

## Original Investigation

# Association of Football Subconcussive Head Impacts With Ocular Near Point of Convergence

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**IMPORTANCE** An increased understanding of the relationship between subconcussive head impacts and near point of convergence (NPC) ocular-motor function may be useful in delineating traumatic brain injury.

**OBJECTIVE** To investigate whether repetitive subconcussive head impacts during preseason football practice cause changes in NPC.

**DESIGN, SETTING, AND PARTICIPANTS** This prospective, observational study of 29 National Collegiate Athletic Association Division I football players included baseline and preseason practices (1 noncontact and 4 contact), and postseason follow-up and outcome measures were obtained for each time. An accelerometer-embedded mouthguard measured head impact kinematics. Based on the sum of head impacts from all 5 practices, players were categorized into lower ( $n = 7$ ) or higher ( $n = 22$ ) impact groups.

**EXPOSURES** Players participated in regular practices, and all head impacts greater than 10g from the 5 practices were recorded using the iBiometrics Vector mouthguard (iBiometrics Inc).

**MAIN OUTCOMES AND MEASURES** Near point of convergence measures and symptom scores.

**RESULTS** A total of 1193 head impacts were recorded from 5 training camp practices in the 29 collegiate football players; 22 were categorized into the higher-impact group and 7 into the lower-impact group. There were significant differences in head impact kinematics between lower- and higher-impact groups (number of impacts, 6 vs 41 [lower impact minus higher impact = 35; 95% CI, 21-51;  $P < .001$ ]; linear acceleration, 99g vs 1112g [lower impact minus higher impact = 1013; 95% CI, 621-1578;  $P < .001$ ]; angular acceleration, 7589 radian/s<sup>2</sup> vs 65 016 radian/s<sup>2</sup> [lower impact minus higher impact = 57 427; 95% CI, 31 123-80 498;  $P < .001$ ], respectively). The trajectory and cumulative burden of subconcussive impacts on NPC differed by group ( $F$  for group  $\times$  linear trend<sub>1, 238</sub> = 12.14,  $P < .001$  and  $F$  for group  $\times$  quadratic trend<sub>1, 238</sub> = 12.97,  $P < .001$ ). In the higher-impact group, there was a linear increase in NPC over time ( $B$  for linear trend, unstandardized coefficient [SE]: 0.76 [0.12],  $P < .001$ ) that plateaued and resolved by postseason follow-up ( $B$  for quadratic trend [SE]: -0.06 [0.008],  $P < .001$ ). In the lower-impact group, there was no change in NPC over time. Group differences were first observed after the first contact practice and remained until the final full-gear practice. No group differences were observed postseason follow-up. There were no differences in symptom scores between groups over time.

**CONCLUSIONS AND RELEVANCE** Although asymptomatic, these data suggest that repetitive subconcussive head impacts were associated with changes in NPC. The increase in NPC highlights the vulnerability and slow recovery of the ocular-motor system following subconcussive head impacts. Changes in NPC may become a useful clinical tool in deciphering brain injury severity.

*JAMA Ophthalmol.* 2016;134(7):763-769. doi:10.1001/jamaophthalmol.2016.1085  
Published online May 12, 2016.

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Subconcussion can be defined as a low-magnitude head impact that does not elicit clinical signs of concussion but potentially causes significant long-term neurological defects.<sup>1-3</sup> Given the concern regarding concussion, understanding the effects of repetitive subconcussive impacts is critical because subconcussive impacts occur more frequently than concussions.<sup>4-6</sup> American football, especially at the college level, is the sport associated with the highest incidence of concussion (0.61 per 1000 athlete exposures)<sup>7,8</sup>; moreover, college football players are reported to endure from 950 to 1353 subconcussive head impacts per season.<sup>4,9-11</sup>

While sports-related concussion is often attributed to a single impact, prior to the concussive blow, athletes in contact sports are frequently exposed to subconcussive head impacts.<sup>12</sup> Establishing a threshold for concussion based on a single impact may be inconclusive given the variation in concussion-associated head acceleration (29g-205g).<sup>5,12</sup> Head impact kinematics in contact sports are investigated using the Head Impact Telemetry system<sup>13,14</sup> and accelerometer-embedded mouthguards.<sup>15,16</sup> However, there are substantial knowledge gaps in the relationships between subconcussive impact kinematics and outcome measures.

