

Heading-Related Slowing by Twenty-Four Hours in Youth Athletes

Radhika Balagopal,^{1,2} Michelle Won,^{1,3} Saamil S. Patel,^{1,4} Alice Z. Chuang,⁵ and Anne B. Sereno^{1,6,7}

Abstract

Research suggests cumulative effects of repetitive head impacts (RHIs) on brain structure, especially with younger age of first exposure. Further, recent evidence suggests no immediate cognitive changes with increased RHIs but impairments across a sports season. The aim was to examine more closely the short-term time course of behavioral effects of exposure to RHI. Across 2 years, 18 female adolescent soccer players were tested on ProPoint (sensorimotor) and AntiPoint (cognitive) tasks with reaction time (RT) being the main outcome measure. The athletes were tested before and after workout with ball heading (immediate effect), as well as 24 h after workout (24 h effect) throughout two consecutive seasons. The number of headers performed 24 h before workout, during workout, and season average per workout were recorded. The athletes showed a decrease in ProPoint and AntiPoint RTs immediately after a workout, with no change or decrease in RTs with increasing RHIs. However, increasing RHIs during workout increased RTs in both tasks when tested 24 h later. The athletes also showed an increase in AntiPoint RTs with increasing season average RHIs. Our findings show a complex time course of effects of RHIs on sensorimotor and cognitive performance in adolescent athletes, with exposure to RHIs associated with no change or immediate benefits and then deficits by 24 h. Pathophysiological changes associated with exercise and traumatic brain injury can account for the sensorimotor and cognitive performance changes occurring within 24 h after RHIs.

Keywords: adolescence; repetitive head impact; sensorimotor and executive function; sports-related trauma; touch responses

Introduction

FOLLOWING FOOTBALL, girls' soccer has the second highest concussion rate of any other sport in the world.¹ Similar to football or boxing, much focus in soccer has been on the long-term cognitive deficits that may occur due to concussions or knock-outs rather than on the numerous repetitive subconcussive head impacts (RHIs), for example, from heading a soccer ball. Despite less attention to RHIs, much evidence suggests that there are greater correlations between these less severe head impacts and long-term negative consequences than concussions, especially if exposed to RHIs at a young age,^{2–8} in part due to the greatly increased frequencies of these subconcussive impacts. Extensive imaging evidence shows that subconcussive blows can cause axonal injury, permeability changes in the blood–brain barrier, and neuroinflammation, as well as neurodegenerative pathology consistent with chronic traumatic encephalopathy upon autopsy.^{9–15} These long-term structural injuries appear even without behavioral or symptomatic changes, and no diagnosis of concussion.⁹ Additionally, magnetic resonance spectroscopy suggests altered neurochemistry for professional soccer players with no history of concussion, particularly changes in myo-inositol

and glutathione correlating with lifetime RHIs.¹⁶ It has also been noted that RHIs, especially in boxers, has led to Alzheimer's-like symptoms and increased risk for dementia.^{17,18} As well, recent findings show increased neurodegenerative disease mortality among former professional soccer players.¹⁹

In addition to long-term cognitive deficits, there is evidence for cognitive and structural deficits following RHIs over shorter time intervals, such as a single sports season.^{14,20–26} The time course and development of these changes are unclear. Many previous studies have been unsuccessful in finding immediate differences in the structure of the brain after heading the ball.²⁷ Further, no previous study using standard cognitive testing has been able to identify any changes after immediate bouts of heading the ball regardless of age, gender, and intelligence.²⁸

A recent study with German pre-professional male adolescent soccer players suggests immediate sensorimotor and cognitive benefit immediately following a soccer workout with ball heading.²⁹ Much scientific evidence demonstrates that physical activity enhances cognitive processing³⁰ during or immediately following exercise.^{31,32} Physical activity is known to increase adrenaline,³³ blood flow and volume,^{34,35} and even select neurotrophic factors

¹Department of Neurobiology and Anatomy, ⁵Department of Ophthalmology and Visual Science, McGovern Medical School, UTHealth, Houston, Texas, USA.

²Department of Biological Sciences, University of California, Santa Barbara, California, USA.

³Department of Neurobiology and Anatomy, Texas A&M College of Medicine, Bryan, Texas, USA.

⁴Department of Neuroscience, Baylor College of Medicine, Houston, Texas, USA.

⁶Department of Psychological Sciences, ⁷Weldon School of Biomedical Engineering, Purdue University, West Lafayette, Indiana, USA.

(e.g., brain-derived neurotrophic factor) involved with synaptic function,^{36,37} perhaps making it more difficult to detect any immediate deleterious effects of subconcussive blows. Additionally, research has shown that these immediate beneficial effects of exercise vary depending on a number of factors including the level of training, intensity, and duration.³³

Further, it is possible that the injury itself is correlated with a heightened adrenaline response. As Koerte and colleagues²⁹ suggest, it is possible that in soccer there is a looming effect during subconcussive blows (i.e., head hits with the object coming towards a player's face) that may further amplify adrenaline response compared with exercise alone, reducing the ability to detect immediate deleterious effects of head impacts. Testing subjects again, perhaps 24 h later, would eliminate some of these immediate effects and also provide an extended time course to examine behavioral changes. To further complicate interpretation, it is likely that some deleterious effects of the injury may not be immediate. In the animal literature, it is well documented that mild traumatic brain injury results in a complex cascade of reparative and injurious events,^{38–41} with some immediate beneficial changes followed by deleterious biochemical changes by 24 h following injury.⁴² Further, recent animal work demonstrates that unilateral lateral closed-head impact injury induces distal bilateral electrophysiological deficits in prefrontal cortex by 24 h.¹³

Given previous reports of an immediate cognitive benefit after soccer playing with heading in German high-performance male adolescent soccer players, we were interested in testing whether there would be a similar finding in U.S. female adolescent soccer players. In this study, we used the same touch-based paradigms, ProPoint and AntiPoint. These tasks are simple, straightforward, and not language dependent. In part because of the task's relatively short response latencies and high temporal resolution, we have had success in being able to detect small cognitive changes under a variety of conditions.^{43–46} We hypothesized that similar to the German male athletes, we expected the competitive U.S. female athletes to show significant benefits immediately following soccer play with heading (perhaps due to any deficits being masked by greater immediate benefits of exercise and/or adrenaline in these competitive athletes). In addition, we were interested in testing for longer-term effects, after 24 h, and across the season. We further hypothesized that by 24 h, we would see greater deficits associated with heading than immediately following workout, given deleterious biochemical and pathophysiological changes in prefrontal cortex by 24 h.^{13,42}

Finally, we hypothesized that girls with greater self-report of headers across the season (2 months) may show greater slowing than girls with lower self-report of headers. Slowing at the shortest time frame but not later time-points would indicate a transient effect with little lasting effect. On the other hand, changes at longer time intervals would suggest that subconcussive blows to the brain from heading the ball may be cumulative and may over time cause a decrease in cognitive or executive function. Hence, using these same tasks, we specifically examined the immediate (comparing players before and after a workout), 24 h (comparing players before workout and 24 h later, before a second workout), and season (change in performance across the season) effects of a soccer workout and tested whether these reaction time (RT) changes were influenced by heading the ball.

