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THE EFFECT OF REPETITIVE SUBCONCUSSIVE HEAD IMPACTS ON OBSERVED PHYSIOLOGICAL, BIOCHEMICAL, AND FUNCTIONAL PERTURBANCES IN THE BRAIN IN HIGH SCHOOL AND COLLEGIATE FOOTBALL PLAYERS: A SYSTEMATIC LITERATURE REVIEW

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Dedication

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Abstract: In this review, we investigated the effects of repetitive subconcussive helmeted head impacts (RSHI) in high school and collegiate athletes. We performed a literature review of all English-language medical literature from 2009 to current. Hippocampal volume changes, white matter diffusion changes, neurocognitive and neurophysiological performance, serum brain marker, diffusion-weighted tensor imaging changes, and head impact telemetry were outcomes of interest. Our initial search strategy identified 564 articles. After restricting to articles focused on subjects aged 13 to 24 years, 151 articles remained. Finally, articles were limited to the past five years of publication (2009 – current). We evaluated preseason, in-session, and postseason outcomes in the study groups and their controls. Studies that used neuroimaging reported that RSHI accrued during football play altered brain physiology to some degree. Studies that used clinical neuroperformance measures, however, did not reach such consensus. Football league regulators, coaches, and players should be cognizant of RSHI and continue to use caution.

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INTRODUCTION

In 2006, Zachery Lystedt was only 13 when he suffered a severe head injury during a football game after returning to the field following a non-diagnosed concussion [1]. His injury galvanized the media and enlightened the public, that middle and high school football players can sustain serious brain injuries from the game similar to their collegiate and professional counterparts. There has been a substantial amount of concussion research in youth and young adults in the 1980's and early 90's, but in light of new technology and better understanding of the brain, there has been a call for further investigation [2].

In recent years, regulators have taken steps to curtail the number of concussions in young football players. In 2013, state high school athletic associations in Arizona, Iowa, Texas, and Washington adopted policies that limited the number of full-contact football practices [3]. Soon after, collegiate conference Pac-12 set the number of contact practices at less than what the NCAA permitted [3]. In 2014, the NCAA recommended limiting full-contact practices to two per week during regular season, four per week during preseason, and no more than eight during spring football [3]. Two weeks after the association's recommendations, California governor Jerry Brown limited middle and high school football contact practices to two per week for preseason and regular season, and he completely banned off-season contact practices [3].

A concussion is a complex pathophysiological process that affects the brain. Traumatic biomechanical forces induce concussion. A direct blow to the head, face, or elsewhere on the body with the transmission of force to the head can cause concussion. A concussion usually causes rapid onset of transient neurological function impairment and

altered mental status. Neuro-pathological changes may be evident, however the acute clinical symptoms are largely the result of functional disturbances rather than structural injury. Concussion results in clinical symptoms that may or may not involve loss of consciousness; resolution of the clinical and cognitive symptoms typically follows a sequential course but in a small percentage of cases post-concussive symptoms may be prolonged. There is no apparent evidence of abnormality on standard structural neuroimaging studies [4].

The Centers for Disease Control and Prevention (CDC) classify concussion as a form of traumatic brain injury (TBI). In the United States, 30% of all injury deaths are the direct result from TBI [5]. TBI survivors have lowered quality of life as they face sequelae from neurological dysfunction such as thinking and memory impairments, impairments in movement (e.g. speech), sensation (e.g. hearing and site) and/or emotions (e.g. depression and personality changes). TBI is a serious public health concern because of its magnitude of effect on the population. In 2010, the CDC reported that TBI was associated with over 2 million emergency department visits, hospitalizations, or deaths. More than 50,000 individuals died after sustained TBI, more than 280,000 individuals received the diagnosis of TBI, and 2.2 million persons with TBI visited emergency department [5]. Close to 250,000 children up to age 19 were treated for concussion or TBI at an emergency department for injuries that were related to sports or recreation in 2009 [5]. From 2001 to 2009, there was a 57% increase among children up to age 19 years who went to the emergency department and were diagnosed with either having a concussion or TBI [5].

The CDC declared an epidemic in sports related concussion [6]. In the United States, 1.6 to 3.8 million sports-related concussions occur annually [7]. Of all sports, football represents the greatest risk for concussion [8]. Brain injury was the second most common cause of death in football, behind cardiac failure [9]. Concussions occur at a rate of 0.45 to 0.60 per 1000 athletic exposures in high school and collegiate football players [6]. There has been an 8% increase of concussions in high school football from 1998 to 2008. Between 2001 and 2009, emergency department visits for concussions have nearly doubled among the children aged 8 to 13 years [6]. Young athletes who sustain concussions tend to have worse outcomes than their professional counterparts [6]. First time concussed players are three times more likely to sustain a second concussion when compared with uninjured players in the same season [10]. Deciding when an athlete who sustained a concussion can safely return to play is a challenge since the complex nature of the brain limits objective assessment of symptoms and signs [11]. Poorly understood are the effects of repeated blows to the head, i.e. subconcussive head impacts, which do not lead to overt clinical concussion [12].