The ocular-motor system orchestrates accommodation and vergence, and their concomitant adjustments enable individuals to visualize an object at various distances and directions.<sup>17</sup> The near point of convergence (NPC) measures the closest point to which one can maintain convergence while focusing on an object before diplopia occurs.<sup>18</sup> Previously, we reported that frontal soccer headings immediately increased (worsened) NPC compared with baseline, with NPC impairment persisting for 24 hours after heading.<sup>19</sup> The near point of convergence immediately after and 24 hours after heading were higher than in control individuals.<sup>19</sup> Thus, we hypothesized that repetitive football subconcussive impacts would worsen NPC, particularly among players with higher magnitude and greater frequency of impacts compared with lower-impact players.

## Methods

### Participants

Thirty-three National Collegiate Athletic Association Division I football players at Temple University volunteered for this study. The study was conducted during a preseason physical examination on June 9, 2015, a series of full contact and no contact training camp practices (August 6-21, 2015), and postseason follow-up. Inclusion criterion was being an active football team member. Exclusion criteria included a history of head, neck, or face injury in the previous 6 months or neurological or ocular disorders. Four players exhibited abnormally high NPC scores (9.75 cm, 10.5 cm, 11 cm, and 12.5 cm) at pre-season baseline that were higher than the team mean [SD] baseline (5.5 [2.0] cm). Because NPC scores higher than 9.5 cm to 10 cm are considered defective or convergence insufficiency,<sup>20,21</sup> these players were excluded from the analysis. Data from participants diagnosed as having an orthopedic injury (n = 2) and concussion (n = 1) were excluded from further analysis. Participants refrained from substances that

### Key Points

**Question** Do repetitive subconcussive head impacts from football alter ocular near point of convergence?

**Findings** This study of 29 college football players showed that participants who sustained higher frequencies and magnitudes of impacts had greater convergence insufficiency compared with those with fewer and less severe impacts. The impairment in convergence remained constant throughout the brief study period; however, after 3 weeks of rest, convergence normalized to baseline levels.

**Meaning** The slow nature of the ocular-motor systems recovery suggests its vulnerability to repetitive subconcussive head impacts.

could affect their nervous system (eg, stimulants), and alcohol use was prohibited. All participants gave written informed consent, and the Temple University institutional review board approved the study.

### Study Procedures

During preseason physical examination, participants were fitted with the Vector mouthguard (i1 Biometrics Inc) that measured the number of hits and magnitude of head acceleration. After being briefly submerged in boiling water, the mouthguard was fitted for each player's bite for a secure custom fit. Demographic information (eg, age and years of American football experience), Sports Concussion Assessment Tool 3 symptom checklist, and ocular-motor function (NPC) were collected. During training camp practices, head impact data were collected from 5 practices with intervals of 3 to 4 days between measures, starting from first noncontact (pads off), first full contact (pads on), and 3 other full-contact practices (**Figure 1**). Post-season follow-up measurements were taken 3 weeks after the final game of season in a subset of participants (n = 18), and no practices occurred during this 3-week period.

Based on the sum from 5-practice impact kinematic data collections, players were categorized into lower- and higher-impact groups for analysis. There were at least 6 impacts, 186g, 9614 radian/s<sup>2</sup>, and 15 head injury criterion differences between the highest value of the lower-impact group and the lowest value of the higher-impact group in the number of hits, peak linear acceleration, peak angular acceleration, and head injury criterion, respectively (**Table**). Symptom checklist and NPC data were collected 1 to 2 hours before and 1 to 2 hours after practices.