Methods

Participants

The study was approved by the University of Texas Health Science Center at Houston Committee for the Protection of Human

Subjects in accordance with the Declaration of Helsinki, as well as by the high school's administration and Women's Varsity soccer coach. After a research assistant explained the study to female high school soccer players and their parental guardians, participants were recruited and informed consent or assent with parental consent was first obtained before commencement of the study. Eighteen female soccer players were enrolled and tested across two high school seasons. Eight players participated in the first season only (Year 1) and four in the second season only (Year 2), and six in both Year 1 and Year 2. All participants had no known neurological conditions (beside five subjects with previous history of concussion; details below) and had normal or corrected to normal vision. Each participant played soccer 8 h per week and on average played video games 0.5 h per week (range: 0.0–8.0 h). As illustrated in Figure 1, all RT data was collected at time-points (T1, T2, T3) before and after practices (Workout A), as well as before games (Workout B). All participants had the same duration of workout during practices (Workout A). Practices did not include head drills. All participants did not have the same duration of workout during games (Workout B). Ten participants played the full game (two participants for both years), three participants played half games (two participants for both years), three participants played half games in Year 1 and full games in Year 2, and two participants typically did not play very much at all in games. Finally, the study included players from various field positions. Seven participants primarily played in a defender position (three participants for both years), seven participants primarily played in a midfielder position (two participants for both years), one participant primarily played in a forward position, one participant primarily played in a midfielder position in Year 1 and a defender position in Year 2, and two participants primarily played as goalie.

For Year 1, the mean age of the 14 players was 16.3 years (\pm 1.0 standard deviation [SD]; range: 15–18) and the mean number of years of soccer playing was 11.1 years (\pm 1.2 SD; range: 10–13). Twelve of the 14 participants (86%) were right-handed. Four of the 14 subjects (29%, one participant, two instances) had experienced a previous concussion more than 1 year prior to the study.

For Year 2, the mean age of the 10 players was 16.3 years (\pm 0.8 SD; range 15–17) and the mean number of years of soccer played was 11.7 years (\pm 0.5 SD; range 11–12). Eight of the 10 participants (80%) tested were right-handed. One of the 10 participants (10%) had experienced a previous concussion more than 10 months before the study.

Instrument and measures

Stimuli. The experiment was conducted on an iPad 2 with refresh rate of 60 Hz. The frame refresh signal was matched with the onset and offset of stimuli, with a precision of 1.6 msec (U.S. Patent No. 9,717,459. 2017; U.S. Patent No. 9,949,693. 2018). The display had a white center circle for fixation (diameter subtending 2.4° visual angle from a 33 cm viewing distance, 1.4 cm) and was surrounded by four boxes (1.4°, 0.8 cm) 7.0° (4.0 cm) from the center circle, which indicated the four possible locations to touch. The participant started each trial by putting their index finger on the fixation circle in the middle of the display and 480 msec later a target (white-filled box, 0.8 cm) would appear in one of the four locations on the display. For the ProPoint task, the participant was instructed to touch the visual target as quickly and accurately as possible. For the AntiPoint task, the participant had to touch the box opposite of the visual target as quickly and accurately as possible (Fig. 2).

Touch responses. The location of the touch responses was captured by the iPad's capacitive touch screen interface with resolution of 52 pixels per cm and a frame refresh rate of 60 Hz. For each trial in each task, RT, defined as the elapsed time in msec between the appearance of the target to the time of touch, was

Session	Days of the Week							
	1	2	3	4	5	6	7	
Beginning	50% of participants:	[no W]	T ₁ W _A T ₂	T ₃ W _B	[W]	[W]	[no W]	[no W]
	50% of participants:	[no W]	[W]	[W]	T ₁ W _A T ₂	T ₃ W _B	[no W]	[no W]
Middle [only Year 1]	... Same as above ...							
End	... Same as above ...							

FIG. 1. Timeline of testing. Participants were tested at three sessions: at the beginning, middle (Year 1 only), and end of their 2-month season. Half the participants were randomly assigned and tested at the beginning of the week throughout their testing (with no exposure to heading the ball in the prior 24-h period, indicated by [no W] for no workout) and half the participants were tested mid-week throughout their testing (with exposure to heading the ball in the prior 24-h period, indicated by [W] for workout). For each session, players were tested at three time-points (T1, T2, T3)—T1: before a workout, Workout A (W_A); T2: immediately following this workout; and T3: 24 h later, which was immediately before another workout, Workout B (W_B).

recorded. Events and response times were aligned with refresh and adjusted by subtracting the externally-measured (with photodiode, microphone and storage oscilloscope) average delay of detecting a touch event on the capacitive device.^{13,22,24,25} If the distance between the actual target location and the touched coordinates was greater than 3.3° (1.9 cm), the trial was counted as an error.

Design and procedure

The study was designed and conducted in a manner to cause no interference or inconvenience to the soccer team and its schedule, thus providing an accurate assessment of real-world soccer players. Participants had their normal soccer workouts (practices or games) on the days of testing.

For Year 1, the soccer players were tested at three sessions: at the beginning, middle and end of their 2-month season. Half the participants were randomly assigned and tested at the beginning of the week throughout their testing (with no exposure to heading the ball

in the prior 24-h period) and half the participants were tested mid-week throughout their testing (with exposure to heading the ball in the prior 24-h period). For each session, players were tested at three time-points (Test Times), before a workout, Workout A (Test Time = 1), immediately following this workout (Test Time = 2), and 24 h later (Test Time = 3), which is immediately before another workout, Workout B. For Year 2, the 10 players were tested only at two sessions, the beginning and end of their 2-month season. Again, half the participants were randomly assigned and tested at the beginning of the week and half were tested mid-week. The testing followed the same format as Year 1 with three Test Times: before Workout A (Test Time = 1), immediately after Workout A (Test Time = 2), and 24 h later (Test Time = 3), before Workout B. Thus, the subjects only participating in Year 1 were tested for a total of nine times (three Test Times and three Sessions), the subjects only participating in Year 2 for a total of six times (three Test Times and two Sessions), and subjects participating in both Years for a total of 15 times (three Test Times and five Sessions).

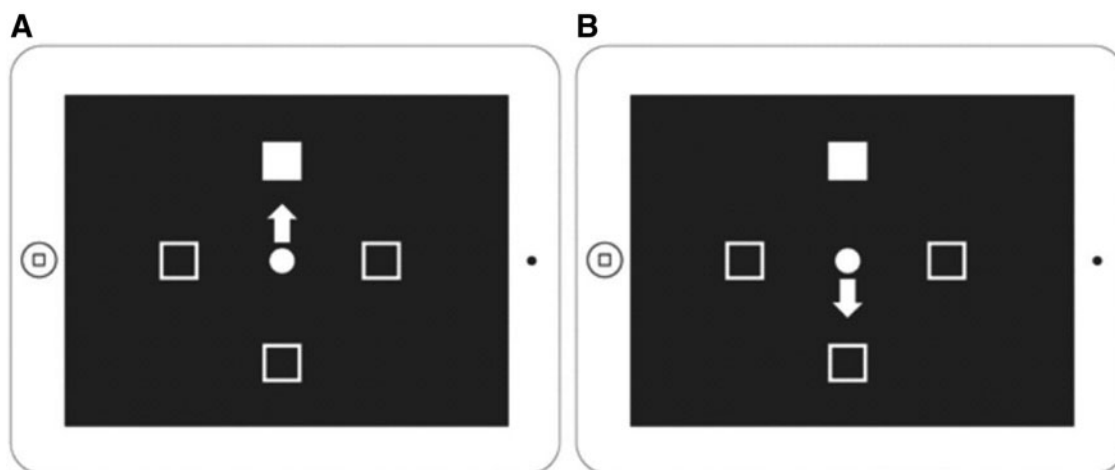


FIG. 2. Schematic of ProPoint and AntiPoint tasks. (A) ProPoint task. Central starting point (circle) and four possible target locations (square outlines) are shown. The target is shown by a filled square and the arrow indicates the direction of a correct response. (B) AntiPoint task. Same as in (A), but notice that the direction of the arrow is now opposite to the target's location (figure adapted from Zhang and colleagues).⁴⁶

At each Test Time, between 3:15 and 5:30 P.M., each participant performed the two tasks (ProPoint and AntiPoint tasks, respectively) in separate blocks until 48 correct trials were completed for each task. Half of the participants started with the AntiPoint task, while the other half started with the ProPoint task.