Since the 1920's, neuropathologists have reported that repetitive traumatic head impacts associated with boxing could cause chronic traumatic encephalopathy, a progressive degenerative disease of the brain [7]. Recently, the neuropathology community has implicated repetitive subconcussive helmeted head impact (RSHI) events as a significant source of brain injury. Long-term sequelae may include chronic traumatic encephalopathy, dementia, depression, and suicide [7] [8] [13].

Many studies have demonstrated a dose-response relationship between the number of previous concussions and risk of subsequent concussions [14]. However, very

few have demonstrated the effect of RSHI not associated with diagnosed concussion [14]. Our study investigated the effects of football related RSHI on the brain in high school and collegiate athletes who have not received a preseason, in-season, or post-season concussion diagnosis. Subclinical effects on the brain from RSHI in non-concussed football high school and collegiate football players were a particular point of focus in this review. This review evaluated outcomes of neuroperformance, i.e. neurocognitive and neuropsychological performance assessments, biochemical, physiological, and functional brain changes after RSHIs in non-concussed football athletes.

METHODS

We performed a literature review of all English-language medical literature from 2009 to current using Ovid and Pubmed (Medline) databases.

Search Strategy

We employed the following basic search strategy:

football [MeSH] OR football*.mp OR american football.mp

AND

brain Injuries [MeSH] OR head* impact*.mp OR helmet*.mp OR concussion*.mp OR concussive*.mp OR sub-concussion*.mp OR sub-concussive*.mp OR repetitive*.mp OR mild*.mp OR subconcussion*.mp OR subconcussive*.mp

AND

brain [MeSH] OR brain*.mp OR cognition [MeSH] OR cognition*.mp OR executive function [MeSH] OR executive* function*.mp OR neuropsychological tests [MeSH] OR neuropsychological*.mp OR neurocognitive*.mp OR neurocognition*.mp OR magnetic resonance imaging [MeSH] OR mri*.mp OR white matter.mp

(mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier)

Study Selection

Exclusion criteria further selected articles following the completion of the above protocol. We excluded review articles, articles that did not have a subconcussive population, articles that did not include a study population that controlled for its subconcussive population, and articles that did not evaluate functional,

neuroperformance, biochemical, or physiological brain changes. We included articles that contained concussive population as long as they had a subconcussive population and met the aforementioned inclusion criteria.

Qualitative Assessment

We used Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to assess the methodological quality for each article [15]. We scored each article with four-quality level GRADE rating - 'high', 'moderate', 'low', and 'very low'. In brief, an article that received a 'high' GRADE rating meant that the true effect was close to that of the estimate of the effect. An article that received a 'moderate' GRADE rating meant moderate confidence in the effect estimate; in other words, when the true effect was likely to be close to the estimate of the effect but there is a chance that it may be very different. An article that received a 'low' GRADE rating meant that the confidence in the effect estimate was limited, in other words, the true effect may differ substantially from the estimate of the effect. An article that received a 'very low' GRADE meant that there was very little confidence in the effect estimate

We attempted to standardize the GRADE ratings for each article. We graded articles by combining numerical scores of several factors. One factor was study design. We gave a '+1' point to articles that were prospective in nature, e.g. prospective cohort or randomized controlled, however we deducted '-1' point to articles that were not prospective, e.g. cross-sectional or retrospective. Another factor was sample size. For the purpose of this review, articles with a sample size of 50 or above were considered large sample size and we gave them a '+1' point. Conversely, we deducted '-1' point to articles with a lower sample size. We gave '+1' point for each outcome variable within an article.

Articles with significant confounders had their scores deducted ‘-1’. If an article had methodologies that were ambiguous, did not include pertinent and significant raw data, and/or lacked other important background information that would have contributed to and strengthened the articles, we deducted ‘-1’ for each infraction. The scoring of the latter factors was at the discretion of B.A. An aggregated score of ‘4’ or higher designated an article as having a ‘high’ GRADE rating. A score of ‘2’ or ‘3’ designated an article as having a ‘moderate’ GRADE rating. A score ‘-1’, ‘0’, or ‘1’ designated an article as having a ‘low’ GRADE rating. Finally, an article with a ‘-2’ score or lower was given a ‘very low’ GRADE rating.

