

Neuro-Ophthalmologic Response to Repetitive Subconcussive Head Impacts

A Randomized Clinical Trial

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IMPORTANCE Subconcussive head impacts have emerged as a complex public health concern. The oculomotor system is sensitive to brain trauma; however, neuro-ophthalmologic response to subconcussive head impacts remains unclear.

OBJECTIVE To examine whether subconcussive head impacts cause impairments in neuro-ophthalmologic function as measured by the King-Devick test (KDT) and oculomotor function as measured by the near point of convergence.

DESIGN, SETTING, AND PARTICIPANTS In this randomized clinical trial, adult soccer players were randomized into either a heading group or kicking (control) group. The heading group executed 10 headers with soccer balls projected at a speed of 25 mph. The kicking-control group followed the same protocol but with 10 kicks. Peak linear and rotational head accelerations were assessed with a triaxial accelerometer. The KDT speed and error and near point of convergence were assessed at baseline (preheading or prekicking) and at 0, 2, and 24 hours after heading or kicking.

EXPOSURES Ten soccer-ball headings or kicks.

MAIN OUTCOMES AND MEASURES The primary outcome was the group-by-time interaction of KDT speed at 0 hours after heading or kicking. The secondary outcomes included KDT speed at 2 hours and 24 hours after heading or kicking, KDT error, and near point of convergence.

RESULTS A total of 78 individuals enrolled (heading group, $n = 40$; kicking-control group, $n = 38$). Eleven individuals (heading group: 4 women; mean [SD] age, 22.5 [1.0] years; kicking-control group, 3 women and 4 men; mean [SD] age, 20.9 [1.1] years) voluntarily withdrew from the study. Data from 67 participants with a mean (SD) age of 20.6 (1.7) years were eligible for analysis (heading, $n = 36$; kicking-control, $n = 31$). Mean (SD) peak linear accelerations and peak rotational accelerations per impact for the heading group were 33.2 (6.8) g and 3.6 (1.4) krad/s^2 , respectively. Conversely, soccer kicking did not induce a detectable level of head acceleration. Both groups showed improvements in KDT speed (heading group: 0 hours, -1.2 [95% CI, -2.2 to -0.1] seconds; $P = .03$; 2 hours, -1.3 [95% CI, -2.6 to 0] seconds; $P = .05$; 24 hours, -3.2 [95% CI, -4.3 to -2.2] seconds; $P < .001$; kicking-control group: 0 hours, -3.3 [95% CI, -4.1 to -2.5] seconds; $P < .001$; 2 hours, -4.1 [95% CI, -5.1 to -3.1] seconds; $P < .001$; 24 hours, -5.2 [95% CI, -6.2 to -4.2] seconds; $P < .001$). Group differences occurred at all postintervention points; the kicking-control group performed KDT faster at 0 hours (-2.2 [95% CI, -0.8 to -3.5] seconds; $P = .001$), 2 hours (-2.8 [95% CI, -1.2 to -4.4] seconds; $P < .001$), and 24 hours after the intervention (-2.0 [95% CI, -0.5 to -3.4] seconds; $P = .007$) compared with those of the heading group.

CONCLUSIONS AND RELEVANCE These data support the hypothesis that neuro-ophthalmologic function is affected, at least in the short term, by subconcussive head impacts that may affect some individuals in some contact sports. Further studies may help determine if these measures can be a useful clinical tool in detecting acute subconcussive injury.

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Subconcussive head impact, defined as an impact to the head that does not induce clinical symptoms of concussion, has emerged as a complex public health issue. Every year, approximately 2.5 million high school and college athletes engage in contact sports, such as US football, soccer, ice hockey, and rugby,¹ in which they can endure several hundred to nearly a thousand subconcussive head impacts in a single season.² Long-term exposure to these head impacts is suggested to increase risk for developing chronic traumatic encephalopathy.³⁻⁵

Prospective studies suggest that oculomotor functions can reflect subtle sensory impairment caused by subconcussive head impacts. For example, our study using the near point of convergence (NPC), which measures the closest point of focus before diplopia occurs, demonstrated that 10 soccer-ball headings significantly impaired NPC immediately after headings, and the impairment persisted longer than 24 hours.⁶ The NPC was chronically impaired in college and high school US football players who sustained high frequencies and magnitudes of head impacts.^{7,8} Furthermore, Caccese et al⁹ recently reported that greater exposure to head impacts in US football in a season was associated with worse King-Devick test (KDT) performance. These sequential investigations yielded follow-up research questions on whether and to what extent acute subconcussive head impacts impair neuro-ophthalmologic integrity, since these head impacts have shown to attenuate oculomotor function⁶⁻⁸ and cognitive efficiency.¹⁰⁻¹²

To address this question, we conducted a randomized clinical trial using our innovative soccer ball-heading model that can eliminate extraneous factors, such as vigorous exercise, musculoskeletal damage, and temperature change,¹³ and measured the neuro-ophthalmologic function using the KDT, which couples saccadic eye movements with multiple facets of brain functions, such as attention, language, and concentration.¹⁴ We hypothesized that control participants who kick a ball would show a significant learning curve and improve KDT performance over time, while the learning curves of participants who head a ball would be blunted by head impacts. We also aimed to reproduce previous findings from a small-scale quasi-experimental study that suggested a subconcussive-induced impairment in NPC.⁶ It was hypothesized that 10 bouts of soccer-ball heading will significantly increase (worsen) NPC, which would persist for longer than 24 hours, while the NPCs of control participants who kicked a ball would remain consistent throughout the study points.