Headers. In addition, we recorded heading behavior for each player. Following Workout A, players self reported the number of headers they had that day (Workout A headers) and the number of headers the previous day (24 h prior to Workout A). Since half of the participants were tested at the beginning of the week (with no exposure to heading the ball on the day before Workout A), the mean for the self-reported number of headers was 0.9 headers (SD=1.9; range 0–10) the day before Workout A and was 2.3 (SD=4.1, range 0–20) during Workout A for all sessions.

Also, at the last testing session of the season, for both Years, players self reported the average number of headers they had per workout during the season (Season Average Heading). The mean for the self-reported Season Average Heading was 3.2 (SD=2.8; range 2–10).

Statistical analysis

Errors and trimming. All trials in the ProPoint and AntiPoint tasks containing an error (finger touched more than 3.3° away from the center of the target location) were excluded (1.8%). Conditional means were then calculated by task for each participant, Session, and Test Time. RTs that were greater than 2.75 standard deviations away from this conditional mean were excluded. This trimming procedure removed an additional 2.1% and 1.9% of trials for ProPoint and AntiPoint task, respectively.

Exclusion and missing data. Two of 14 Year 1 participants experienced a concussion with no loss of consciousness. One experienced a concussion after Session 1 testing in Year 1 and did not participate in Year 2, thus the tests after Session 1 were excluded. Another participant had a concussion immediately after the final testing session in Year 1, which was more than 10 months before beginning of the Year 2, thus all tests were included. None of the participants experienced a head injury during Year 2.

Due to illness on the testing days, three participants (one participating in only Year 1, one participating in both Year 1 and 2, and one participating in only Year 2) left the Workout early and were not tested for Test Time 2. Two of these participants also missed Test Time 3. The missed testing times occurred in sessions at the beginning (two participants) or end (one participant) of the season.

In addition, due to a large learning effect, the first test performed by each participant was excluded. The RTs of the remaining trimmed trials for each pointing task were used for statistical analyses.

First analysis (immediate and 24-h effects). In the first analysis, separately for each pointing task, we estimated the immediate and 24-h effects of a soccer workout using a mixed effects model where the fixed effects were Test Time (1, 2, 3), the number of headers within the previous hour or so (H-1hr), the number of headers approximately 24 h earlier (H-24hr) and time played in games (Workout B). The random effect was the participant assuming a spatial exponential power structure, SP(EXP)(Session-by-Test Time), correlation structure within each participant and repeated measurements within each testing session of a participant assuming an autocorrelation with order 1, AR(1). In this analysis, we used all data collected in the first year of participation in the study only, so that second season effects were not confounded with short term effects. Thus, the four participants who participated in Year 2 for the first time were considered in their first year and included in the analysis. However, two participants (one from

concussion, one from illness) were not included in this analysis (see the “Exclusion and missing data” section). Additionally, since the first test time of each participant’s first session was excluded due to a learning effect (see the “Exclusion and missing data” section) and to avoid the imbalance in test time, the first session of each participant was excluded for these analyses. For significant Test Time effects, we followed with mixed effects model *post hoc* planned comparisons among the Test Times (1 vs. 2, immediate effects; and 2 vs. 3, 24-h effects) to evaluate test time effects.

Second analysis (season effects). In the second analysis, again separately for each pointing task, we estimated season effects of soccer playing using a mixed effects model where the fixed effects were Season (beginning vs. end), the number of headers within the previous hour or so (H-1hr), the number of headers approximately 24 h earlier (H-24hr), the Season Average Heading (H-s) and time played in games. The random effect was the participant assuming a spatial exponential power structure, SP(EXP)(Session), correlation structure within each participant and repeated measurements within each testing session of a participant assuming an autocorrelation with order 1, AR(1). For these analyses, we included only Test Time 2 at the beginning and end of the season. Fifteen players had Test Time 2 at both the beginning and end of the season in at least 1 year and were used for statistical analyses.

Additional analysis. We compared the season average heading between defenders and non-defenders (including midfielders, a forward, and two goalies) and we found no difference between the positions [3.6 headers (SD=2.7) for defender; 2.8 headers (SD=2.9) for non-defenders; $F(1,22)=0.56, p=0.46$]. Thus, we do not think that position is an important factor in this study.

See Table 1 for a summary of unadjusted ProPoint and AntiPoint mean RTs (\pm SD) for the First Analysis across Test Time (A Panel) and the Second Analysis across Season (B Panel), respectively. All statistical analyses were performed using SAS for Windows V9.4 (Cary, NC). A p value of <0.05 was considered statistically significant.

Results

Immediate and 24-h effects

ProPoint. As shown in Table 2, there was a significant decrease in ProPoint RT from pre-Workout (Test Time 1) to immediately post-Workout (Test Time 2) in the soccer players [mean RT change = -20.4 msec, standard error [SE]=4.4, $t(78)=-4.61, p<0.001$]. There was no additional significant change in ProPoint RT from post-Workout (Test Time 2) to 24 h later (Test Time 3) in the soccer players [mean RT change = 0.8 msec, SE = 3.6, $t(78)=0.17, p=0.86$]. ProPoint RT was not affected by the number of headers performed in the previous hour or so [H-1 hr; 0.6 msec per header; SE = 1.3, $t(78)=0.46, p=0.64$]. In contrast, ProPoint RT increased as the number of headers performed in the previous 24-h (H-24hr) increased [2.7 msec per header; SE = 0.7, $t(78)=3.83, p<0.001$]. ProPoint RT was not significantly affected by whether the athlete played full or partial games in the actual games [Workout B; 2.7 msec, $t(78)=0.85, p=0.40$].

AntiPoint. As shown in Table 2, There was a significant decrease in AntiPoint RT from pre-Workout (Test Time 1) to immediately post-Workout (Test Time 2) in the soccer players [mean RT change = -11.0 msec, SE = 4.2, $t(78)=-2.60, p=0.011$]. There was no additional significant change in AntiPoint RT from post-Workout (Test Time 2) to 24 h later (Test Time 3) in the soccer players [mean RT change = -7.1 msec, SE = 4.2, $t(78)=-1.69,$

TABLE 1. SUMMARY OF REACTION TIME MEANS AND STANDARD DEVIATIONS (SDs) FOR THE FIRST ANALYSIS ACROSS TEST TIME (A) AND FOR THE SECOND ANALYSIS ACROSS SEASON (B)

A.			
Task	Test Time	Number of participants (number of trials)	Mean (SD)
ProPoint	1	16 (1297)	521.7 (64.6)
	2	16 (1290)	502.9 (50.4)
	3	16 (1296)	504.3 (51.9)
AntiPoint	1	16 (1315)	598.3 (69.3)
	2	16 (1314)	586.4 (66.2)
	3	16 (1319)	582.1 (69.5)
B.			
Task	Season	Number of participants (number of trials)	Mean (SD)
ProPoint	Beginning	15 (940)	531.8 (62.4)
	End	15 (931)	501.1 (51.9)
AntiPoint	Beginning	15 (946)	625.5 (79.4)
	End	15 (933)	584.8 (65.2)

$p=0.096$]. AntiPoint RT was not affected by the number of headers performed in the previous hour or so [H-1hr; -0.7 msec per header; $SE=1.3$, $t(78)=-0.53$, $p=0.60$]. In contrast, AntiPoint RT increased as the number of headers performed in the previous 24 h (H-24hr) increased [2.7 msec per header; $SE=0.7$, $t(78)=3.94$, $p<0.001$]. AntiPoint RT was not significantly affected by whether the athlete played full or partial games in the actual games [Workout B; 0.9 msec, $SE=3.0$, $t(78)=0.3$, $p=0.76$].