RESULTS

The search strategy identified 564 articles. After restricting our search to studies that assessed persons aged 13 to 24 years, 151 articles remained (Figure 1). Finally, we limited our search to articles published in the last five years (2009 – 2014). Most of the earliest studies that investigated outcomes from sports related RSHI on humans emerged during this period. Ten articles remained. Of the 10 articles, three received a 'high' GRADE rating for quality of evidence, four received a 'moderate' GRADE, two received a 'low' GRADE, and one received a 'very low' GRADE. *Table 1* shows the factors extracted from the articles and their associated point values. Aggregated total score are located in the GRADE rating column within the table.

Summary of selected articles

Singh *et al*. evaluated hippocampal volume and cognitive performance of NCAA division I football-playing athletes who did not have a history of concussion [16]. The authors found that the left hippocampal mean volume were 14.1% smaller in athletes than the controls (i.e. non-football players without any history of traumatic brain injury), and the difference was statistically significant ($P < .001$). Likewise, right hippocampal volume was 16.7% smaller in athletes when compared against the controls. Again, this difference was significant ($P < .001$). However, the cognitive performance arm of the study did not show any difference between the groups. The authors brought forward several limitations. The clinical significance of hippocampal size has yet to be established. The interpretation of the association of hippocampal volume with football play may have been subjected to multiple confounders that include genetic and environmental influence on the hippocampal volume. The finding of no difference in

cognitive performance may be due to small sample size and underreporting of concussion symptoms by athletes [17]. The study's small sample size also prevented the authors to perform stratified analyses among a multitude of possible confounders. Another limitation is the cross-sectional study design, since it is impossible to assess temporality between hippocampal volume changes and years of football played. The article received a 'low' GRADE rating for quality of evidence due to cross sectional study design, lack of adjusting for confounders, and low sample size [17].

In a prospective cohort study, McAllister *et al.* investigated the relationship between helmeted contact sports and white matter changes [18]. They measured the mean diffusivity of the brains of 159 athletes (n = 79 non-contact sport athletes; n = 80 contact sport athletes). Their study found the number of RSHIs significantly correlated with white matter diffusivity measures in different areas of the brain ($p = 0.001$). Their study also found that athletes who performed poorly on post-season performance of verbal learning and memory had significantly meaningful white matter changes in the corpus collosum. Limitations brought forth were the image acquisition inter-variability due to phenotypic uniqueness of each athlete and non-generalizability of results again due to the inter-variability of subject and due to subjects originating from a single setting. The article received a 'high' GRADE rating for quality of evidence [18].

Gajawelli *et al.* used diffusion tensor imaging (DTI) to quantify physiological white matter changes in the brains of 11 contact sport athletes age-matched with 13 controls [11]. The authors found statistically significant white matter changes in the corpus callosum, external capsule, inferior fronto-occipital fasciculus, and superior/posterior corona radiata in the brains of athletes from pre-season to post-season.

Two different algorithms metrics, fractional anisotropy and median diffusion, were used. The authors endorsed limitations of technical limitations of imaging acquisition itself, small sample size, and the inclusion of non-diagnosed concussion participants. Also, one athlete was known to have a history of concussion and data from the participant was included in the analysis. Demographics of each study participant were not disclosed as well. From the study, it cannot be determined when post-season image acquisition occurred; hence, any conclusion resulting from combined analysis of the athletes would be weak. The article received a 'low' GRADE for quality of evidence [11].

A prospective cohort study used a serum protein as a surrogate marker to detect blood-brain barrier disruption. Marchi *et al.* postulated that RSHI during football play could disrupt the blood-brain barrier and increase serum S100B. The authors measured pre-season, pre-game, and post-game serum S100B from 67 college football players from two colleges [19]. DTI images and S100B auto-antibodies were also obtain from 10 athletes from the second college. The authors found that serum S100B was elevated in players after a football game from their pre-game or baseline levels. S100B post-game – pre-game change was 0.045 ± 0.05 ng/ml and S100B post-game – baseline change was 0.051 ± 0.05ng/ml [19]. Since there was no statistical difference between the two measures, the authors believe that baseline serum S100B is all that is required for brain injury comparative assessment. The study found that there was a dose-dependent relationship between the number and severity of hits to the head and serum S100B ($P<0.01$). Auto-antibodies to the marker were found in players who had extensive serum S100B levels throughout the season. Higher auto-antibodies levels positively correlated with DTI mean diffusion changes. Further, the study found dose-dependent relationship

of auto-antibody level and performance of impulse control (P = 0.07, r = 0.58) and postural stability (P = 0.04, r = 0.04) [19]. A limitation that was brought forth was that data of the number and intensity of head hits came from a subjective questionnaire form. The study would have been stronger if the study participants' helmets had been equipped with impact sensors. Nevertheless, this study had a number of strengths including a large sample size from two different sites, having an unambiguous and rigorous protocol, establishing clear temporality, validating results using more than one established and standardized technique, and providing evidence that associates RSHIs to long-term neurocognitive decline after football play. The article received a 'high' GRADE rating for quality of evidence [19].