Methods

Trial Design and Randomization

This randomized clinical trial was a single-center prospective evaluation of oculomotor functions in healthy participants in response to 10 acute bouts of mild, repetitive subconcussive head impacts. Using a simple, dice-based randomization method, participants were randomized into either soccer ball-heading or soccer ball-kicking (control) groups. Participants were assessed at 4 points (preheading or prekicking and 0, 2, and 24 hours after heading or kicking). At each point, the KDT

Key Points

Question How and what extent do subconcussive head impacts from 10 soccer-ball headings influence neuro-ophthalmologic function, as measured by the King-Devick test and near point of convergence test?

Findings This randomized clinical trial assessed King-Devick test speed and error and near point of convergence before and at 0, 2, and 24 hours after soccer-ball headings and found that 10 soccer-ball headings transiently blunted the neuro-ophthalmologic ability to learn and adapt to the King-Devick test.

Meaning These data suggest that the neural circuitry linking cognitive and oculomotor functions may be temporarily vulnerable to acute subconcussive head impacts.

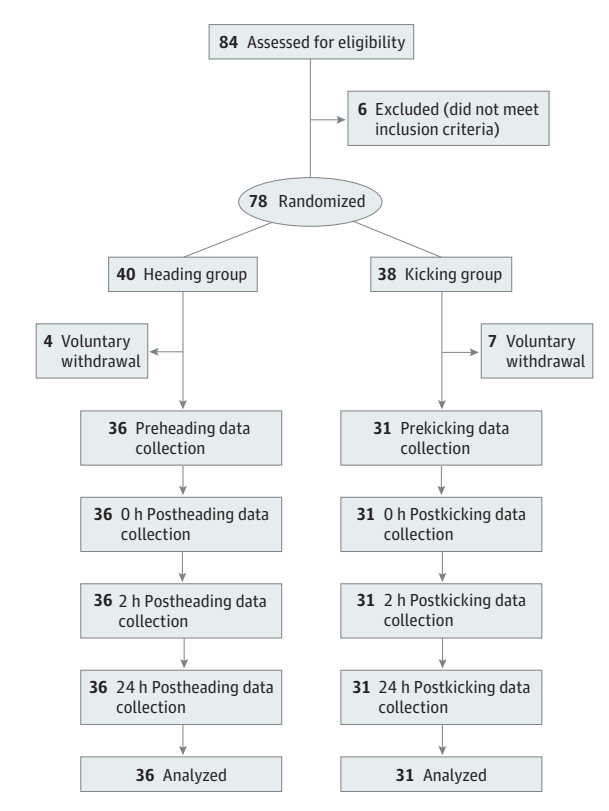
and NPC were collected. Between the preintervention measurement and measurement at 0 hours, the heading group performed 10 soccer-ball headers, while the kicking-control group performed 10 kicks of a soccer ball. Participants in both groups remained in the laboratory until 2 hours postintervention without engaging in strenuous cognitive and physical activities and returned to the laboratory approximately 24 hours later for the final data collection. The Indiana University institutional review board approved the study (protocol registered under ClinicalTrials.gov identifier: [NCT03488381](#); Protocol in [Supplement 1](#)), and written informed consent was obtained from participants (eAppendix in [Supplement 2](#)).

The trial protocol was registered 7 months after the commencement of the study. This late registration was because of the authors' misunderstanding of the use of the soccer ball-heading protocol being categorized as an interventional trial until a federal agency suggested otherwise. The trial registration occurred on April 5, 2018, and the first participant was enrolled on August 31, 2017. Thirty-seven participants were enrolled in the study prior to the registration, which accounts for 55% of the final sample size. No interval analysis was conducted prior to the registration.

Participants

From August 2017 through April 2019, we recruited potential participants who met the following inclusion criteria and were free of exclusion criteria. For inclusion, participants were required to have at least 5 years of soccer ball-heading experience and be between the ages of 18 and 26 years. Participants were excluded for a history of head injury in the year prior to the study; a history of vestibular, ocular, or vision dysfunction; or a history of neurological disorders. Based on the previous subconcussion studies, which showed mean (SD) increases in NPC after subconcussive head impacts ranging between 2.32 (1.96) cm,⁶ 1.81 (2.11) cm,⁷ and 1.3 (1.71) cm,⁸ 30 participants per group would yield a statistical power of at least 0.90 with a significance level of $\alpha = .05$. As a result, 78 healthy adult soccer players were included in the study and were randomly assigned into either a heading group or kicking-control group ([Figure 1](#)). The study was conducted during the participants' off season. Participants were instructed to refrain from any activity that involved head impacts during the study period.

Figure 1. Study Flowchart



Subconcussion Intervention

A standardized and reliable soccer ball-heading protocol was used as a means to induce subconcussive head impacts.^{6,13,15} Bevilacqua et al¹³ contains the video version of the soccer ball-heading protocol. A triaxial accelerometer (SIM-G; Triax Technologies Inc) was secured inside a headband and positioned directly below the external occipital protuberance (inion) to measure linear and rotational head acceleration. A JUGS soccer machine (JPS Sports) was used to launch a size-5 soccer ball, and the ball's traveling speed was set at 25 mph (11.2 m/s). This ball speed is similar to that occurring when soccer players make a long throw-in from the sideline to the midfield.¹⁶ Participants in both groups were situated at 40 ft away from the machine to perform the headers or kicks, but given the possibility that the participants may have moved a few steps to perform the headers, the distance from the machine was approximately 40 ft. Along with a tester's demonstration, participants in the heading group were instructed to head a ball in the air and aim for a tester standing approximately 16 ft in front of the participants. Participants in the kicking-control group were given an identical set of instructions about kicking the ball, rather than heading. Participants performed 10 headers or kicks with a 1-minute interval between each launch.