### Instruments

#### Head Impact Measurement

The Vector mouthguard (i1 Biometrics Inc) was used for measuring linear and rotational head kinematics during impact. The mouthguard uses a triaxial accelerometer (ADXL377, Analog Devices) with 200g maximum per axis to detect linear acceleration. For rotational kinematics, a triaxial rotational rate gyroscope (L3GD20H, ST Microelectronics) was used. Accelerometer and gyroscope data were low-pass filtered at 180-Hz and 40-Hz cutoffs, respectively. When a preset threshold was triggered (peak linear acceleration magnitude >10g, 16 pretrigger

and 80 posttrigger samples [1024 Hz sampling frequency] with a standard hit duration of 93.75 milliseconds) data were transmitted wirelessly and stored on a secure Internet database (Figure 2).

### Near Point of Convergence

Near point of convergence was assessed based on our established protocol.<sup>19,22</sup> Participants were seated with their head in neutral anatomical position. No spectacles were permitted; participants wore contact lenses if needed. The accommodative ruler (Bernell Inc) rested on the participant's upper lip, and an accommodative target (reduced-size Snellen chart) was adjusted horizontally to participant's eye level. The target was moved down the length of the ruler toward the eyes at a rate of approximately 1 to 2 cm/s. Near point of convergence was taken when the tester observed eye misalignment or when participants verbally signaled experiencing diplopia. On verbal signal, the tester stopped moving the target and recorded the distance between the participant and object. The assessment was repeated twice, and mean NPC was used for analyses. One trained tester assessed all players at all time points, with intrarater reliability resulting in high association between trials of all time points ( $r = 0.93$ ,  $P < .001$ ).

### Symptom Checklist

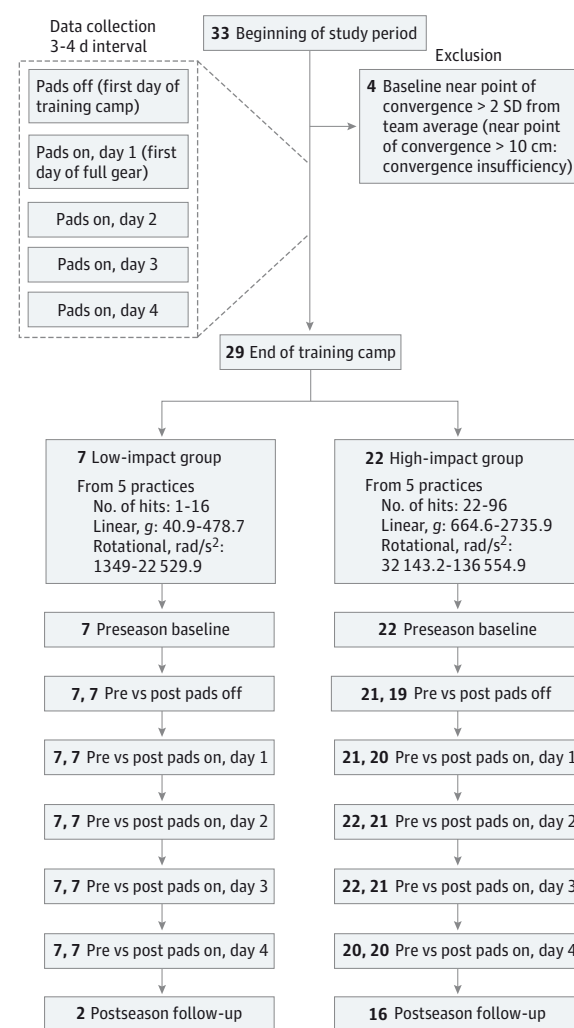
Participants were instructed to rate the presence of any symptom at each time point using the symptom checklist, a subset of the Sports Concussion Assessment Tool 3.<sup>23</sup>

### Statistical Analysis

Group differences (lower and higher impact) in baseline characteristics were compared using independent-sample  $t$  tests for continuous variables and  $\chi^2$  tests for categorical variables. To examine group differences in the effects of subconcussive impacts, we conducted a series of mixed-effects regression models (MRMs) on the primary outcomes (NPC and symptoms). The MRMs were used to accommodate repeated measurements across 12 times that were correlated with different degrees. Relative to other analytic approaches (eg, repeated measures analysis of variance), MRM accounts for missing data, which increases statistical power and preserves the representativeness of the results to the larger population.<sup>24</sup>