Mulligan *et al*. examined the neurocognitive and neurophysiologic functioning of 45 Division IA collegiate football players two days after their final game of the season and compared them with their preseason baseline results [20]. Athletes completed the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), Post-concussion Symptom Scale, and Balance Error Scoring System (BESS) testing. In the study, 32 (71.1%) athletes who did not report having symptoms were found to have neurocognitive and/or balance impairments that are otherwise associated with concussion. Based on their findings, the authors postulated that concussion diagnosis was limited to athletes who report symptoms or who clinically show signs and symptoms of concussion. The authors reported study limitations such as small sample size, possibly including athletes with subclinical concussion in the analysis, and not controlling the participants' activity between the end of the game and time of testing. The article received a 'low' GRADE rating for quality of evidence [20].

McAllister *et al.* prospective cohort study examined a cohort of 214 Division I collegiate contact sports athletes, which included football and ice hockey players, (control n = 45) from three institutions [21]. The participants took preseason and postseason neurocognitive performance assessments. Forty-five of the 214 athletes (noncontact controls n = 55) also took a neuropsychological assessment. Postseason neurocognitive testing occurred on average 25 days after the athletes' last game of the season; the neuropsychological assessment averaged 27 ± 24 days [21]. During a course of a season, contact sport athletes accrued an average of 469 RSHIs. The study found a significant, albeit modest, correlation between neurocognitive performance and measures of biomechanical head impact exposure. The study found a higher percentage of contact sport athletes performed who performed poorer on neurocognitive performance tests, findings that were statistically significant [21]. However, at group level, contact sport athletes' preseason and postseason cognitive performance did not differ significantly from one another. Limitations explicitly expressed by the authors were that study participants were limited to collegiate athletes, performing cognitive assessment almost a month after the last game, and the cognitive tests problem of controlling for effort and motivation required of study participants. This prospective cohort study had a large sample size, several outcomes that were analyzed, populations from more than one site, and a noncontact control group to control for confounders such as a 'learning effect' from test taking. The article received a 'high' GRADE rating for quality of evidence [21].

Breedlove *et al.* investigated the relationship between neurophysiological change and biomechanical history in 38 high school football athletes over two seasons [22]. The authors used helmets equipped with sensors that can measure impact time and magnitude,

functional magnetic resonance imaging (fMRI), and computer-based neuropsychological testing. From preseason baseline and postseason clinical and neuropsychological testing results, study participants were categorized into three different groups based on measurements obtained from fMRI and neuropsychological testing; clinically observed impairment (i.e. concussion) and functional impairment (COI+/FOI+) group, non-symptomatic and functional impairment (COI-/FOI+) group, and non-symptomatic and absent functional impairment (COI-/FOI-) group. The study did not find a statistically significant difference in the median head-on collision force between the three groups ($p>0.52$) [22]. It did, however, report a statistically significant difference in the average total number of head hits ($p<0.05$), with a subsequent pairwise test showing that the COI-/FOI+ group sustained more head hits than the COI-/FOI- group ($p<0.05$). The study also investigated temporal head hits and found that COI-/FOI+ group accrued more temporal hits than the COI+/FOI+ group ($p<0.05$). fMRI analysis revealed changes in 33 of 116 regions of interests (ROIs) in the COI-/FOI+ and COI-/FOI- groups (COI-/FOIx) combined ($p<2x10^{-16}$), whereas the COI+/FOI+ group had 39. fMRI analysis revealed that the COI-/FOIx group had significant involvement of the visual processing center, whereas results from the COI+/FOI+ group also involved the language processing center. The authors concluded that the number of helmeted head impacts and their distribution was an important determinate for altered brain functioning within the magnitude range of 20-80 G-Force [22]. The authors stressed some limitations to their work. Study participants' helmets were not able to record angular acceleration force, which is known to contribute significantly to concussion along with linear acceleration force. The study also did not investigate healing and recovery. The article received a 'moderate' GRADE

rating for quality of evidence [22].