Season effects

ProPoint. As shown in Table 2, there was a significant decrease in ProPoint RT from the beginning to the end of the season [mean RT change = -34.8 msec, $SE=4.8$, $t(34)=-7.25$, $p<0.001$]. ProPoint RT decreased as the number of headers performed in the previous hour or so (H-1hr) increased [-2.6 msec per header; $SE=0.6$, $t(34)=-4.10$, $p<0.001$]. In contrast, ProPoint RT in-

creased as the number of headers performed in the previous 24 h (H-24hr) increased [6.2 msec per header; $SE=1.6$, $t(34)=3.86$, $p=0.001$]. The season average headers (H-s) and time played in actual games had no effect on ProPoint RT, [1.0 msec per header, $t(34)=1.05$, $p=0.30$ and (2.07 , $SE=4.8$, $t(34)=0.43$, $p=0.67$, respectively].

AntiPoint. As shown in Table 2, there was a significant decrease in AntiPoint RT from the beginning to the end of the season [mean RT change = -45.8 msec, $SE=4.9$, $t(34)=-9.24$, $p<0.001$]. AntiPoint RT decreased as the number of headers performed in the previous hour or so (H-1hr) increased [-2.8 msec per header; $SE=0.7$, $t(34)=-4.36$, $p<0.001$]. In contrast, AntiPoint RT increased as the number of headers performed in the previous 24 h (H-24hr) increased [6.1 msec per header; $SE=1.7$, $t(34)=3.66$, $p<0.001$]. Additionally, AntiPoint RT increased as the season average headers (H-s) increased [2.2 msec per header, $SE=0.9$,

TABLE 2. SUMMARY OF EFFECTS ON RESPONSE TIME WITH ADJUSTMENTS AS NEEDED

Effect	Analysis 1 (16 subjects)	
	ProPoint	AntiPoint
Immediate effect (Test Time 2 – Test Time 1)	-20.4 , $SE=4.4$, $t(78)=-4.61$, $p<0.001$	-11.0 , $SE=4.2$, $t(78)=-2.60$, $p=0.011$
24-hour Effect (Test Time 3 – Test Time 2)	0.8 , $SE=4.4$, $t(78)=0.17$, $p=0.86$	-7.1 , $SE=4.2$, $t(78)=-1.69$, $p=0.096$
Headers: 1 h before test	0.6 , $SE=1.3$, $t(78)=0.46$, $p=0.64$	-0.7 , $SE=1.3$, $t(78)=-0.53$, $p=0.60$
Headers: 24 h before test	2.7 , $SE=0.7$, $t(78)=3.83$, $p<0.001$	2.7 , $SE=0.7$, $t(78)=3.94$, $p<0.001$
Time played at actual game (partial game vs. full game)	2.7 , $SE=3.2$, $t(78)=0.85$, $p=0.40$	0.9 , $SE=3.0$, $t(78)=0.30$, $p=0.76$
Analysis 2 (15 subjects)		
Season Effect (End – Beginning)	-34.8 , $SE=4.8$, $t(34)=-7.25$, $p<0.001$	-45.8 , $SE=4.9$, $t(34)=-9.24$, $p<0.001$
Headers: 1 h before test	-2.6 , $SE=0.6$, $t(34)=-4.10$, $p<0.001$	-2.8 , $SE=0.7$, $t(34)=-4.36$, $p<0.001$
Headers: 24 h before test	6.2 , $SE=1.6$, $t(34)=3.86$, $p=0.001$	6.1 , $SE=1.7$, $t(34)=3.66$, $p<0.001$
Average Season Headers	1.0 , $SE=0.9$, $t(34)=1.05$, $p=0.30$	2.2 , $SE=0.9$, $t(34)=2.33$, $p=0.026$
Time played at actual game (partial game vs. full game)	2.1 , $SE=4.8$, $t(34)=0.43$, $p=0.67$	5.7 , $SE=5.0$, $t(34)=1.13$, $p=0.27$

SE, standard error.

$t(34)=2.33, p=0.026]$. Time played in the actual games had no effect on AntiPoint RT [5.7 msec , $SE=5.0$ $t(34)=1.13, p=0.27]$.

Discussion

The aim of this study was to examine the immediate and short-term time course of sensorimotor and cognitive changes in youth soccer players using a rapidly administered tablet-based task and test whether heading the ball influences these response times. The results indicate that there are measurable and significant decreases in ProPoint and AntiPoint RTs immediately across a workout, with no additional significant decreases in RTs about 24 h later. Our findings also indicate that the immediate effect of heading the ball (within an hour or so) did not alter sensorimotor (ProPoint) and cognitive (AntiPoint) RTs. In contrast, we found that by about 24 h after heading the ball, heading increased both sensorimotor and cognitive RTs. Additionally, we examined changes in sensorimotor and cognitive function across the season and tested whether heading influences RT across the play season. We found significant decreases in ProPoint and AntiPoint RTs from the beginning to end of a play season, with AntiPoint RTs significantly increasing as the season average headers (H-s) increased. In the second seasonal analysis, and somewhat consistent with the immediate and short-term RT changes occurring with heading in the first analysis, we found that heading the ball immediately before (an hour or so before RT measurement) decreased RTs whereas heading the ball about 24 h prior increased RTs in both tasks. We used time played during actual games (full game versus partial game) and found that the time played during games was not a significant factor in both tasks and both analyses. These findings show that we are able to measure small but reliable changes in sensorimotor and cognitive function in adolescent players across immediate (hour), short (day), and longer (play season) intervals and show that the effects of heading the ball on sensorimotor and cognitive function varies across time scales, with either no change or immediate facilitation of RTs followed by slowing by 24 h later.

Potential factors producing RT improvements over testing

Youth soccer players showed an improvement in sensorimotor and cognitive performance immediately after a workout. These findings are consistent with a previous report, Koerte and colleagues,²⁹ that also found immediate improvements in male German high performance athletes of about the same age range immediately following a workout. Together, these findings suggest that this immediate improvement occurs with physical activity, in both genders, and in relatively competitive playing levels (i.e., found in both a relatively competitive California high school varsity team as well as in German high-performance athletes).