King-Devick Test

The KDT is designed to examine neuro-ophthalmologic functional integrity by performing a total of 145 saccades while rapidly reading numbers aloud to complete the test.¹⁴ The KDT was

administered on a tablet held by participants. The participants were given 1 trial of demonstration cards for practice, followed by 3 different test cards. The tablet recorded the total amount of time it took participants to complete all 3 cards. The participants were asked to read aloud, left to right and top to bottom, a series of numbers on the test cards as fast as they could while refraining from using fingers as a reading guide. As the cards progress, numbers become denser. The tester stood behind the participants and recorded any errors made during the testing. The total time (in seconds) and errors from 3 cards served as outcome variables.

Near Point of Convergence

Participants' NPCs were assessed based on our established protocol.^{6,7} Briefly, participants were seated with their head in a neutral anatomical position. No spectacles were permitted; participants wore contact lenses if needed. Using the accommodative ruler (Gulden Ophthalmics), an accommodative target (14-point letter) was moved toward the eyes at a rate of approximately 1 to 2 cm/s. The NPC measurement was taken when participants verbally signaled diplopia had occurred or the tester observed eye misalignment. On a verbal signal, the tester stopped moving the target and recorded the distance between the participant and object. The assessment was repeated twice, and the mean NPC value was used for analyses. We had 3 trained testers for this study (M.K.N., Z.W.B., and M.E.H.), whose mean inter-rater reliability was excellent (intraclass correlation coefficient, 0.90 [95% CI, 0.84-0.93]; $P < .001$).

Outcome Measures

The primary outcome of the study was the group-by-time interaction of KDT speed at 0 hours after heading or kicking. The secondary outcomes included within-group and between-group analyses on KDT speed at 2 hours and 24 hours after heading or kicking and KDT error and NPC at all postintervention points. Within-group KDT speed at 0 hours after heading or kicking was also a secondary outcome (Statistical Analysis Plan in Supplement 3).

Statistical Analysis

We examined the within-group and between-group pattern of neuro-ophthalmologic impairments, as reflected in primary and secondary outcomes, in response to subconcussive head impacts using mixed-effects regression models. The primary (fixed-effect) factors were groups (heading vs kicking), time of measurement (preintervention and 0, 2, and 24 hours postintervention), and the group-by-time interaction. The group differences were obtained by using a group-by-time interaction. We treated time as a categorical variable by providing dummy variables for each time and participants as a random effect. The model accounted for the repeated measures from the same participants and included the potential covariates of sex, age, body mass index, years of soccer ball-heading experience, and number of concussions in the participant's history. We calculated 95% CIs for each estimated outcome value. All analyses were conducted using statistical software R version 3.4.1 (R Foundation for Statistical Computing) with the package nlme. The significance level for the primary analysis on KDT speed was set as a 2-tailed P value equal to or less than .05. All other P values were not adjusted for multiple analyses.

Results

Demographic and Head-Impact Kinematics

Eighty-four individuals were assessed for eligibility, and 78 individuals who met inclusion criteria and were free of exclusion criteria proceeded to the study (heading group, $n = 40$; kicking-control group, $n = 38$). Eleven individuals voluntarily withdrew (heading group, $n = 4$ women; mean [SD] age, 22.5 [1.0] years; kicking-control group, $n = 3$ women and 4 men; mean [SD] age, 20.9 [1.1] years) prior to the preintervention points (eTable 2 in Supplement 2 for their demographic characteristics). Data from 67 participants were eligible for analysis (heading group, $n = 36$; kicking-control group, $n = 31$; Figure 1). Mean (SD) peak linear and rotational head accelerations per impact for the heading group were 33.2 (6.8) g and 3.6 (1.4) krad/s², respectively, whereas soccer-ball kicking did not cause a detectable level of head acceleration. Demographics and head-impact kinematics are detailed in Table 1.

Subconcussive Effects on KDT Speed

We found both groups exhibited improvements in KDT speed over time (heading group: 0 hours, -1.2 [95% CI, -2.2 to -0.1] seconds; $P = .03$; 2 hours, -1.3 [95% CI, -2.6 to 0] seconds; $P = .05$; 24 hours, -3.2 [95% CI, -4.3 to -2.2] seconds; $P < .001$; kicking-control group: 0 hours, -3.3 [95% CI, -4.1 to -2.5] seconds; $P < .001$; 2 hours, -4.1 [95% CI, -5.1 to -3.1] seconds; $P < .001$; 24 hours, -5.2 [95% CI, -6.2 to -4.2] seconds; $P < .001$; Figure 2A). The magnitude of improvement in the heading group was dampened by 10 headings, as supported by significant group differences. Specifically, for our primary outcome testing, the group difference at 0 hours postintervention, the kicking-control group performed faster by -2.2 (95% CI, -0.8 to -3.5) seconds ($P = .001$) than the heading group. The group difference was also present at 2 hours and 24 hours postintervention, as part of our secondary outcome, in which the kicking-control group performed faster by -2.8 (95% CI, -1.2 to -4.4) seconds ($P < .001$) and -2.0 (95% CI, -0.5 to -3.4) seconds ($P = .007$), respectively, compared with those of the heading group (Figure 2A). There was no difference between the groups at baseline (1.0 [95% CI, -2.6 to 4.6] seconds; $P = .58$). Within-group changes from the baseline are in Table 2. The full models with all covariates are in eTable 1 in Supplement 2.

