title in their request and each should reference the others in the Research Use Statement.
3. Sign and date the Section VII. Recipient Information and Certification page, and obtain an Institutional Official's signature and date. Only signatures by institutional officials listed as a signing official (SO) in the eRA Commons system will be accepted.
4. Provide a scanned copy of this complete document including the instructions and DUC pages, with appropriate signatures, to the NDA within the systems described or email the document to NDAHelp@mail.nih.gov.
5. The appropriate Data Access Committee (DAC) will review the DUC and will decide whether to permit the access based on the expectations outlined in the DUC. In the event that access raises a concern related to privacy and confidentiality, risks to populations or groups, or other concerns, the DAC will consult with other experts as appropriate.
6. The DAC(s) will notify NDA staff if the access request has been approved, and appropriate permissions to the Recipient's account will then be provided. The user will receive a notification of their account update with any modified user name, passwords, or instructions for accessing the appropriate data.
7. Optional: System Training (if request approved): Contact NDA Staff through NDAHelp@mail.nih.gov to discuss specific training needs the user may have and schedule the training and/or to be directed to the appropriate online tutorials.

IV. Terms and Conditions

I request approval to access data from one or more of the datasets within the NDA for the purpose of scientific investigation or the planning of clinical research studies as described in the following DUC. I, and my collaborating investigators at my institution, agree to the following terms:

1. Research Project/Research Use

These data will be used by Recipient in connection with the "Research Project" generally indicated and described in the Research Use Statement on the DUC. If the Project involves collaborator(s), their

names and the work they will perform is also included in the Recipient Information and Certifications section.

2. Non-transferability of Agreement

This DUC is not transferable. If the Recipient changes institutions and wishes to retain access to the NDA, a new DUC in which the new institution acknowledges and agrees to the provisions of the DUC is necessary. If the Recipient changes Institutions and does not complete a new DUC, the Recipient agrees to destroy all copies of NDA dataset(s) obtained under this DUC, including backup or working copies at the original site.

3. Non-Identification of Subjects

Recipient agrees that data will not be used to establish the individual identities of any of the study participants from whom data were obtained and/or contact the individual study participant, except as permitted by law (e.g., in connection with a separately negotiated collaboration with the original research team or the enrollment of the consented subject in the Recipient's study). Recipient agrees to notify the NIH as soon as possible if, upon use of NDA data, the Recipient discovers identifying information in that data.

4. GUID and Access to Submitted Data

The Global Unique Identifier (GUID) is a computer-generated alphanumeric code that is unique to each research participant. The GUID allows the NDA to link together all submitted information on a single participant, giving researchers access to information even if the data were collected at different locations or through different studies. If Recipients request access to data on individuals for whom they themselves have previously submitted data to the NDA, they may gain access to more data about an individual participant than they themselves collected. Consequently, these research activities may be considered "human subjects research" within the scope of 45 C.F.R. 46. Recipients must comply with the requirements contained in 45 C.F.R. 46, as applicable, which may require that they obtain Institutional Review Board (IRB) approval of their Research Project. For more guidance, check with your local IRB and/or OHRP.

5. Data Disclaimers

Recipient acknowledges that the NIH does not and cannot warrant the results that may be obtained by using any data included therein. The NIH disclaims all warranties as to the accuracy of the data in the NDA or the performance or fitness of the data for any particular purpose.
https://data-archive.nimh.nih.gov/tools#cloud.

6. Notification to the NIH of Publication

Recipient agrees to promptly notify the NIH via email at NDAHelp@mail.nih.gov as to when and where a publication (or other public disclosure) from the Research Project will appear, whether reporting positive or negative results. The notification will include the title, authors, place of publication, and publication date. **Recipient also agrees to create an NDA Study** (https://data-archive.nimh.nih.gov/training/modules/study.html) to further define the publication (or other disclosure) and link it to the underlying data.

7. Data Access for Research

Data in the NDA are eligible for access by qualified researchers, pursuant to the terms set forth in this DUC. Recipients acknowledge that other researchers have access to the data and that downloading, utilization, and duplication of research is a distinct possibility.