Bazarian *et al.* performed a prospective cohort study of 9 high school athletes who participated in football (n=6) and ice hockey (n=3) [23]. There were six non-athlete controls. One athlete sustained a concussion during play. One of the goals of the study was to use wild bootstrapping statistical approach on DTI results to determine if RSHI correlated to subject-specific change in white matter diffusion. In the study, the largest proportion of white matter voxels came from the concussed athlete, who also had a statistically significant preseason-post injury change (3.19% change in FA, 3.44% change in MD) mostly in voxels co-localized in the right inferior longitudinal fasiculus. This area is involved in language semantics and verbal memory, and right corona radiata. Also observed in the concussed athlete was left/right hemispheric asymmetry. Conversely controls had the smallest proportion of white matter voxels and the smallest statistically significant preseason-postseason change [23]. The RSHI group had higher proportion of white matter voxels and statistically significant changes in FA (1.05% ± 0.15% vs. 0.28% ± 0.01%, p=0.002) and MD (1.48% ± 0.17% vs. 0.48% ± 0.05%, p=0.002) when compared to controls. Cognitive performance was similar between the subconcussive group and controls. Study limitations were a small sample size, the possibility that athletes intentionally performed poorly on baseline cognitive tests, and image mis-registration. The article received a ‘moderate’ rating GRADE for quality of evidence [23].

Gysland *et al.* explored the relationship between RSHI and neurological dysfunction [14]. This study monitored head impacts sustained by 46 collegiate football players (age = 19.65 ± 1.16 years) during one season. In the study, the collegiate football

players accrued 1177.3 ± 772.9 RSHI over the course of a football season. Regardless of whether or not they were on defense or offense, linemen accrued the most RSHIs; however, there was no difference in magnitude of impact between all the playing positions [14]. The study correlated the findings with five different neurocognitive or neurophysiologic tests. The authors found that head impact variables (number of impacts, number of impacts exceeding 90 G-force, aggregate magnitude of impacts, number of impacts to the top of the head) were independent from the changes found with neurocognitive tests, with the findings being statistically significant. However, they also found that increased college football exposure was associated with poorer neurophysiological performance. Limitations expressed by the authors are that the study lacked a nonathletic control group, underreporting of concussions by athletes enrolled in the study, and that some players sustained injuries that required the termination of play resulting in limited impact exposure. Studying the athletes for more than one season may have correlated head impact variable with football exposure neuro-performance results. The article received a 'moderate' GRADE rating for quality of evidence [14].

Broglio and colleagues conducted the first prospective study evaluating the association of head impact biomechanics, subconcussive and concussive, and cognitive outcomes [24]. The study sample consisted of high school football players who underwent subconcussive or concussive-causing helmeted head impacts. Ninety-five high school football athletes from a Class 3A team participated in the study. Similar to Gysland and colleague's findings, the authors did not report a statistically significant difference between pre-and post-concussion impact biomechanical measures and clinical measures, i.e. symptom or neurocognitive testing measures (p's > 0.05). The study also

concluded that the cumulative sum of impact measures was not predictive brain injury risk, when using clinical measures to assess for injury. Limitations mentioned in this study were the inability to ascertain a single impact variable that can accurately quantify helmeted head impacts, the study's low sensitivity measuring the outcome from RSHI, and not using sensitive tests such as standardized balance or motor tests that were known to be sensitive to the effects of concussion. The article received a 'moderate' GRADE rating for quality of evidence [24].

DISCUSSION

All studies that used neuroimaging agreed that accrued RSHI during football play altered the physiology and functionality of brains of football athletes who did not show signs and symptoms of clinical concussion. Four studies showed evidence of increased white matter changes from baseline [11] [16] [18] [23], one study showed evidence of decreased visual processing by fMRI [22], and one article showed evidence of decreased hippocampal volume [16]. One study observed an increase in a brain serum marker, S100B, in athletes following a game, which indicated disruption of blood brain barrier [19]. The evidence showed that RSHI contributed to subclinical brain changes in football athletes.

Studies that used clinical neuroperformance assessments to detect brain changes following RSHI, however, did not reach the same consensus as that of the aforementioned neuroimaging and molecular studies. Three studies supported neurocognitive decline in players [20] [21] [22], however another three found no association [14] [16] [23] [24]. The lack of consensus may be due to the low sensitivity of tests used to evaluate neurocognitive performance, i.e. neurophysiological and neurocognitive tests. Two studies supported this premise by detecting physiological brain changes with neuroimaging in RSHI group but were not able to detect cognitive changes in the same study population when compared against controls [16] [23]. One reason why neuroperformance assessments may not be sensitive enough to detect brain function alterations following RSHIs is that they evaluate a certain functional component of the brain [22]. Hence, results from assessments that evaluate verbal memory only provide insight to certain regions of the brain, e.g., Wernicke's and Broca's areas, while not

detecting changes in other regions. Another probable reason for the lack of consensus was that most of the studies assessed for association of head impact and clinical neuro-performance after only one season of play. A longer time interval, i.e. more than one football season, may be needed to observe neuroperformance changes following RSHIs. Gysland *et al.* supported the premise by detecting the association of football players experience poor neurophysiological performance only after following the players throughout many seasons [14]. Studies should consider following former players for life. Corrigan *et al.* believe that the effects mild trauma to the head such as those experienced from RHSIs may not be evident until a decade later [25].