Subconcussive Effects on KDT Error

For our secondary analysis on KDT errors, we were unable to determine a group difference at all points (0 hours postintervention, 0.33 [95% CI, -0.2 to 0.86]; $P = .22$; 2 hours postintervention, 0.35 [95% CI, -0.07 to 0.77]; $P = .10$; and 24 hours postintervention, 0.45 [95% CI, 0.02 to 0.88]; $P = .04$). There was no difference in the baseline KDT errors between groups (-0.03 [95% CI, -0.41 to 0.35]; $P = .87$). Within-group changes from baseline are in Table 2.

Validation of Previous Findings in NPC

For our secondary analysis on NPC measurements, group differences were observed at all postintervention points. Specifically,

Table 1. Demographics and Impact Kinematics by Group

Variables	Mean (SD)	
	Heading	Kicking Control
Total participants	36	31
Sex, No.		
Male	16	15
Female	20	16
Age, y	20.4 (1.7)	20.9 (1.7)
BMI	23.2 (2.5)	24.3 (3.6)
No. of previous concussions	0.61 (0.9)	0.42 (0.8)
Soccer ball-heading experience, y	9.3 (4.0)	10.2 (4.4)
Head-impact kinematics ^a		
Peak linear acceleration, median (IQR), g	31.9 (28.8-36.3)	NA ^b
Mean (SD)	33.2 (6.8)	
Peak rotational acceleration, median (IQR), krad/s ²	3.3 (2.6-4.2)	NA ^b
Mean (SD)	3.6 (1.4)	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; krad, kiloradian; NA, not applicable.

^a Based on the sum of 10 soccer-ball headers.

^b Soccer-ball kicking did not cause a detectable level of head acceleration.

NPC results of the heading group were higher than those of the kicking-control group by 1.4 (95% CI, 0.7 to 2.0) cm ($P < .001$) at 0 hours postintervention, 0.6 (95% CI, 0.0 to 1.2) cm ($P = .03$) at 2 hours postintervention, and 0.6 (95% CI, 0.0 to 1.3) cm ($P = .02$) at 24 hours postintervention (Figure 3), suggesting that the lingering oculomotor impairments were because of subconcussive head impacts. We did not observe a difference between the groups at baseline (0.8 [95% CI, -0.4 to 2.0] cm; $P = .20$). Within-group changes from the baseline are in Table 2.

Discussion

The data from this randomized clinical trial confirm previous findings on the oculomotor impairment after subconcussive head impacts and generate new evidence that repetitive subconcussive head impacts can impair neuro-ophthalmologic function, as measured by the KDT. The chief findings from this study are that (1) there was a significant learning curve in KDT when it was administered repeatedly in a short time frame, which was consistent to the existing literature,¹⁷⁻¹⁹ (2) the magnitude of improvement in neuro-ophthalmologic function was significantly attenuated by subconcussive head impacts, whereby KDT speed in the kicking-control group was significantly faster at all follow-up points than those in the heading group, (3) subconcussive head impacts led to an increase in KDT errors, and (4) NPC significantly worsened and persisted up to 24 hours after subconcussive head impacts. These findings indicate that even mild head impacts can induce impairments in neuro-ophthalmologic function that can persist for at least 24 hours.

These findings translate beyond soccer cohort, in that a US football player incurs a mean of 7.0, 7.6, and 9.4 hits per practice, per Kawata et al,⁷ Duma et al,²⁰ and Crisco et al,²¹ respectively,^{7,20,21} with a mean PLA per impact ranging from

A KDT performance

KDT Performance Time, s

Time: Pre, 0 h Post, 2 h Post, 24 h Post

Tasks: Heading (orange line), Kicking (teal line)

Significance values (Pre vs Post):

- Heading vs 0 h Post: $P = .03$
- Heading vs 2 h Post: $P = .05$
- Heading vs 24 h Post: $P < .001$
- Kicking vs 0 h Post: $P < .001$
- Kicking vs 2 h Post: $P < .001$
- Kicking vs 24 h Post: $P < .001$
- Heading vs Kicking at 0 h Post: $P = .001$
- Heading vs Kicking at 2 h Post: $P < .001$
- Heading vs Kicking at 24 h Post: $P = .007$

B KDT errors

KDT Performance, No. of Errors

Time: Pre, 0 h Post, 2 h Post, 24 h Post

Tasks: Heading (orange line), Kicking (teal line)

Significance values (Pre vs Post):

- Heading vs 0 h Post: $P = .008$
- Heading vs 2 h Post: $P = .02$
- Heading vs 24 h Post: $P = .04$
- Kicking vs 0 h Post: $P = .04$
- Kicking vs 2 h Post: $P = .04$
- Kicking vs 24 h Post: $P = .04$