Our study did not demonstrate additional RT benefits in the next 24 h but did see benefits in sensorimotor and cognitive performance across the play season. Previous work has demonstrated immediate,³¹ short-term,³² and longer-term benefits of physical exercise on cognitive performance.⁴⁷ Further, the benefits of exercise at one time frame (e.g., immediate increases in adrenaline following exercise)³³ may not be the exact same factor driving longer-term benefits (e.g., increased blood flow or volume and molecular cascades)³⁷ Nevertheless, some of the improvements across the different time intervals are sure to be a direct result of physical exercise. Secondly, the improvements across short intervals following a workout with RHIs may also be a result of the pathophysiology of the brain injury itself. Much work in the animal

literature suggests that there are rapid biochemical changes (initial hyperglycolysis and cytokine releases followed by hypoglycolysis by 6 or so hours) that seem to first have beneficial effects and then a later detrimental effect.⁴² Thus, the temporal profile of the pathophysiology of brain injury is also qualitatively consistent with the behavioral changes that we report. Thirdly, in youth athletes, the improvements across the play season may also include developmental changes. Changes on cognitive tasks⁴⁸ and similar eye tracking tasks⁴⁹ are well documented in adolescence, continuing until early 20s when the prefrontal cortex finishes myelination.^{50,51}

Finally, performance can improve over time due to practice effects. It is likely that all of these factors, increased adrenaline, increased blood volume, developmental changes, and practice effects, as well as rapid beneficial biochemical changes following injury, played a role in the RT improvements we report. Importantly, such improvements make it more difficult to detect injuries because they may mask any negative effects of head blows. A control group without RHIs would have been helpful to control for some of these factors. However, such a design would have required careful group matching, minimally in age and athletics, and testing in a design with equivalent exertion (but no RHIs) across the play season. Due to the complexities and inherent variability of team sports, exercise physiologists have difficulty even designing appropriate conditioning drills within a sport that match play demands,^{52,53} much less match the intensity, frequency, duration, and density of specific activities across sports. Hence, finding a control sport that would be considered valid would have been difficult to achieve. Hence, our focus here was on testing for within group changes.

Effects of RHIs on RT

Immediate effects (1–2 h following repeated subconcussive blows). In the first analysis, we found no evidence that heading about 1-h prior to tablet testing affected either ProPoint or AntiPoint RTs. However, in the second seasonal analysis, we found that heading about 1-h prior to tablet testing decreased both ProPoint and AntiPoint RTs. Participants were 2.6 msec/header and 2.8 msec/header faster on ProPoint and AntiPoint RTs, respectively. Although the findings of the two analyses are not consistent, both findings suggest that there are no immediate deleterious effects of heading on RTs. The first finding is in agreement with Koerte and colleagues,²⁹ who found no statistical relation between heading the ball and the immediate RT improvements in male high-performance athletes of about the same ages (i.e., they showed equivalent improvement in athletes with and without repetitive subconcussive head impacts). However, as Koerte and colleagues²⁹ suggested, it is possible that heading may produce an additional immediate increase in arousal because of a visual looming effect. This looming effect, or head hits with the object coming towards a player's face, may enhance tactile sensitivity, activating the inter-cortical connection in the brain and in turn increasing sensorimotor function.^{54–56}

In addition, much work with animal models of brain injury suggests immediate biochemical changes that are beneficial at short intervals.⁴² Either or both of these effects may explain our finding of immediately decreasing RTs with increasing headers. In addition, given that the athletes in the present study had about half the number of headers in the previous hour as Koerte and colleagues,²⁹ it is possible that both groups had equivalent beneficial effects (looming and/or biochemical cascades) but that Koerte and colleagues²⁹ athletes had greater negative impact from heading (twice

as many headers), resulting in the appearance of no relation between heading the ball and our finding of immediate RT benefits.

Alternatively, German high-performance soccer athletes may have had a greater level of adrenaline, contributing to a greater immediate cognitive benefit than the varsity-level women. Previous work does suggest that higher performance athletes have greater cognitive benefits after equivalent exertion.^{57,58} Although the study was designed to reduce interference and provide an accurate assessment of real-world soccer, there were a number of factors even within our study that could have influenced the findings. The first analysis used only the first season of play so that second season effects were not confounded with short term effects but included data from all three test times, whereas the second seasonal analysis included all years of play but only included Test Time 2 (the only test time with headers 1–2 h prior to testing). Additional work, with more quantitative heading measures and additional control of potential temporal factors including number of tests, interval between tests, or time-point in the season may be needed to determine what factors influence the immediate effects of heading on RT.

Short-term slowing (24 h following RHIs). Despite no additional significant decreases in both ProPoint and AntiPoint RTs 24 h after workout, we found that heading 24 h earlier increased both ProPoint and AntiPoint RTs. These results suggest that although cognitive performance in youth athletes improves even over short intervals of time after exercise, this benefit is reduced by RHIs. By 24 h, any immediate effects (e.g., due to physical exercise, adrenaline, initial beneficial biochemical changes, looming, or tactile sensitivity in the previous h) have gone and it is likely that remaining RT benefits are due to more sustained or longer-term beneficial effects of exercise. This supposition is in agreement with prior findings showing cognitive benefits of exercise 24 h following a workout.^{59–61} In addition, deleterious effects of RHI appear over this interval, as demonstrated in studies by Giza and Havdam,⁶² Yoshino and colleagues,⁶³ and Iverson and colleagues.⁶⁴ Thus, this sensitive tool can help illuminate the behavioral changes occurring across time due to the overlapping beneficial and deleterious factors with varying time course that occur after exercise with RHIs.

Seasonal effects. We examined performance at the beginning and end of a play season and found a similar deleterious shift between immediate (decrease in RT) and short-term (increase in RT) effects of heading on these RTs. We found significant decreases in ProPoint and AntiPoint RTs from the beginning to end of a play season, with AntiPoint RTs significantly increasing as the season average headers (H-s) increased. We did not see an effect of average season heading on ProPoint RT.

Previous work postulates that there may be differences in force between heading a high ball or long header compared with a ball that is thrown in⁶⁵. It is possible that these different kinds of headers performed throughout the season had differential effects on RT. In a previous study of high-performance German soccer players, Koerte and colleagues²⁹ found that the total number of headers (on average 7.2 per workout per athlete) had no statistically significant effect on the soccer player's rate of improvement over the entire play season. However, they did find that the more long headers (defined qualitatively as goalkeeper kick or corner crosses of more than 30 m) that a player performed (on average 0.9 per workout per athlete), the less his improvement in RT across the play season.

In the present study, there were fewer total headers reported per workout (on average only 2.3 per workout per athlete) and each header, although confirmed by a trained observer, was not inde-

pendently recorded and classified by an observer. Although the present study examined a highly competitive varsity high school team, on average they performed more than 68% fewer headers than the high-performance German athletes. Given the smaller number of total headers per workout, and the reduced number of tests (two vs. up to 22 sessions) it is striking that we were able to detect an effect of heading on AntiPoint RTs across the season. Although we did not qualitatively differentiate headers, these findings suggest that even a small number of headers may be detrimental. Although the study included players from various field positions, we did not see a difference in average season heading between the positions (3.6 headers for defender; 2.8 headers for non-defenders). Thus, we don't think that position was an important factor in this study.

Further, previous work suggests several factors are important in determining head impact severity, including velocity,⁶⁶ and rotational versus linear acceleration.⁶⁷ It is possible that there would be systematic differences between German high-performance male athletes and a U.S. high school female varsity team. It is also possible that there may be differences in neck musculature between girls and boys at this age, leading to differing impact of even the same head impacts.^{68–71} However, some prior research has suggested that players with greater static neck strength did not experience lower resultant head accelerations.⁷² Additional studies are needed to focus more carefully on changes during the play season and include qualitative and quantitative measures of the type, frequency, intervals of head impact exposure, as well as duration of the season to further explore the changes during a play season.

Study limitations

The study was relatively small and included players from various field positions. Future work with larger samples is needed to determine if the findings would vary depending on field position or other factors such as gender, age, height, time played in games, and playing level. The study also did not qualitatively or quantitatively differentiate headers. Future studies might consider the inclusion of multiple observers (to allow for a measure of interrater reliability) and/or other quantitative measures of head impact severity. As well, future studies may test whether headgear is an ameliorating factor in decreasing the impact of subconcussive hits. A recent study concluded that headgear did not lessen the chance of getting a sports-related concussion.⁷³ Future work using quantitative measures could examine rotational versus linear velocity, neck muscle strength, size/weight of ball, athlete's body mass, and role of heading technique, including lack of anticipation as potential variables.