Two separate MRMs were conducted on each outcome. The first MRM focused on group differences in the cumulative burden of subconcussive impacts across the study duration to determine whether the trajectory/burden differed between lower- and higher-impact groups. To this end, we conducted random linear and polynomial trend (quadratic) modeling, a subclass of MRM that accounts for both individual differences at baseline and over time (which may not be linear). Variables included in the model were group (lower and higher), time (linear trend), time  $\times$  time (quadratic trend), and group by trend interactions. Significant group by trend interactions indicate that the pattern of change in an outcome measure over time differs between individuals in the lower- and higher-impact groups. The second MRM identified the initial time where group differences emerged (relative to baseline), remained, and declined across the study duration. The focus was on the rate

Figure 1. Study Flowchart



Pads off indicates a noncontact practice; pads on indicates a full-contact practice.

of change in each outcome from baseline to each time point (eg, pads-off 1). Variables included in the analysis were group (low and high) and dummy variables for each time (eg, pads-off 1 prepractice, pads-off 1 postpractice, pads-on 1 prepractice, pads-on 1 postpractice, etc) and all 2-way interactions (eg, group  $\times$  pads-off 1 prepractice, etc). The group  $\times$  time interactions are the primary interest, and significance indicates that the change in an outcome from baseline to each time point differs for individuals in the lower- and higher-impact group. All MRMs were analyzed with SAS, version 9.4 for Windows (SAS Institute Inc) and significance was set at  $P < .05$ .

## Results

### Demographic and Head Impact Kinematics

A total of 1193 head impacts were recorded from 5 training camp practices in the 29 collegiate football players using a Vector

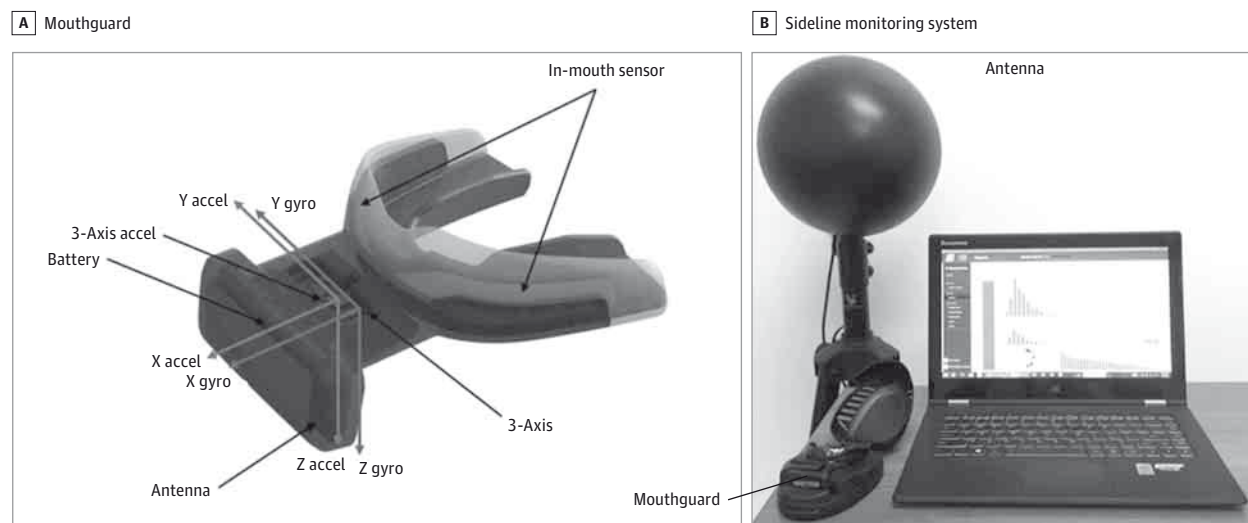
Table. Group Characteristics: Demographics, Position, and Head Impact Kinematics