Table 2. Within-Group Changes From Baseline

Variables	Group	Postintervention Test Differences (95% CI)					
		0 h	P Value	2 h	P Value	24 h	P Value
King-Devick test							
Speed, s	Heading	−1.2 (−2.2 to −0.1)	.03	−1.3 (−2.6 to 0.0)	.05	−3.2 (−4.3 to −2.2)	<.001
	Kicking	−3.3 (−4.1 to −2.5)	<.001	−4.1 (−6.2 to −4.2)	<.001	−5.2 (−6.2 to −4.2)	<.001
No. of error	Heading	0.33 (−0.06 to 0.73)	.10	0.42 (0.11-0.72)	.008	0.42 (0.08-0.75)	.02
	Kicking	0.0 (−0.36 to 0.36)	>.99	0.06 (−0.22 to 0.35)	.66	−0.03 (−0.3 to 0.23)	.81
Near point of convergence, cm	Heading	1.3 (0.8-1.8)	<.001	0.8 (0.4-1.1)	<.001	1.0 (0.5 to 1.4)	<.001
	Kicking	−0.1 (−0.5 to 0.4)	.74	0.2 (−0.3 to 0.6)	.48	0.3 (−0.1 to 0.8)	.11

tant for the memory, concentration, anticipation, and language needed to perform KDT. Our data showed that even as few as 10 soccer-ball headings blunted participants' learning effects on KDT for longer than 24 hours, indicating that cognitive adaptational property may be vulnerable to subconcussive head impacts. This pattern is consistent with Di Virgilio et al,³⁰ who demonstrated that 20 soccer-ball headings triggered an acute and transient worsening in working memory function, as well as an acute inhibition of motor cortex.

On the contrary, KDT errors gradually increased and peaked at 24 hours postheading. This trend is similar to that of oculomotor impairments, which reflect chronic and lingering neural disruption from concussive^{31,32} and subconcussive head impacts.^{6,7} A KDT error is counted when an individual skips and/or misreads a number, indicating a dysregulation of saccadic eye movement. However, our measure lacks data regarding intersaccadic interval, saccadic amplitude, and velocity; hence, an interpretation of the different patterns between KDT speed and error is speculative.

Nonetheless, our data support previous findings from field studies suggesting that when mild head impacts occur in chronicity, one can develop a persistent and cumulative deficit in neural function. For example, Talavage et al¹¹ observed a significant decline at postseason in visual work-

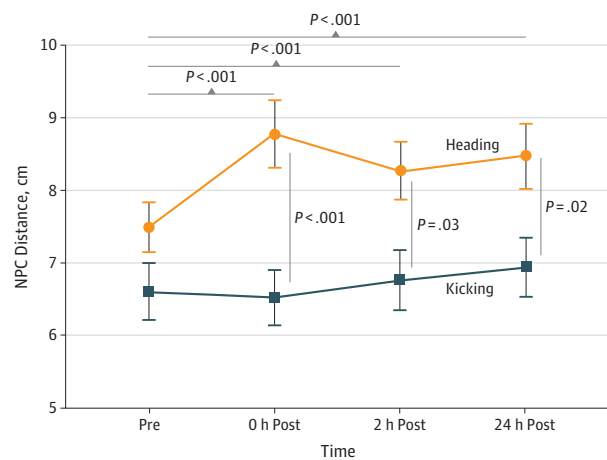
ing memory and altered activation in the dorsolateral prefrontal cortex in high school US football players who experienced higher frequency of subconcussive head impacts compared with a preseason baseline. In addition, McAllister et al³³ suggested an association between head impact exposure, white-matter diffusion changes, and cognition decline primarily in verbal learning and memory over a season in division I US football and hockey players. Results from these studies emphasize the deleterious subconcussive effects on cognition efficiency. Even as few as 10 subconcussive head impacts is enough to cause statistically significant declines, indicating that repetitive impacts experienced over an extended duration, such as a season or entire career, may amplify neurological deficits. Professional soccer players exhibit significantly impaired performances in memory, planning, and visual processing compared with a control group consisting of elite noncontact sport athletes. The decline in cognitive processing was associated with the frequency of soccer-ball heading.³⁴

The data from the current study are similar to the normative data of the KDT. The mean KDT speed at baseline was 43.6 (7.8) seconds for the heading group and 42.7 (5.5) seconds for the kicking-control group, which were consistent with a meta-analysis result of normative value (mean, 43.8 seconds) along with professional ice hockey players (mean, 40.0 seconds) and healthy adults (mean, 42.2 seconds). Ten soccer-ball headings did not worsen KDT speed yet blunted participants' learning effects. As a result, the postheading KDT speed (mean, 42.9 seconds) was faster than that of mixed martial arts fighters after a concussion (mean, 59.1 seconds)¹⁸ and adults with post-concussion syndrome (mean, 64.1 seconds).³⁵ Athletes in various sports without concussive injury have been shown to improve KDT speed, ranging between 2.8 and 5.5 seconds, after a single season.³⁶⁻³⁸ These data collectively indicate that the effects of 10 headings manifest in subtle and transient impairment in learning curve and are considerably milder than concussive effects. Our data also agree with previous subconcussion studies demonstrating that NPC increases in response to subconcussive head impacts.⁶⁻⁸ We were able to reproduce the data from the previous study that NPC increased after the intervention and then persisted for at least 24 hours in those who incurred 10 soccer-ball headings.⁶ It is worth noting that the NPC change (17% from baseline) caused by 10 headers is likely not clinically significant, despite being statistically significant. However, our data highlight that 10 impacts are sufficient to cause mild oculomotor impairment, calling for a standardized guideline to monitor athletes' safety, given that US football, soccer, ice hockey, and rugby players can sustain a mean frequency of 650 subconcussive head impacts per single season.^{2,21,39,40}