Although all studies that used neurocognitive tests to evaluate the effects of RSHIs did not have harmonious consensus as did the studies that used imaging, all studies surmised that RSHI's altered normal brain physiology and function to some degree. The nature in their ability to assess certain brain regions such as verbal memory and speech limits neuroperformance assessments, whereas neuroimaging and biochemical analysis is a global approach to ascertain metrics of deviation from the normal brain processes that RSHI may incite [22].

This systematic review has some limitations. Only ten articles were evaluated. It's only been since the 2010 Purdue University publication, which first identified subconcussive category of football players who receive RSHIs during football play [3] [26], did related studies emerge. Hence, due the infancy of the field there is not a plethora of articles pertaining to RSHI. Another limitation of this systematic review is the subjective nature of the grading system of the articles. Only one author, BA, rated each article.

There are some major limitations in the studies reviewed. There is no standard imaging measurement technique that can appropriately assess subconcussive effects of RSHI on the brain. Those that were used may not be sensitive enough to capture the full spectrum of degree of effect [4] [24]. There were technical limitations of imaging acquisition itself [11]. For instance, there is image acquisition inter-variability due to phenotypic uniqueness of each athlete thus making any result non-generalizable [18]. Gold standard measurement techniques to assess neurophysiological function do exist, however they were not used [24]. Another major limitation was not controlling for the time of observation when measuring the effects of RSHI to the brain. For instance, players were imaged at different time points, e.g. months apart [20]. Likewise, cognitive assessments that should have been done couple of days after post game may have been done a month later [21]. Finally, several studies had small sample size, which limited their statistical power [20] [11] [17].

Conclusion

There remain questions unresolved by this literature review. How long do the white matter changes associated with RSHI last? Do they resolve with rest? Do they lower the threshold for developing a clinically evident concussion? Are they a normal phenomenon in the brain to prevent injury, or is this the response to injury?

1.3 million high school and 100,000 collegiate athletes participate in tackle football [6]. Because the majority of athletes have participated in contact sport and have not had any long-term sequelae, perhaps the research focus should shift towards identifying individuals who are susceptible to sustaining concussions. Future studies should have adequate sample sizes, be prospective in nature, and have study periods that span greater than a single football season in order to obtain better estimates of effect. Future research should include neuroimaging acquisition of greater spatial and temporal breadth to search for evidence of brain healing.

The literature suggests that RSHI may have adverse effect on some athletes after correlating clinical assessments with neuroimaging and biochemical data. It remains inconclusive whether or not the induced physiological brain changes are protective to allow for the continuation of normal brain function or are sentinel signs of lowered threshold of neurological deterioration that can lead to concussion. However, it is possible the findings of white matter changes that may indicate axonal injury and the associated findings of circulating S100B antibody circulating in the bloodstream, may provide snapshots of corrosion in affected areas of the brain.

There is significant variability between individuals' brains on a genetic, cellular, structural, physiological, functional, cranial, and vascular morphological level. Genes that modulate response to neuro-trauma (*APOE*, *BDNF*, *ANKKI*) and other host factors may play a role in cognitive outcome following RSHI [21]. These may be the reasons why not all players who endure RSHI sustain a concussive injury during their football career. It is likely that their brains have a higher threshold preventing them from succumbing to the sometimes devastating clinical effects of impact trauma, and they may be better equipped in restoring brain integrity more quickly.

Each individual has his or her breaking point. It is important that one can recognize this point to avoid reaching it. However, this is very challenging. Most athletes are not aware of neurological injury resulting from RSHI because it is usually subclinical, such as small deficits in working memory that require imperceptible time increase to complete an everyday task. Those that notice changes may not think much of them and may brush it off as having an off day. Although there are sideline assessments for concussion, there has yet to exist an assessment that can disclose athletes who have sustained subclinical brain injury from RSHI [3]. Unfortunately, these athletes will continue to play the game and rely on ambiguous odds to not receive a potentially life ending traumatic brain injury.