| Variables                                           | Players<br>(n = 29)      | Group                 |                            | Group Difference (95% CI) | P Value |
|-----------------------------------------------------|--------------------------|-----------------------|----------------------------|---------------------------|---------|
|                                                     |                          | Low Impact<br>(n = 7) | High Impact<br>(n = 22)    |                           |         |
| Demographics, mean (SD)                             |                          |                       |                            |                           |         |
| Age, y                                              | 20.6 (1.5)               | 20.9 (0.9)            | 20.5 (1.6)                 | −0.31 (−1.62 to 0.99)     | .63     |
| BMI                                                 | 30.0 (4.4)               | 28.3 (4.9)            | 30.6 (4.1)                 | 2.33 (−1.51 to 6.18)      | .22     |
| No. of previous mTBI                                | 0.61 (0.8)               | 0.7 (1.1)             | 0.55 (0.7)                 | −0.17 (−0.91 to 0.58)     | .61     |
| Years of football experience                        | 9.4 (5.0)                | 9.14 (5.5)            | 9.09 (4.9)                 | −0.05 (−4.56 to 4.46)     | .97     |
| Position, No. (%)                                   |                          |                       |                            |                           |         |
| Linemen (OL, DL)                                    | 8 (28)                   | 1 (14)                | 7 (32)                     | NA                        | NA      |
| Linebacker, tight end                               | 7 (24)                   | NA                    | 7 (32)                     | NA                        | NA      |
| Skill players (WR, DB, RB, QB)                      | 12 (41)                  | 4 (57)                | 8 (36)                     | NA                        | NA      |
| Special team (K)                                    | 2 (7)                    | 2 (29)                | NA                         | NA                        | NA      |
| Head impact kinematics, median (range) <sup>a</sup> |                          |                       |                            |                           |         |
| No. of hits                                         | 29 (1 to 96)             | 6.0 (1 to 16)         | 41.0 (22 to 96)            | 35.0 (20.6 to 50.9)       | <.001   |
| PLA, g                                              | 940.5 (40.9 to 2735.9)   | 99.4 (40.9 to 478.7)  | 1112.3 (664.6 to 2735.9)   | 1012.9 (621.3 to 1578.5)  | <.001   |
| PAA, rad/s <sup>2</sup>                             | 56 672 (1348 to 136 554) | 7589 (1348 to 22 529) | 65 016 (32 143 to 136 554) | 57 427 (31 123 to 80 498) | <.001   |
| HIC                                                 | 897.93 (9.8 to 6282.1)   | 72.1 (9.8 to 426.1)   | 1049.1 (439 to 6282.1)     | 977 (273.2 to 2294.0)     | .02     |

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; DB, defensive back; DL, defensive lineman; HIC, head injury criterion; K, kicker; mTBI, mild traumatic brain injury; NA, not applicable; OL, offensive lineman; PAA, peak angular acceleration; PLA, peak linear acceleration; QB, quarterback; RB, running back; WR, wide receiver.

<sup>a</sup> Based on the sum from 5-practice impact kinematic data collections (see Methods section).

Figure 2. Head Impact Kinematic Measurements Using Mouthguard and Sideline Monitoring System



A, Triaxial accel senses linear acceleration and triaxial gyro senses angular acceleration. B, Sideline antenna receives impact data by radio transmission and store in the network server. Accel indicates accelerometer and gyro indicates gyroscope.