Data from ongoing studies which have not yet been made broadly accessible to NDA account holders may be eligible for restricted "Ongoing Study Access" following coordination and consultation with the Submitter and pursuant to the Additional Standards for Accessing Data While a Study is Ongoing (see https://data-archive.nimh.nih.gov/rdocdb/s/sharedcontent/about/standard-operating-procedures.html#sop9). This Ongoing Study Access policy pertains to NDAR, NDCT, RDoCdb, and ABCD datasets.

8. No Distribution of Data

Recipient agrees to retain control over data, and further agrees not to transfer data, with or without charge, to any other entity or any individual. Recipient agrees not to sell the data in any form to any entity or individual or to distribute the data to anyone other than his/her research staff who will also agree to the terms within this DUC. This applies to all versions of NDAR data, all versions of PedsMRI data, all versions of NDCT data, all versions of RDoCdb data, and all versions of ABCD Study data.

9. Acknowledgments

Submitters have made a substantial long-term contribution to NDAR, PedsMRI, NDCT, RDoCdb, and/or ABCD by submitting data to the NDA. The NIH seeks to encourage appropriate data use and collaborative relationships by outside investigators with the Submitters and to ensure that the contribution of the Submitters is appropriately acknowledged.

Recipient agrees to acknowledge the NDA informatics platform; the appropriate repository (NDAR, and/or PedsMRI, and/or NDCT, and/or RDoCdb, and/or ABCD); the relevant data identifier(s) (e.g., a serial number generated via the NDA Study feature [see http://ndar.nih.gov/access_ndar_study.html or similar feature to be made available on the NDCT and RDoCdb Websites]); and, the Recipient's federal research funding sources in any and all oral and written presentations, disclosures, and publications (including abstracts, as space allows) resulting from any and all analyses of data using the NDA tools, whether or not Recipient is collaborating with Submitter(s). The oral or written presentation, disclosure, or publication should include the following acknowledgement or other similar language, which includes a disclaimer of NIH endorsement, as appropriate:

NDAR Acknowledgement

Data and/or research tools used in the preparation of this manuscript were obtained from the NIH-supported National Database for Autism Research (NDAR). NDAR is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in autism. Dataset identifier(s): [NDA Collection ID(s) or NDA Digital Object Identifier (DOI)]. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDAR.

Pediatric MRI Acknowledgement

Data used in the preparation of this article were obtained from the NIH Pediatric MRI Data Repository created by the NIH MRI Study of Normal Brain Development. This is a multisite, longitudinal study of typically developing children from ages newborn through young adulthood conducted by the Brain Development Cooperative Group and supported by the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke (Contract #s N01-HD02-3343, N01-MH9-0002, and N01-NS-9-2314, -2315, -2316, -2317, -2319 and -2320). A listing of the participating sites and a complete listing of the study investigators can be found at

http://pediatricmri.nih.gov/nihpd/info/participating_centers.html. Dataset identifier(s): [NDA Collection ID(s) or NDA Digital Object Identifier (DOI)]. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH.

NDCT Acknowledgement

Data and/or research tools used in the preparation of this manuscript were obtained and analyzed from the controlled access datasets distributed from the NIMH-supported National Database for Clinical Trials (NDCT). NDCT is a collaborative informatics system created by the National Institute of Mental Health to provide a national resource to support and accelerate discovery related to clinical trial research in mental health. Dataset identifier(s): [NDA Collection ID(s) or NDA Digital Object Identifier (DOI)]. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIMH or of the Submitters submitting original data to NDCT.

RDoCdb Acknowledgement

Data and/or research tools used in the preparation of this manuscript were obtained and analyzed from the controlled access datasets distributed from the NIMH-supported Research Domain Criteria Database (RDoCdb). RDoCdb is a collaborative informatics system created by the National Institute of Mental Health to store and share data resulting from grants funded through the Research Domain Criteria (RDoC) project. Dataset identifier(s): [NDA Collection ID(s) or NDA Digital Object Identifier (DOI)]. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to RDoCdb.