This review addressed a real public health issue because many teenagers and young adults participate in football and may be at risk for concussion. There is a dearth of literature on RSHI in student athletes and additional research is warranted. Until we know more about RSHI impact on the brain, government, football league regulators, coaches, and players should continue to use caution.

Figure 1. Literature Search Strategy to Ascertain Articles that Studied the Effects of RSHI in the Brains of Football players between the ages of 13 to 24

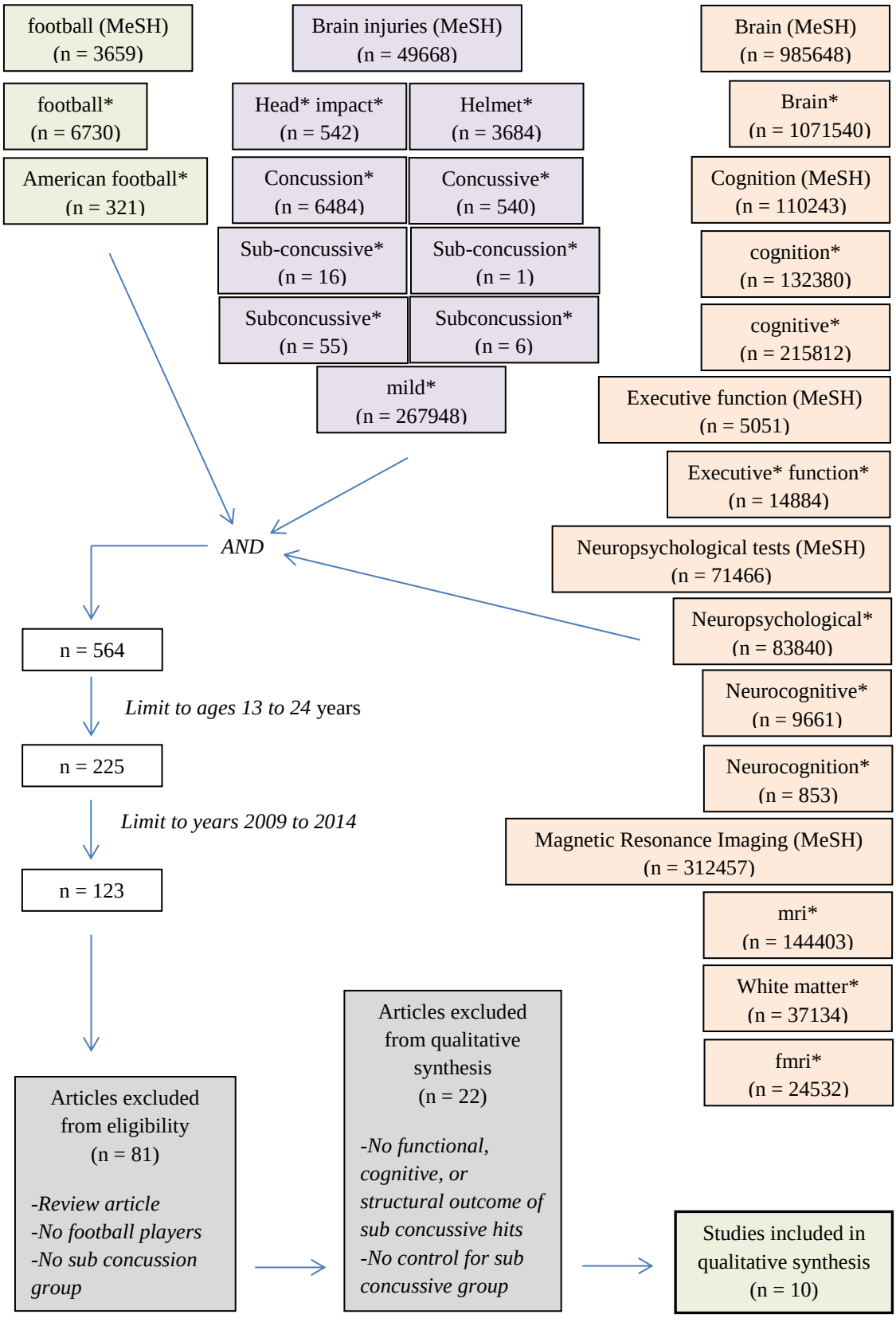

Table 1. Characteristics of the Included Articles ascertained after Systematic Review Literature Search