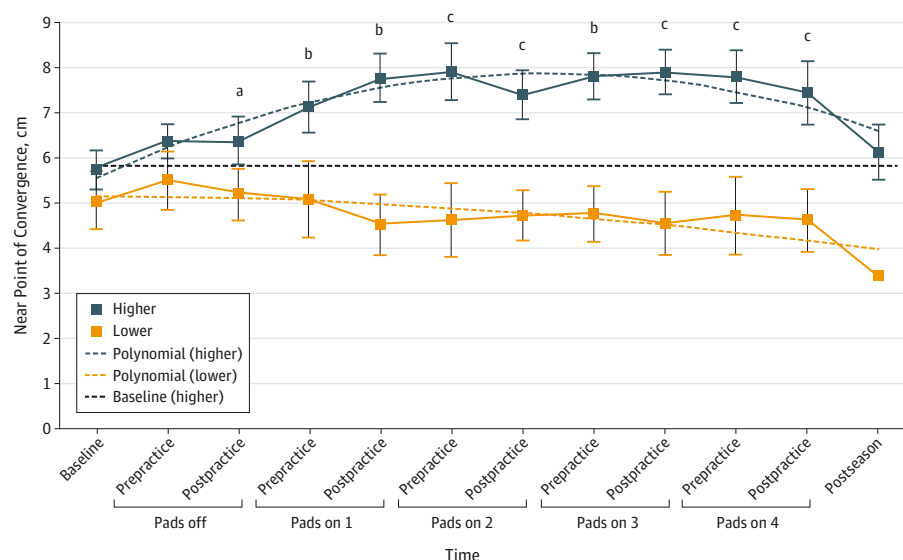
mouthguard (Figure 2). Demographic and kinematic data for each group are summarized in the Table. There were no significant differences between lower and higher groups in age, body mass index (calculated as weight in kilograms divided by height in meters squared), number of previous concussions, and years of football experience. Conversely, there were significant differences in head impact kinematics between lower- and higher-impact groups (number of impacts, 6 vs 41 [lower impact minus higher impact = 35; 95% CI, 21-51;  $P < .001$ ]; linear acceleration, 99g vs

1112g [lower impact minus higher impact = 1013; 95% CI, 621-1578;  $P < .001$ ]; and angular acceleration, 7589 vs 65 016 radian/s<sup>2</sup> [lower impact minus higher impact = 57 427; 95% CI, 31 123-80 498;  $P < .001$ ], respectively) (Table).

### Near Point of Convergence

The mean NPC by impact group did not differ at baseline ( $F_{1, 238} = 0.15$ ,  $P = .70$ ) (Figure 3). Regarding group differences, the trajectory and cumulative burden of subconcus-

Figure 3. Near Point of Convergence Between Groups Across Time Points



There was a group  $\times$  time point interaction vs baseline. Polynomial indicates quadratic trend. Linear  $\times$  time and quadratic  $\times$  time interaction ( $P < .001$ ) were driven by the near point of convergence change after pads-on 1 postpractice in the higher-impact group ( $P < .001$ ). Pads off indicates a noncontact practice; pads on indicates a full-contact practice.

<sup>a</sup> $P = .06$ .

<sup>b</sup> $P < .01$ .

<sup>c</sup> $P < .001$ .

sive impacts on NPC differed for the lower- and higher-impact groups ( $F$  for group  $\times$  linear trend<sub>1, 238</sub> = 12.14,  $P < .001$  and  $F$  for group  $\times$  quadratic trend<sub>1, 238</sub> = 12.97,  $P < .001$ ). In the higher-impact group, there was a significant increase (worsening) in NPC over time (B, unstandardized coefficient for linear trend [SE], 0.76 [0.12];  $P < .001$ ) that resolved by the postseason time point (B for quadratic trend [SE], -0.06 [0.008];  $P < .001$ ). Conversely, in the lower-impact group, there was no change in trajectory/cumulative burden of subconcussive impacts across the study duration (B for linear trend [SE], -0.10 [0.22];  $P = .64$  and B for quadratic trend [SE], -0.002 [0.01],  $P = .89$ ).

In the second MRM analysis, we aimed to identify the specific point where change occurred relative to baseline and to determine whether changes differed for those in the lower- vs higher-impact groups. Overall, changes in NPC relative to baseline were different for those in the lower- vs higher-impact groups ( $F_{11, 274} = 3.66$ ,  $P < .001$ ) (Figure 3). While the change in NPC from baseline to pads-off 1 prepractice through the pads-on 1 prepractice did not differ by group ( $P > .06$ ), the change in NPC from baseline to pads-on 1 postpractice through the pads-on 4 postpractice did differ by group ( $P < .01$ ). Specifically, the higher-impact group demonstrated an increase (worsening) in NPC from baseline to the pads-on 1 postpractice (B [SE], 2.70 [0.72];  $P < .001$ ) and this increase persisted over the remaining times ( $P < .01$ ) until the pads-on 4 postpractice time (B [SE], 2.12 [0.73];  $P < .01$ ). The change in NPC from baseline to postseason follow-up did not statistically differ between the lower- and higher-impact groups ( $F_{1, 274} = 1.46$ ,  $P = .23$ ) (Figure 3).