Limitations

There are several limitations to this study. All 3 outcome variables remained significantly compromised at the 24-hour postheading point. Because of a study design monitoring the participants up to 24 hours, we were unable to determine how long would these observed deficits last. Additionally, we observed a significant increase and peak in KDT errors at the 24-hour

Figure 3. Near Point of Convergence (NPC) Performance in Response to Subconcussive Head Impacts



Ten soccer-ball headings significantly worsened NPC. Post indicates after heading and pre, baseline.

postheading point, yet participants' behavior nor activity was monitored between 2 hours and 24 hours postheading. There is a possibility that external factors we were unaware of may have contributed to the increase. As mentioned, we were unable to assess other saccadic parameters (eg, intersaccadic amplitude, velocity), but it is noteworthy that KDT, one of the most commonly used clinical tools, was able to delineate subconcussive effects, while subjective parameters, such as symptom score, failed to reflect such effects. Although our study design and soccer ball-heading model control extraneous factors (eg, fatigue, exercise effects, body damage), we did not collect measurements, other than years of heading experience, on previous head impact exposure-associated factors, such as starting age, position, and level of play. Therefore, it is unknown whether prior heading exposure modulates individuals' response to 10 acute headers. We encountered a 15% dropout rate, which was mostly attributed to changes in participants' schedules during the semester, because all participants were full-time college students. Also, because of a lack of race/ethnicity data, we are unsure of the unique differences based on race/ethnicity. The present study was conducted in a single-site university setting, and thus the generalizability of the study results is limited.

Conclusions

The current study suggests that KDT performance immediately after 10 bouts of soccer-ball headings can be impaired. Our data support the concept that repetitive subconcussive head impacts can result in short-term neurophysiological alterations that can be observed as acute neuro-ophthalmologic functional impairment. These data highlight the temporal vulnerability of neuro-ophthalmologic function following subconcussive head impacts. These measures can be a useful clinical tool in detecting acute subconcussive injury.