Conclusion

Adolescent athletes with or without RHIs show improvement in cognitive and/or sensorimotor performance at all time intervals (starting immediately following workout as well as across a play season) and these changes can be attributed to physical exercise and, for longer time intervals, developmental changes. Further, we suggest that there may be different factors (e.g., adrenaline, looming, and beneficial early biochemical cascades following brain injury versus later injurious biochemical cascades) with varying time courses that cause RHIs to first have no effect or decrease RTs immediately following workout, but increase RTs by about 24 h later. We also found that athletes showed an increase in AntiPoint RTs with increasing season average RHIs, consistent with prior research suggesting a longer-term RT increase with increased heading. Importantly, the demonstration here of an association between exposure to RHI while heading the ball in soccer and

increase in sensorimotor and cognitive RTs by 24 h after workout, is certain to help clarify the time course of changes associated with RHIs. At this age, any slowing by 24 h may have impact more generally on development and learning.

Acknowledgments

The authors would like to thank Stuart Red for his help with aspects of experimental design and guidance on project related procedures. The authors would also like to thank Jasmine Stütz for her assistance in aspects of data management and analysis and Farzin Shamloo for providing valuable feedback on earlier drafts of the manuscript.

Funding Information

This work was supported in part by NSF BS 0924636, NIH P30EY010608, and Purdue University start-up funds.

Author Disclosure Statement

Co-authors ABS and SSP are named inventors of patents US-9,717,459, August 1, 2017 and US-9,949,693, April 24, 2018; and ABS is founder and member of CogNeuro Solutions LLC. For the remaining authors, no competing financial interests exist.

References

- Marar, M., McIlvain, N.M., Fields, S.K., and Comstock, R.D. (2012). Epidemiology of concussions among United States high school athletes in 20 sports. *Am. J. Sports Med.* 40, 47–755.
- Stern, R.A., Riley, D.O., Daneshvar, D.H., Nowinski, C.J., Cantu, R.C., and McKee, A.C. (2011). Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy. *PM R* 3, S460–S467.
- Breedlove, E.L., Robinson, M., Talavage, T.M., Morigaki, K.E., Yoruk, U., O'Keefe, K., King, J., Leverenz, L.J., Gilger, J.W., and Nauman, E.A. (2012). Biomechanical correlates of symptomatic and asymptomatic neurophysiological impairment in high school football. *J. Biomech.* 45, 1265–1272.
- Montenegro, P.H., Alosco, M.L., Martin, B.M., Daneshvar, D.H., Mez, J., Chaisson, C.E., Nowinski, C.J., Au, R., McKee, A.C., Cantu, R.C., McClean, M.D., Stern, R.A., and Tripodis, Y. (2017). Cumulative head impact exposure predicts later-life depression, apathy, executive dysfunction, and cognitive impairment in former high school and college football players. *J. Neurotrauma* 34, 328–340.
- Alosco, M.L., Kasimis, A.B., Stamm, J.M., Chua, A.S., Baugh, C.M., Daneshvar, D.H., Robbins, C.A., Mariani, M.D., Hayden, J.C., Conneely, S.C., Au, R.J., Torres, A.M., McClean, M.E., McKee, A.A., Cantu, R., Mez, J., Nowinski, C., Martin, B., Chaisson, C., Tripodis, Y., and Stern, R. (2017). Age of first exposure to American football and long-term neuropsychiatric and cognitive outcomes. *Transl. Psychiatry* 7, e1236.
- Schultz, V., Stern, R.A., Tripodis, Y., Stamm, J., Wrobel, P., Lepage, C., Weir, I., Guenette, J.P., Chua, A., Alosco, M.L., Baugh, C.M., Fritts, N.G., Martin, B.M., Chaisson, C.E., Coleman, M.J., Lin, A.P., Pasternak, O., Shenton, M.E., and Koerte, I.K. (2018). Age at first exposure to repetitive head impacts is associated with smaller thalamic volumes in former professional American football players. *J. Neurotrauma* 35, 278–285.
- Stemper, B.D., Shah, A.S., Harezlak, J., Rowson, S., Mihalik, J.P., Duma, S.M., Riggen, L.D., Brooks, A., Cameron, K.L., Campbell, D., DiFiori, J.P., Giza, C.C., Guskiewicz, K.M., Jackson, J., McGinty, G.T., Svoboda, S.J., McAllister, T.W., Broglio, S.P., and McCreary, M.; CARE Consortium Investigators. (2018). Comparison of head impact exposure between concussed football athletes and matched controls: evidence for a possible second mechanism of sport-related concussion. *Ann. Biomed. Eng.* 47, 2057–2072.
- Stemper, B.D., Shah, A.S., Harezlak, J., Rowson, S., Duma, S., Mihalik, J.P., Riggen, L.D., Brooks, A., Cameron, K.L., Giza, C.C., Houston, M.N., Jackson, J., Posner, M.A., McGinty, G., DiFiori, J., Broglio, S.P., McAllister, T.W., and McCreary, M.; CARE Consortium Investigators (2019). Repetitive head impact exposure in college football following an NCAA rule change to eliminate two-a-day preseason practices: a study from the NCAA-DoD CARE Consortium. *Ann. Biomed. Eng.* 47, 2073–2085.
- Bailes, J.E., Petraglia, A.L., Omalu, B.I., Nauman, E., and Talavage, T. (2013). Role of subconcussion in repetitive mild traumatic brain injury. *J. Neurosurg.* 119, 1235–1245.
- Hirad, A.A., Bazarian, J.J., Merchant-Borna, K., Garcea, F.E., Heilbronner, S., Paul, D., Hintz, E.B., Wijngaarde, E.V., Schifitto, G., Wright, D.W., Espinoza, T.R., and Mahon, B.Z. (2019). A common neural signature of brain injury in concussion and subconcussion. *Sci. Adv.* 5, eaau3460.
- Jang, I., Chun, I.Y., Brosch, J.R., Bari, S., Zou, Y., Cummiskey, B.R., Lee, T.E., Lycke, R.O., Poole, V.G., Shenk, T.J., Svaldi, D.A., Tamer, G.M., Dydak, U., Leverenz, U., Nauman, E., and Talavage, T.M. (2019). Every hit matters: white matter diffusivity changes in high school football athletes are correlated with repetitive head acceleration event exposure. *Neuroimage Clin.* 24, 101930.
- Slobounov, S.M., Walter, A., Breiter, H.C., Zhu, D.C., Bai, X., Bream, T., Seidenberg, P., Mao, X., Johnson, B., and Talavage, T.M. (2017). 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.* 14, 708–718.
- Tagge, C.A., Fisher, A.M., Minaeva, O.V., Gaudreau-Balderrama, A., Moncaster, J.A., Zhang, X.L., Wojnarowics, M.W., Casey, N., Lu, H., Kokiko-Cochran, O.N., Saman, S., Ericsson, M., Onos, K.D., Veksler, R., Senatorov, V.V., Kondo, A., Zhou, X.Z., Miry, O., Vose L.R., Gopaul, K.R., Upreti, C., Nowinski, C.J., Cantu, R.C., Alvarez, V.E., Hildebrandt, A.M., Franz, E.S., Konrad, J., Hamilton, J.A., Hua, N., Tripodis, Y., Anderson, A.T., Howell, G.R., Kaufer, D., Hall, G.F., Lu, K.P., Ransohoff, R.M., Cleveland, R.O., Kowall, N.W., Stein, T.D., Lamb, B.T., Huber, B.R., Moss, W.C., Friedman, A., Stanton, P.K., and McKee, A.C. (2018). Concussion, microvascular injury, and early tauopathy in young athletes after impact head injury and an impact concussion mouse model. *Brain* 141, 422–458.
- Talavage, T.M., Nauman, E.A., Breedlove, E.L., Yoruk, U., Dye, A.E., Morigaki, K.E., Feuer, H., and Leverenz, L.J. (2014). Functionally-detected cognitive impairment in high school football players without clinically-diagnosed concussion. *J. Neurotrauma* 31, 327–338.
- Di Virgilio, T.G., Ietswaart, M., Wilson, L., Donaldson, D.I., and Hunter, A.M. (2019). Understanding the consequences of repetitive subconcussive head impacts in sport: brain changes and dampened motor control are seen after boxing practice. *Front. Hum. Neurosci.* 13, 294.
- Koerte, I.K., Lin, A.P., Muehlmann, M., Merugumala, S., Liao, H., Starr, T., Kaufmann, D., Mayinger, M., Steffinger, D., Fisch, B., Karch, S., Heinen, F., Ertl-Wagner, B., Stern, R.A., Zafonte, R., and Shenton, M.E. (2015). Altered neurochemistry in former professional soccer players without a history of concussion. *J. Neurotrauma* 32, 1287–1293.
- Allsop, D., Haga, S., Bruton, C., Ishii, T., and Roberts, G.W. (1990). Neurofibrillary tangles in some cases of dementia pugilistica share antigens with amyloid beta-protein of Alzheimer's disease. *Am. J. Pathol.* 136, 255.
- Areza-Fegyveres, R., Roseberg, S., Castro, R.M.R., Porto, C.S., Bahia, V.S., Caramelli, P., and Nitrini, R. (2007). Dementia pugilistica with clinical features of Alzheimer's disease. *Arq. Neuropsiquiatr.* 65, 830–833.
- Mackay, D.F., Russell, E.R., Stewart, K., Maclean, J.A., Pell, J.P., and Stewart, W. (2019). Neurodegenerative disease mortality among former professional soccer players. *N. Engl. J. Med.* 381, 1801–1808.
- Abbas, K., Shenk, T.E., Poole, V.N., Breedlove, E.L., Leverenz, L.J., Nauman, E.A., Talavage, T.E., and Robinson, M.E. (2015). Alteration of default mode network in high school football athletes due to repetitive subconcussive mild traumatic brain injury: a resting-state functional magnetic resonance imaging study. *Brain Connect.* 5, 91–101.
- Boutté, A.M., Thangavelu, B., Lavalle, C.R., Nemes, J., Gilsdorf, J., Shear, D.A., and Kamimori, G.H. (2019). Brain-related proteins as serum biomarkers of acute, subconcussive blast overpressure exposure: a cohort study of military personnel. *Plos One* 14.
- Koerte, I.K., Wagner, B., Zafonte, R., and Shenton, M.E. (2012). White matter integrity in the brains of professional soccer players without a symptomatic concussion. *JAMA* 308, 1859–1861.
- Lipton, M.L., Kim, N., Zimmerman, M.E., Kim, M., Stewart, W.F., Branch, C.A., and Lipton, R.B. (2013). Soccer heading is associated