ABCD Acknowledgment

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9-10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners *under award numbers U01DA041022, U01DA041025, U01DA041028, U01DA041048, U01DA041089, U01DA041093, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, and U24DA041147*. A full list of supporters is available at https://abcdstudy.org/nih-collaborators. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/principal-investigators.html. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

(Add the following sentence for a report that uses data from a versioned release)
The ABCD data repository grows and changes over time. The ABCD data used in this report came from (insert the appropriate doi here. Dois can be found at ###).

(Add the following sentence for a report that uses data from the fast track release)
The ABCD data repository grows and changes over time. The ABCD data used in this report came from the fast track data release. The raw data are available at (insert the doi here for a NDA study. Instructions on how to create a NDA study are available at https://data-archive.nimh.nih.gov/training/modules/study.html).

If the Research Project involves collaboration with Submitters or NIH staff (as indicated in the DUC), then Recipient will acknowledge Submitters or NIH staff as co-authors, if appropriate, on any presentation, disclosure, or publication.

10. Non-Governmental Endorsement; Liability

Recipient agrees not to claim, infer, or imply endorsement by the United States Government, the Department of Health & Human Services, the National Institute of Health, or the National Institute of Mental Health of the Research Project, the entity, or personnel conducting the Research Project or any resulting commercial product(s). The United States Government assumes no liability except to the extent provided under the Federal Tort Claims Act (28 U.S.C. § 2671-2680).

11. Recipient's Compliance with Institutional Requirements

Recipient acknowledges that access, if provided, is for research that is approved by the Institution, which must be operating under an OHRP-approved Federal-wide Assurance. Furthermore, Recipient agrees to comply with all applicable rules for the protection of human subjects, which may include Department of Health and Human Services regulations at 45 C.F.R. Part 46, and other federal and state laws for the use of this data. Recipient agrees to report promptly to the NIH any unanticipated problems involving risks to subjects or others. This DUC is made in addition to, and does not supersede, any of Recipient's institutional policies or any local, State, and/or Federal laws and regulations that provide additional protections for human subjects.

12. Recipient's Permission to Post Information Publicly

Recipient agrees to permit the NIH to summarize, on the appropriate NDA web site, the Recipient's research use of data along with the Recipient's name and organizational/institutional affiliation.

13. Privacy Act Notification

The Recipient agrees that information collected from the Recipient, as part of the DUC, may be made public in part or in whole for tracking and reporting purposes. This Privacy Act Notification is provided pursuant to Public Law 93-579, Privacy Act of 1974, 5 U.S.C. Section 552a. Authority for the collection of the information requested below from the recipient comes from the authorities regarding the establishment of the National Institutes of Health, its general authority to conduct and fund research and to provide training assistance, and its general authority to maintain records in connection with these and its other functions (42 U.S.C. 203, 241, 289l-1 and 44 U.S.C. 3101), and Section 301 and 493 of the Public Health Service Act. These records will be maintained in accordance with the Privacy Act System of Record Notice 09-25-0156 () covering "Records of Participants in Programs and Respondents in Surveys Used to Evaluate Programs of the Public Health Service, HHS/PHS/NIH/OD." The primary uses of this information are to document, track, and monitor and evaluate the use of NDA datasets, as well as to notify interested recipients of updates, corrections or other changes to the database.

The Federal Privacy Act protects the confidentiality of some NIH records. The NIH and any sites that are provided access to the datasets will have access to the information collected by the NIH from the Recipient, as part of the DUC for the purposes described above. In addition, the Act allows the release of some information without the Recipient's permission; for example, if it is requested by members of Congress or other authorized individuals. The information requested in this DUC is voluntary, but necessary for obtaining access to data in the NDA.

14. Security
Recipient acknowledges the expectations set forth by the attached "Information Technology Security Best Practices and Security Standards" for the use and security of data.

15. Annual Update/Research Use Reporting
When requested, Recipient will provide to NDAHelp@mail.nih.gov, as applicable, an annual summary of research accomplishments from using NDA data in an updated biographical sketch or CV. This annual summary may also be submitted via an NDA web site link if the function is available. The NIH encourages Recipients who publish manuscripts based on a combination of NDA data and data collected independent of the NDA to consider submitting the complete analyzed dataset to the NDA, if possible.