Given the reduced number of data points at postseason follow-up among the higher-impact group, a series of secondary MRM analyses were conducted on the kinematics variables to ensure that the return of NPC to baseline levels at postseason follow-up was not driven by the loss of follow-up data among players possibly receiving the highest number of impacts

(higher kinematics over time). Importantly, players returning postseason vs players not returning postseason sustained a similar frequency and magnitude of subconcussive head impacts across the study duration ( $P > .38$ ), suggesting that the normalized NPC to baseline levels at postseason was not driven by players receiving the highest number and magnitude of impacts.

### Symptoms

In contrast to NPC, the trajectory of symptom scores did not differ as a function of group  $F$  for group  $\times$  linear trend<sub>1, 267</sub> = 0.87,  $P = .35$  (eFigure in the Supplement). Additionally, changes in symptom scores from baseline to each time were similar for all players in the lower- and higher-impact groups ( $F_{11, 274} = 0.34$ ,  $P = .97$ ).

### Discussion

To our knowledge, this is the first prospective, longitudinal cohort study of collegiate football players examining the effects of repetitive subconcussive head impacts on NPC and self-reported symptoms. The first notable finding was that subconcussive head impacts were not associated with noticeable changes in players' symptom reports, regardless of frequency and magnitude of impacts. Second, consistent with previous studies,<sup>25,26</sup> we found that exposure to repetitive subconcussive impacts compromised NPC function, but only among players in the higher-impact group. Lastly, after a 3-week rest period, postseason NPC was normalized to the pre-season baseline in the higher-impact group, suggesting that ocular-motor function has the potential to reflect subclinical brain damage and its recovery.

While the team mean (SD) baseline NPC (5.5 [2.0] cm) was consistent with our previous study with healthy young adults



(5.9 [1.6] cm),<sup>22</sup> among players in the higher-impact group, exposure to repetitive subconcussive impacts during contact practices increased NPC scores by approximately 29% to 38% relative to baseline levels. This is notable, given that a 3-fold increase in NPC has been demonstrated in both soldiers with blast-induced mild traumatic brain injury compared with non-mild traumatic brain injury control individuals<sup>25</sup> and among 64 athletes with concussions compared with control individuals.<sup>26,27</sup>

When interpreting these findings, it is vital to consider the data collection days in relation to the summer camp schedule. Pads-off 1 practice was the first day of the camp, and players had not sustained any significant impacts for at least the past 3 months. In the helmet-only pads-off 1 practice, most players incurred none or a few subconcussive head impacts (Table). Therefore, there was no NPC change in prepractice vs postpractice or in preseason baseline in either higher- or lower-impact groups. After pads-off 1, we collected the data on the first full-gear practice of the camp (pads-on 1). While prepractice NPC score from pads-on 1 remained similar to the baseline and pads-off 1 data, postpractice NPC scores were significantly increased in the higher-impact group, with no change in the lower impact group. There were 3- to 4-day intervals between each pads-on data collection. We observed consistently increased NPC scores in the higher-impact group, even at prepractice assessments, suggesting incomplete recovery of the ocular-motor system.

When considering the validity of head injury assessment tools, it is imperative to rule out the potential contribution of exercise and/or fatigue in relation to outcomes. The linear increase in NPC scores over time in the high impact group argues against the alternative hypothesis that fatigue and/or exercise influenced NPC. If NPC scores were impacted by fatigue and/or exercise, we would expect to see nonlinear fluctuations in prepractice vs postpractice scores.