- with white matter microstructural and cognitive abnormalities. *Radiology* 268, 850–857.
24. Matsler, J.T., Kessels, A.G.H., Jordan, B.D., Lezak, M.D., and Troost, J. (1998). Chronic traumatic brain injury in professional soccer players. *Neurology* 51, 791–796.
 25. Papa, L., Slobounov, S.M., Breiter, H.C., Walter, A., Bream, T., Seidenberg, P., Bailes, J.E., Bravo, S., Johnson, B., Kaufman, D., Molfese, D.L., Talavage, T.M., Zhu, D.C., Knollmann-Ritschel, B., and Bhomia, M., 14M. (2019). Elevations in microRNA biomarkers in serum are associated with measures of concussion, neurocognitive function, and subconcussive trauma over a single National Collegiate Athletic Association Division I season in collegiate football players. *J. Neurotrauma* 36, 1343–1351.
 26. Papa, L., Zonfrillo, M.R., Welch, R.D., Lewis, L.M., Braga, C.F., Tan, C.N., Ameli, N.J., Lopez, J.E., Haeussler, C.A., Mendez Giordano, D., Giordano, P.A., Ramirez, J., and Mittal, M.K. (2019). Evaluating glial and neuronal blood biomarkers GFAP and UCH-L1 as gradients of brain injury in concussive, subconcussive and non-concussive trauma: a prospective cohort study. *BMJ Paediatr. Open* 3, e000473.
 27. Stephens, R., Rutherford, A., Potter, D., and Fernie, G. (2010). Neuropsychological consequence of soccer play in adolescent U.K. School team soccer players. *J. Neuropsychiatry Clin. Neurosci.* 22, 295–303.
 28. Rieder, C. and Jansen, P. (2011). No neuropsychological consequence in male and female soccer players after a short heading training. *Arch. Clin. Neuropsychol.* 26, 583–591.
 29. Koerte, I.K., Nichols, E., Tripodis, Y., Schultz, V., Lehner, S., Igbinoba, R., Chuang, A.Z., Mayinger, M., Klier, E.M., Muehlmann, M., Kaufmann, D., Lepage, C., Heinen, F., Schulte-Korne, G., Zafonte, R., Shenton, M.E., Sereno, A.B. (2017). Impaired cognitive performance in youth athletes exposed to repetitive head impacts. *J. Neurotrauma* 34, 2389–2395.
 30. Hogan, C.L., Mata, J., and Carstensen, L.L. (2013). Exercise holds immediate benefits for affect and cognition in younger and older adults. *Psychol. Aging* 28(2), 587.
 31. Audiffren, M., Tomporowski, P.D., and Zagrodnik, J. (2008). Acute aerobic exercise and information processing: energizing motor processes during a choice reaction time task. *Acta Psychol.* 129, 410–419.
 32. Joyce, J., Graydon, J., McMorris, T., and Davranche, K. (2009). The time course effect of moderate intensity exercise on response execution and response inhibition. *Brain Cogn.* 71, 14–19.
 33. Zouhal, H., Jacob, C., Delamarche, P., and Gratas-Delamarche, A. (2008). Catecholamines and the effects of exercise, training and gender. *Sports Med.* 38, 401–423.
 34. Querido, J.S. and Sheel, A.W. (2007). Regulation of cerebral blood flow during exercise. *Sports Med.* 37, 765–782.
 35. Pereira, A.C., Huddleston, D.E., Brickman, A.M., Sosunov, A.A., Hen, R., McKhann, G.M., Sloan, R., Gage, F.H., Brown, T.R., and Small, S.A. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc. Natl. Acad. Sci.* 104, 5638–5643.
 36. Zoladz, P.R., Park, C.R., Halonen, J.D., Salim, S., Alzoubi, K.H., Srivareerat, M., Fleshner, M., Alkadhi, K.A. and Diamond, D.M. (2012). Differential expression of molecular markers of synaptic plasticity in the hippocampus, prefrontal cortex, and amygdala in response to spatial learning, predator exposure, and stress-induced amnesia. *Hippocampus* 22, 577–589.
 37. Gomez-Pinilla, F., and Hillman, C. (2013). The influence of exercise on cognitive abilities. *Compr. Physiol.* 3, 403–428.
 38. Bolouri, H. and Zetterberg, H. (2015). Animal models for concussion: molecular and cognitive assessments— Relevance to sport and military concussions, in: *Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects*, F.H. Kobeissy (ed). CRC Press/Taylor and Francis: Boca Raton, FL.
 39. Bramlett, H.M., and Dietrich, W.D. (2007). Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. *Prog. Brain Res.* 161, 125–141.
 40. Masek, B.E. and DeWitt, D.S. (2010). Traumatic brain injury: a disease process, not an event. *J. Neurotrauma* 27, 1529–1540.
 41. Thompson, H.J., Lifshitz, J., Marklund, N., Grady, M.S., Graham, D.I., Hovda, D.A., and McIntosh, T.K. (2005). Lateral fluid percussion brain injury: a 15-year review and evaluation. *J. Neurotrauma* 22, 42–75.
 42. Barkhoudarian, G., Hovda, D.A., and Giza, C.C. (2011). The Molecular Pathophysiology of Concussive Brain Injury. *Clin. Sports Med.* 30, 33–48.
 43. Williams, G.W., Shankar, B., Klier, E.M., Chuang, A.Z., El Marjiya-Villarreal, S., Nwokolo, O.O., Sharma, A., and Sereno, A.B. (2017). Sensorimotor and executive function slowing in anesthesiology residents after overnight shifts. *J. Clin. Anesth.* 40, 110–116.
 44. Kirchgessner, M.A., Chuang, A.Z., Patel, S.S., and Sereno, A.B. (2015). Intact reflexive but deficient voluntary social orienting in autism spectrum disorder. *Front. Neurosci.* 9, 453.
 45. Fischer, T.D., Red, S.D., Chuang, A.Z., Jones, E.B., McCarthy, J.J., Patel, S.S., and Sereno, A.B. (2016). Detection of subtle cognitive changes after mTBI using a novel tablet-based task. *J. Neurotrauma* 33, 1237–1246.
 46. Zhang, M.R., Red, S.D., Lin, A.H., Patel, S.S., and Sereno, A.B. (2013). Evidence of cognitive dysfunction after soccer playing with ball heading using a novel tablet-based approach. *PLoS One* 8, e57364.
 47. Weuve, J., Kang, J.H., Manson, J.E., Breteler, M.M., Ware, J.H., and Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *JAMA* 292, 1454–1461.
 48. Steinberg, L. (2005). Cognitive and affective development in adolescence. *Trends Cogn. Sci.* 9, 69–74.
 49. Karatekin, C. (2007). Eye tracking studies of normative and atypical development. *Dev. Rev.* 27, 283–348.
 50. Benes, F.M. (1989). Myelination of cortical-hippocampal relays during late adolescence. *Schizophr. Bull.* 15, 585.
 51. Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends Cogn. Sci.* 9, 60–68.
 52. Gabbett, T., King, T., and Jenkins, D. (2008). Applied physiology of rugby league. *Sports Med.* 38, 119–138.
 53. Gamble, P. (2007). Challenges and game-related solutions to metabolic conditioning for team sports. *Strength Conditioning J.* 29, 60.
 54. Cléry, J., Guipponi, O., Odouard, S., Wardak, C., and Hamed, S.B. (2015). Impact prediction by looming visual stimuli enhances tactile detection. *J. Neurosci.* 35, 4179–4189.
 55. Field, D.T. and Wann, J.P. (2005). Perceiving time to collision activates the sensorimotor cortex. *Curr. Biol.* 15, 453–458.
 56. Maier, J.X., Chandrasekaran, C., and Ghazanfar, A.A. (2008). Integration of bimodal looming signals through neuronal coherence in the temporal lobe. *Curr. Biol.* 18, 963–968.
 57. Verburch, L., Scherder, E.J., van Lange, P.A., and Oosterlaan, J. (2014). Executive functioning in highly talented soccer players. *PLoS One* 9, e91254.
 58. Ward, P. and Williams, A.M. (2003). Perceptual and cognitive skill development in soccer: the multidimensional nature of expert performance. *J. Sport Exerc. Psychol.* 25, 93–111.
 59. Roig, M., Skriver, K., Lundbye-Jensen, J., Kiens, B., and Nielsen, J.B. (2012). A single bout of exercise improves motor memory. *PLoS One* 7, e44594.
 60. Roig, M., Thomas, R., Mang, C.S., Snow, N.J., Ostadan, F., Boyd, L.A., and Lundbye-Jensen, J. (2016). Time-dependent effects of cardiovascular exercise on memory. *Exerc. Sport Sci. Rev.* 44, 81–88.
 61. Mang, C.S., Snow, N.J., Campbell, K.L., Ross, C.J., and Boyd, L.A. (2014). A single bout of high-intensity aerobic exercise facilitates response to paired associative stimulation and promotes sequence-specific implicit motor learning. *J. Applied Physiol.* 117, 1325–1336.
 62. Giza, C.C. and Hovda, D.A. (2001). The neurometabolic cascade of concussion. *J. Athletic Training* 36, 228.
 63. Yoshino, A., Hovda, D.A., Kawamata, T., Katayama, Y., and Becker, D.P. (1991). Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res.* 561, 106–119.
 64. Iverson, G.L., Brooks, B.L., Collins, M.W., and Lovell, M.R. (2006). Tracking neuropsychological recovery following concussion in sport. *Brain Inj.* 20, 245–252.
 65. Mehnert, M.J., Agesen, T., and Malanga, G.A. (2005). “Heading” and neck injuries in soccer: a review of biomechanics and potential long-term effects. *Pain Physician*, 8, 391–397.
 66. Kirkendall, D.T., and Garrett Jr, W.E. (2001). Heading in soccer: integral skill or grounds for cognitive dysfunction? *J. Athl. Training* 36, 328.
 67. Funk, J.R., Cormier, J.M., Bain, C.E., Guzman, H., and Bonugli, E. (2008). Relationship between linear and rotational head acceleration in various activities. *Biomed. Sci. Instrum.* 44, 207–212.