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REFERENCES

- National Collegiate Athletic Association. Estimated probability of competing in college athletics. <http://www.ncaa.org/about/resources/research/estimated-probability-competing-professional-athletics>. Published 2017. Accessed July 20, 2017.
- Bailes JE, Petraglia AL, Omalu BI, Nauman E, Talavage T. Role of subconcussion in repetitive mild traumatic brain injury. *J Neurosurg*. 2013;119(5):1235-1245. doi:10.3171/2013.7.JNS121822
- Goldstein LE, Fisher AM, Tagge CA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Sci Transl Med*. 2012;4(134):134ra60. doi:10.1126/scitranslmed.3003716
- McKee AC, Stern RA, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. 2013;136(pt 1):43-64. doi:10.1093/brain/awt307
- Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA*. 2017;318(4):360-370. doi:10.1001/jama.2017.8334
- Kawata K, Tierney R, Phillips J, Jeka JJ. Effect of repetitive sub-concussive head impacts on ocular near point of convergence. *Int J Sports Med*. 2016;37(5):405-410. doi:10.1055/s-0035-1569290
- Kawata K, Rubin LH, Lee JH, et al. Association of football subconcussive head impacts with ocular near point of convergence. *JAMA Ophthalmol*. 2016;134(7):763-769. doi:10.1001/jamaophthalmol.2016.1085
- Zonner SW, Ejima K, Fulgar CC, et al. Oculomotor response to cumulative subconcussive head impacts in US high school football players: a pilot longitudinal study. *JAMA Ophthalmol*. 2019;137(3):265-270. doi:10.1001/jamaophthalmol.2018.6193
- Caccese JB, Best C, Lamond LC, et al. Effects of repetitive head impacts on a concussion assessment battery. *Med Sci Sports Exerc*. 2019;51(7):1355-1361. doi:10.1249/MSS.0000000000001905
- Davenport EM, Whitlow CT, Urban JE, et al. Abnormal white matter integrity related to head impact exposure in a season of high school varsity football. *J Neurotrauma*. 2014;31(19):1617-1624. doi:10.1089/neu.2013.3233
- Talavage TM, Nauman EA, Breedlove EL, et al. Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. *J Neurotrauma*. 2014;31(4):327-338. doi:10.1089/neu.2010.1512
- Breedlove EL, Robinson M, Talavage TM, et al. Biomechanical correlates of symptomatic and asymptomatic neurophysiological impairment in high school football. *J Biomech*. 2012;45(7):1265-1272. doi:10.1016/j.jbiomech.2012.01.034
- Bevilacqua ZW, Huibregtse ME, Kawata K. In vivo protocol of controlled subconcussive head impacts for the validation of field study data. *J Vis Exp*. 2019;146(146):e59381. doi:10.3791/59381
- Rizzo JR, Hudson TE, Dai W, et al. Objectifying eye movements during rapid number naming: methodology for assessment of normative data for the King-Devick test. *J Neural Sci*. 2016;362:232-239. doi:10.1016/j.jns.2016.01.045
- Wirsching A, Chen Z, Bevilacqua ZW, Huibregtse ME, Kawata K. Association of acute increase in plasma neurofilament light with repetitive subconcussive head impacts: a pilot randomized control trial. *J Neurotrauma*. 2019;36(4):548-553. doi:10.1089/neu.2018.5836
- Linthorne NP, Everet DJ. Release angle for attaining maximum distance in the soccer throw-in. *Sports Biomech*. 2006;5(2):243-260. doi:10.1080/14763140608522877
- Oberlander TJ, Olson BL, Weidauer L. Test-retest reliability of the King-Devick test in an adolescent population. *J Athl Train*. 2017;52(5):439-445. doi:10.4085/1062-6050-52.2.12
- Galetta KM, Barrett J, Allen M, et al. The King-Devick test as a determinant of head trauma and concussion in boxers and MMA fighters. *Neurology*. 2011;76(17):1456-1462. doi:10.1212/WNL.0b013e31821184c9
- Davies EC, Henderson S, Balcer LJ, Galetta SL. Residency training: the King-Devick test and sleep deprivation, study in pre- and post-call neurology residents. *Neurology*. 2012;78(17):e103-e106. doi:10.1212/WNL.0b013e318215833d
- Duma SM, Manoogian SJ, Bussone WR, et al. Analysis of real-time head accelerations in collegiate football players. *Clin J Sport Med*. 2005;15(1):3-8. doi:10.1097/OJ0042752-200501000-00002
- Crisco JJ, Fiore R, Beckwith JG, et al. Frequency and location of head impact exposures in individual collegiate football players. *J Athl Train*. 2010;45(6):549-559. doi:10.4085/1062-6050-45.6.549
- Reynolds BB, Patrie J, Henry EJ, et al. Practice type effects on head impact in collegiate football. *J Neurosurg*. 2016;124(2):501-510
- Slobounov SM, Walter A, Breiter HC, et al. The effect of repetitive subconcussive collisions on brain integrity in collegiate football players over a single football season: a multi-modal neuroimaging study. *Neuroimage Clin*. 2017;14:708-718. doi:10.1016/j.nicl.2017.03.006
- Reynolds BB, Stanton AN, Soldozy S, Goodkin HP, Wintermark M, Druzgal TJ. Investigating the effects of subconcussion on functional connectivity using mass-univariate and multivariate approaches. *Brain Imaging Behav*. 2018;12(5):1332-1345.
- Bahrani N, Sharma D, Rosenthal S, et al. Subconcussive head impact exposure and white matter tract changes over a single season of youth football. *Radiology*. 2016;281(3):919-926. doi:10.1148/radiol.2016160564
- Lipton ML, Kim N, Zimmerman ME, et al. Soccer heading is associated with white matter microstructural and cognitive abnormalities. *Radiology*. 2013;268(3):850-857. doi:10.1148/radiol.13130545
- Bazarian JJ, Zhu T, Zhong J, et al. Persistent, long-term cerebral white matter changes after sports-related repetitive head impacts. *PLoS One*. 2014;9(4):e94734. doi:10.1371/journal.pone.0094734
- Gong NJ, Kuzminski S, Clark M, et al. Microstructural alterations of cortical and deep gray matter over a season of high school football revealed by diffusion kurtosis imaging. *Neurobiol Dis*. 2018;119:79-87. doi:10.1016/j.nbd.2018.07.020
- Laksari K, Kurt M, Babae H, Kleiven S, Camarillo D. Mechanistic insights into human brain impact dynamics through modal analysis. *Phys Rev Lett*. 2018;120(13):138101. doi:10.1103/PhysRevLett.120.138101
- Di Virgilio TG, Hunter A, Wilson L, et al. Evidence for acute electrophysiological and cognitive changes following routine soccer heading. *EBioMedicine*. 2016;13:66-71. doi:10.1016/j.ebiom.2016.10.029
- Johnson B, Hallett M, Slobounov S. Follow-up evaluation of oculomotor performance with fMRI in the subacute phase of concussion. *Neurology*. 2015;85(13):1163-1166. doi:10.1212/WNL.0000000000001968
- Johnson B, Zhang K, Hallett M, Slobounov S. Functional neuroimaging of acute oculomotor deficits in concussed athletes. *Brain Imaging Behav*. 2015;9(3):564-573. doi:10.1007/s11682-014-9316-x
- McAllister TW, Ford JC, Flashman LA, et al. Effect of head impacts on diffusivity measures in a cohort of collegiate contact sport athletes. *Neurology*. 2014;82(1):63-69. doi:10.1212/01.wnl.0000438220.16190.42
- Matser JT, Kessels AG, Jordan BD, Lezak MD, Troost J. Chronic traumatic brain injury in professional soccer players. *Neurology*. 1998;51(3):791-796. doi:10.1212/WNL.51.3.791
- Subotic A, Ting WK, Cusimano MD. Characteristics of the King-Devick test in the assessment of concussed patients in the subacute and later stages after injury. *PLoS One*. 2017;12(8):e0183092. doi:10.1371/journal.pone.0183092
- King D, Hume P, Gissane C, Clark T. Use of the King-Devick test for sideline concussion screening in junior rugby league. *J Neurol Sci*. 2015;357(1-2):75-79. doi:10.1016/j.jns.2015.06.069
- Galetta KM, Brandes LE, Maki K, et al. The King-Devick test and sports-related concussion: study of a rapid visual screening tool in a collegiate cohort. *J Neurol Sci*. 2011;309(1-2):34-39. doi:10.1016/j.jns.2011.07.039
- King D, Gissane C, Hume PA, Flaws M. The King-Devick test was useful in management of concussion in amateur rugby union and rugby league in