Our kinematic data are consistent with several studies using the Head Impact Telemetry system. Mean numbers of hits per player per practice were 7.0, 7.6, and 9.4 hits in our study, Duma et al,<sup>14</sup> and Crisco et al,<sup>13</sup> respectively. Similarly, mean peak linear acceleration per hit was 30.3g, 32.0g, and 28.8g in our study, Duma et al,<sup>14</sup> and Reynolds et al,<sup>28</sup> respectively. Our motivation for using the mouthguard sensor was to avoid factors that may produce considerable measurement errors in a helmet-based approach such as helmet fit and padding type.<sup>29-31</sup> Kinematic accuracy of the instrumented mouthguard resulted in an excellent correlation with the matched data from an anthropomorphic testing device (crash test dummy).<sup>15,32</sup> Moreover, Wu et al<sup>33</sup> used a human soccer heading model to test the kinematic accuracy among headgear-

mounted, mouthguard, and skin patch sensors, compared them with high-speed video, and showed that mouthguard displacements were less than 1 mm, whereas headgear and skin patch displaced as much as 13 mm and 4 mm from the ear canal reference points, respectively.

While larger prospective studies are needed to replicate our findings, this study detected changes in NPC over time as a function of group (higher vs lower impact). The 29 players studied contributed 325 observations for each of the primary analyses. Moreover, our validated NPC measurement<sup>19,22</sup> does not require administration by an experienced physician but exhibits an excellent test-retest reliability ( $r = 0.93$ ,  $P < .001$ ), suggesting its potential to be used in clinical practice. Future studies should consider additional time points for assessments, particularly during mid and late season. Additional time points might help to determine whether NPC would continue to increase throughout the duration of the season or stabilize before returning back to baseline levels postseason. Although the NPC measurement that we used provides a robust implication to clinical/sideline usage, the effect of subconcussive impact on dynamic convergence parameters, including slower peak velocity, longer latency period, and shorter duration of contractility, remain speculative.<sup>34,35</sup> Traumatic brain injury produces heterogeneous signs and symptoms, and although eye movement metrics show vulnerability in response to various forms of traumatic brain injury,<sup>19,25,26,36</sup> a single measure of eye movement/alignment does not have the sensitivity and specificity to accurately assess brain damage. Therefore, multiple approaches, including blood biomarkers,<sup>37</sup> neuroimaging,<sup>38,39</sup> and vestibular function,<sup>40</sup> may be key in delineating concussion/subconcussion pathophysiology.

## Conclusions

There is growing concern that even low-level head impacts (subconcussive) can cause significant injury if sustained repetitively. While behavioral changes in response to subconcussive head impacts are difficult to measure, evidence coupled with neuroimaging data suggest that the ocular-motor system is particularly vulnerable and sensitive to head impacts.<sup>19,38,39,41</sup> Our data provide evidence of cumulative defect in the ocular NPC, and these changes may be head impact frequency- and magnitude-dependent. After a 3-week rest period, NPC normalized to the baseline. Future prospective cohort studies to investigate the clinical relevance of these NPC changes induced by subconcussive impacts compared with concussion are warranted.

### ARTICLE INFORMATION

**Accepted for Publication:** March 22, 2016.

**Published Online:** May 12, 2016.

doi:10.1001/jamaophthalmol.2016.1085.

**Author Contributions:** Dr Langford and Kawata had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Kawata, Takahagi, Szwanki, Bellamy, Tierney, Langford.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Kawata, Rubin, Lee, Sim, Tierney, Langford.

**Critical revision of the manuscript for important**

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**Statistical analysis:** Kawata, Rubin, Lee, Sim, Assari, Tierney.

**Obtained funding:** Kawata, Takahagi, Bellamy, Langford.

**Administrative, technical, or material support:** Kawata, Lee, Sim, Takahagi, Szwanki, Bellamy, Assari, Langford.

**Study supervision:** Kawata, Takahagi, Szwanki, Bellamy, Tierney, Langford.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

**Funding/Support:** Dr Kawata received support from a research grant from the Pennsylvania Athletic Trainers' Society. Dr Langford received support from Athole G. Jacobi, MD, the Marianne Garman Burton Foundation for Caregivers, and a seed grant from Temple University Office of the Vice Provost for Research.

**Role of the Funder/Sponsor:** The funding sources had no role in design or execution of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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