16. Amendments
Amendments to this DUC must be made in writing and signed by authorized representatives of all parties.

17. Termination
Either party may terminate this DUC, without cause, provided 30 days' written notice to the other party. Recipients agree to immediately report violations of this agreement to the NDA DAC. Additionally, the NIH may terminate this agreement with 5 days' written notice if the NIH determines, in its sole discretion, that the Recipient has committed a material breach of this DUC. The NIH may, in its sole discretion, provide Recipient with 30 days' notice to remedy a breach before termination. Closed accounts may be reactivated upon submission of an updated NDA DUC.

18. One-Year Term and Access Period
Recipients who are granted permission to access data from any of the NDA repositories receive an account with permission to access the data from a specified repository that is valid for a period of one year. This DUC will automatically terminate at the end of one year. An account may be renewed upon recertification of a new DUC. Accounts that remain inactive for 12 consecutive months may be closed at the discretion of the NIH.

19. Accurate Representations
Recipient expressly certifies that the contents of any statements made or reflected in this document are truthful and accurate.

V. Information Security Best Practices and Security Standards

The purpose of these Security Best Practices and Security Standards, which are subject to applicable law, is to provide minimum security standards and best practices for individuals who use the NDA to submit, access, and analyze data. Keeping information from the NDA secure through these best practices is important. Subject to applicable law, Recipients agree to immediately report breaches of data confidentiality to the NDA DAC.

Security Best Practices

We suggest that you:

- Do not attempt to override technical or management controls to access data for which you have not been expressly authorized.

- Do not use your trusted position and access rights to exploit system controls or access data for any reason other than in the performance of the proposed research.
- Do not allow others to use your account. Each user must obtain and use their own account.
- Ensure that anyone directed to use the system has access to, and is aware of, Information Security Best Practices and Security Standards as well as all existing policies and procedures relevant to the use of the NDA, including but not limited to, the NDA Policy at http://ndar.nih.gov/policies.html and 45 C.F.R. Part 46.
- Follow the password policy which includes:
  - Choose passwords of at least seven characters including at least three of the following types of characters: capital letters, lower case letters, numeric characters and other special characters.
  - Change your passwords every six months.
  - Protect your password from access by other individuals—for example, store it electronically in a secure location.
- Notify NDA staff, as permitted by law, at NDAHelp@mail.nih.gov of security incidents, or any incidents of suspected fraud, waste or misuse of NDA or when access to NDA is no longer required.

Security Standards

- Protect the data, providing access solely to authorized researchers permitted access to such data by your institution or to others as required by law.
- When you download NDA data, download the data to a secured computer or server with strong password protection.
- For the computers hosting NDA data, ensure that they have the latest security patches and are running virus protection software.
- Make sure the data are protected from anonymous access over the Internet.
- If you leave your office, close out of data files or lock your computer. Consider the installation of a timed screen saver with password protection.
- Avoid storing data on a laptop or other portable medium. If storing data on such a device, consider encrypting the data.
- When finished using the data, destroy the data or otherwise dispose of it properly, as permitted by law.

VI. Burden Disclosure Statement

Public reporting burden for this collection of information is estimated to vary from 15 min to 1.5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. **An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.** Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0667). Do not return the completed form to this address.

VII. NIMH Data Archive Recipient Information and Certifications

Date: 11/07/2017

1. Access Request Type:

Application Type		
NEW	RENEWAL	
☐	☐	National Database for Autism Research (NDAR)
☑	☐	Pediatric MRI Data Repository (PedsMRI)
☐	☐	National Database for Clinical Trials (NDCT)
☐	☐	Research Domain Criteria Database (RDoCdb)
☑	☐	Adolescent Brain Cognitive Development (ABCD)

2. Lead Recipient:

First Name: Melissa

Last Name: Pangelinan

Academic Position (or Title): Assistant Professor

Degree: Ph.D.

Institution: Auburn University

Department: School of Kinesiology

Street Address: 301 Wire Road

City: Auburn

State/Province: AL

Zip/Postal Code: 36849

Country: USA

Phone: 334-744-4142

FAX:

Institutional E-mail Address: mgp0020@auburn.edu

Research Project(title):

Trajectories of brain and neurocognitive development following pediatric mild traumatic brain injury.