New Zealand. *J Neurol Sci*. 2015;351(1-2):58-64. doi:10.1016/j.jns.2015.02.035

39. Guskiewicz KM, Mihalik JP, Shankar V, et al. Measurement of head impacts in collegiate football players: relationship between head impact

biomechanics and acute clinical outcome after concussion. *Neurosurgery*. 2007;61(6):1244-1252. doi:10.1227/01.neu.0000306103.68635.1a

40. Schnebel B, Gwin JT, Anderson S, Gatlin R. In vivo study of head impacts in football: a comparison of

National Collegiate Athletic Association Division I versus high school impacts. *Neurosurgery*. 2007;60(3):490-495. doi:10.1227/01.NEU.0000249286.92255.7F

Invited Commentary

Repetitive Subconcussive Head Impact and Neuro-Ophthalmology

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Subconcussive head impacts (SCHIs), although not as severe as full concussive head impacts, occur much more frequently, and they have emerged as a public health concern in recent years. Research over the past few years has shown that repeated exposures to SCHI can have a cumulative effect and might increase one's risk of developing



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permanent neurological impairment in the future. However, the extent of the neuro-ophthalmologic repercussions from these type of injuries have not been studied in much detail previously. In this issue of *JAMA Ophthalmology*, Nowak and colleagues¹ present a study of a standardized soccer ball-heading protocol and SCHIs and test the outcomes on the King-Devick test (KDT) and near point of convergence to quantitate neuro-ophthalmologic function.

Nowak et al¹ studied participants with at least 5 years of soccer ball-heading experience, who were randomized to a soccer ball-heading group or control group. The active-group participants were subjected to 10 experimentally induced SCHIs by heading a ball projected from a soccer machine; the control group kicked the ball. Participants were assessed at baseline and various points up to 24 hours after soccer-ball heading or kicking with the KDT and near point of convergence test.¹ Prior studies²⁻⁴ have shown that when serial testing is performed with KDT within a narrow time frame, there is a significant learning curve, with improvement in KDT speed with time. This was confirmed by the study by Nowak et al,¹ wherein both test and control groups showed improvements in KDT speed over time. However, the magnitude of improvement

seemed to be diminished by SCHI, with the kicking (control) group demonstrating a -2.2-second increase in KDT speed compared with the test (SCHI) group. This increase in KDT speed persisted at 2 hours and 24 hours. The authors concluded that even seemingly mild SCHIs can impair neuro-ophthalmologic function for at least 24 hours. The heading group also showed a significant and persistent increase in near point of convergence.

While field studies have been performed in the past to look at the outcomes of SCHIs in the past (eg, among ice hockey players and mixed martial arts fighters³), this study is unique in that it used a standardized soccer ball-heading model as a means to create SCHIs in a controlled environment. The mean peak linear acceleration impact in US football has previously been shown to range from 28.0g to 32.0g, with a mean of 7.0 to 9.4 hits per practice,⁵⁻⁷ which is similar to the 10 headers with a peak linear acceleration of 33.2g per header used in this study.¹ The study is limited, however, by its short follow-up time, small sample size, and lack of information regarding previous head impacts in the study participants.

Despite these limitations, this study¹ shows that repeated SCHIs can result in acute impairment in function. The authors recommend that the KDT and near point of convergence test can be useful clinical tools for detection of these types of impacts. We agree, given that many young athletes in various contact sports may sustain multiple SCHIs and that there is a need for more studies regarding this important topic and standardized guidelines and tests to quantify and monitor possible functional impairments in these at-risk populations.

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REFERENCES

- Nowak MK, Bevilacqua ZW, Ejima K, et al. Neuro-ophthalmologic response to repetitive subconcussive head impacts [published online February 13, 2020]. *JAMA Ophthalmol*. doi:10.1001/jamaophthalmol.2019.6128
- Oberlander TJ, Olson BL, Weidauer L. Test-retest reliability of the King-Devick Test in an adolescent population. *J Athl Train*. 2017;52(5):439-445. doi:10.4085/1062-6050-52.2.12
- Galetta KM, Barrett J, Allen M, et al. The King-Devick test as a determinant of head trauma and concussion in boxers and MMA fighters. *Neurology*. 2011;76(17):1456-1462. doi:10.1212/WNL.Ob013e31821184c9

- Davies EC, Henderson S, Balcer LJ, Galetta SL. Residency training: the King-Devick test and sleep deprivation, study in pre- and post-call neurology residents. *Neurology*. 2012;78(17):e103-e106. doi:10.1212/WNL.Ob013e318251833d

- Kawata K, Rubin LH, Lee JH, et al. Association of football subconcussive head impacts with ocular near point of convergence. *JAMA Ophthalmol*. 2016;134(7):763-769. doi:10.1001/jamaophthalmol.2016.1085

- Duma SM, Manoogian SJ, Bussone WR, et al. Analysis of real-time head accelerations in collegiate football players. *Clin J Sport Med*. 2005;15(1):3-8. doi:10.1097/00042752-200501000-00002
- Crisco JJ, Fiore R, Beckwith JG, et al. Frequency and location of head impact exposures in individual collegiate football players. *J Athl Train*. 2010;45(6):549-559. doi:10.4085/1062-6050-45.6.549