Author (Year)	Study Design	Population	Exposure	Outcomes	Results	Shortcomings	Grade
Singh (2014)	Cross-sectional (-1)	n = 25 with / n = 25 without history clinician diagnosed concussion. n = 25 matched controls (non-athletes) (-1)	Football	Hippocampal volume (+1)	Hippocampal volume athletes < non-athletes Hippocampal volume inversely correlated to years played No difference found cognitive assessment	Cross-sectional Small sample size Unadjusted confounders (-1)	Very Low -2
McAllister (2014)	Prospective cohort (+1)	80 contact sport athletes; 79 non-contact sport athletes (+1)	Contact sports (include football)	White matter diffusion change (+1) Neurocognitive performance (+1)	Positive association of repetitive head impact and white matter changes Poorer neurocognitive tests associated with increased white matter changes	Image acquisition Single source	High +4
Gajawelli (2014)	Prospective cohort (+1)	11 contact sport athletes; 13 age-matched controls (-1)	Contact sports	White matter diffusion change (+1)	Association of repetitive head impact and white matter changes	Image acquisition Small sample size Limited information of study participants (-1) Quantitative data absent (-1)	Low -1

Author (Year)	Study Design	Population	Exposure	Outcomes	Results	Shortcomings	Grade
Marchi (2013)	Prospective cohort (+1)	67 collegiate football players (+1)	Subconcussive helmeted head hits football	Serum brain marker S100B (+1) DTI changes (+1)	Serum S100B elevated after football game Increased impact number/severity increases S100B levels Higher autoantibodies correlated to DTI changes Higher autoantibodies, worse neuro-physiological testing score	Subjective assessment of head impact	High +4
Mulligan (2012)	Prospective cohort (+1)	45 athletes from a Division IA football team (age 19.56 ± 1.16) (-1)	Football	Neurocognitive/ neuro-physiologic performance (+2)	Neurocognitive/ neurophysiologic performance degradation	Small sample Potential inclusion of subclinical concussed athletes (-1) Poor controlling leading to testing (-1)	Low -1
McAllister (2012)	Prospective cohort (+1)	214 Division I college varsity football and ice hockey players (+1); 45 noncontact sport athletes; 3 sites (+1)	Contact sport (includes football)	Neurocognitive/ Neuro-physiological performance (+2) Head impact telemetry (+1)	No all group short-term cognitive decline Higher impact exposure associated with cognitive decline Subgroup with poorer cognitive performance	Cognitive assessment assessed almost a month after last play	High +6

Author (Year)	Study Design	Population	Exposure	Outcomes	Results	Shortcomings	Grade
Breedlove (2012)	Prospective cohort (+1)	High school football players (n=38, mean age=17) (-1)	Helmeted head impacts	Head impact telemetry (+1) fMRI changes (+1) Neuro-psychological performance (+1)	Head hit accumulation associated with cognitive impairment Visual processing affected in non-concussed fMRI changes in all groups Impact force attributed no difference in functional performance	No angular force measurements Healing and recovery not investigated	Mod-erate +3
Bazarian (2012)	Prospective cohort (+1)	High school athletes (football n=6; ice hockey n=3) control n=6 (-1)	Contact sport (includes football)	DTI changes (+1) Cognitive performance (+1)	Increased proportion of white matter Increased white matter change Similar cognitive performance to controls	Small sample size Intentional poor performance on cognitive tests Image mis-registration	Mod-erate +2
Gysland (2012)	Prospective cohort (+1)	46 collegiate football players (-1)	Football	Head impact (+1) Neurocognitive changes (+1) Neurophysiolog ic changes (+1)	Head impact frequency and magnitude independent from neurocognitive performance Experience associated with poor neurophysiologic performance	Lack of control group (-1) Concussion underreporting Time-loss due injury	Mod-erate +2
Broglio (2011)	Prospective cohort (+1)	95 male high school football players (+1)	Football	Biomechanical properties of concussion (+1) Neurocognitive changes (+1)	Lack of correlation between impact magnitude and cognitive decline	Inability to ascertain single biomechanical variable for impact measurement Cumulative sum of impact not predictive of brain disease risk Poor sensitivity (-1) Some outcome measures for concussion not used	Mod-erate +3

List of Abbreviations

NCAA	National Collegiate Athletics Association
CDC	Centers for Disease Control and Prevention
TBI	Traumatic brain injury
RSHI	Repetitive subconcussive helmeted impact
MeSH	Medical subject heading
GRADE	Grading of Recommendations and Assessment, Development, and Evaluation
B.A.	Best Anyama
DTI	Diffusion tensor imaging
ImPACT	Immediate Post Concussion Assessment and Cognitive Testing
BESS	Balance Error Scoring System
fMRI	Functional magnetic resonance imaging
COI	Clinically observed impairment
FOI	Functional impairment
ROI	Region of interest
FA	Fractional anisotropy
MD	Median diffusion

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Vita

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