3. Research Data Use Statement: Describe the purpose of the scientific investigation, scholarship or teaching, or other form of research and research development for which you are requesting access to the NIMH Data Archive.

The purpose of this study is to examine differences in the trajectory of brain and cognitive development in children and adolescents that have sustained a mild traumatic brain injury compared to a normative sample. The present study will evaluate structural MRI and diffusion tensor imaging to determine if long-term differences emerge following mild traumatic brain injury. These data will be compared with data acquired from children and adolescents that have sustained a sports-related concussion. The ultimate goal is to identify neural and cognitive phenotypes that are consistent across mild traumatic brain injury and those that are specific to youth sports-related concussion. These data will be used for publication in peer-reviewed journals and presentation at scientific conferences. These data will also be used to teach graduate students about pediatric neuroimaging data processing and statistical analyses. Findings from this study will serve as pilot data for grants.

Senior/Key Person Profile (Collaborating Investigator)

First Name: Jaimie Last Name: Roper

Degree: Ph.D. Academic Position (or Title): Assistant Professor

Institution: Auburn Univeristy Department: School of Kinesiology

Street Address: 301 Wire Road

City: Auburn State/Province: AL Zip/Postal Code: 36849

Country: Phone: 334-844-1597 FAX:

Institutional E-mail Address: jar0105@auburn.edu

Project Role: Co-Investigator Other Project Role Category:

Senior/Key Person Profile (Collaborating Investigator)

First Name: Justin Last Name: Moody

Degree: M.Ed. Academic Position (or Title): Graduate student

Institution: Auburn University Department: School of Kinesiology

Street Address: 301 Wire Road

City: Auburn State/Province: AL Zip/Postal Code: 36849

Country: USA Phone: 334-844-1548 FAX:

Institutional E-mail Address: jrm0063@auburn.edu

Project Role: Data analyst Other Project Role Category:

Senior/Key Person Profile (Collaborating Investigator)

First Name: Last Name:

Degree: Academic Position (or Title):

Institution: Department:

Street Address:

City: State/Province: Zip/Postal Code:

Country: Phone: FAX:

Institutional E-mail Address:

Project Role: Other Project Role Category:

Senior/Key Person Profile (Collaborating Investigator)

First Name: Last Name:

Degree: Academic Position (or Title):

Institution:_____ Department: _____

Street Address:_____

City:_____ State/Province:_____ Zip/Postal Code: _____

Country:_____ Phone:_____ FAX:_____

Institutional E-mail Address: _____

Project Role:_____ Other Project Role Category:_____

Use additional sheets for additional profiles as needed.

4. **Authorized Institutional Business Official** (as registered in the NIH eRA Commons: *https://commons.era.nih.gov/commons*)

Name: John M. Mason Email Address: ospadmn@auburn.edu

5. **Signatures:**

By signing and dating this DUC to request access to data in the NIMH Data Archive, I and my Institutional Official certify that we will abide by the Data Use Terms and Conditions defined in this DUC. I further acknowledge that I have shared this document with any Other Recipients who will participate in the use of data from the NIMH Data Archive. My Institutional Business Official also acknowledges that they have shared this document with appropriate institutional organizations.

Melissa Pam — 11/7/2017

Lead Recipient Signature — Date

Gene Taylor for John Mason — 11/08/2017

Digitally signed by Gene Taylor for John
DN: cn=Gene Taylor for John Mason, o=Auburn University, ou=Office of Sponsored Programs, email=taylol2@auburn.edu, c=US

Authorized Institutional Business Official Signature *(if required)* — Date

Inquiries and requests to access data in the NIMH Data Archive should be sent, preferably by email, to:
Office of Technology Development and Coordination
(OTDC), Program Director National Institute of Mental
Health | National Institutes of Health
6001 Executive Boulevard, Room 7163, MSC 9640
Bethesda, MD 20892-9640 Telephone: 301-443-3265 |
Email**:** NDAHelp@mail.nih.gov