68. Garces G.L., Medina D., Milutinovic L., Garavote P, and Guerado E. Normative database of isometric cervical strength in a healthy population. *Med. Sci. Sports Exerc.* 34, 464–470.
69. Gutierrez, G.M., Conte, C., and Lightbourne, K. (2014). The relationship between impact force, neck strength, and neurocognitive performance in soccer heading in adolescent females. *Ped. Exerc. Sci.* 26, 33–40.
70. Tierney, R.T., Sitler, M.R., Swanik, C.B., Swanik, K.A., Higgins, M., and Torg, J.S. Gender differences in head-neck dynamic stabilization during head acceleration. *Med. Sci. Sports Exerc.* 37, 272–279.
71. Stemper, B.D., Yoganandan, N., Pintar, F.A., Maiman, D.J., Meyer, M.A., DeRosia, J., Shender, B.S. and Paskoff, G. (2008). Anatomical gender differences in cervical vertebrae of size-matched volunteers. *Spine* 33, E44–E49.
72. Mihalik, J.P., Guskiewicz, K.M., Marshall, S.W., Greenwald, R.M., Blackburn, J.T., and Cantu, R.C. (2011). Does cervical muscle strength in youth ice hockey players affect head impact biomechanics? *Clin. J. Sport Med.* 21, 416–421.
73. McGuine, T., Post, E., Pfaller, A.Y., Hetzel, S., Schwarz, A., Brooks, M.A., and Kliethermes, S.A. (2019). Does soccer headgear reduce the incidence of sport-related concussion? A cluster, randomised controlled trial of adolescent athletes. *Br. J. Sports Med.* 54, 408–413.

Address correspondence to:

Anne B. Sereno, PhD
Psychological Sciences and Weldon School
of Biomedical Engineering
Purdue University
703 Third Street
West Lafayette, IN 47907
USA

E-mail: asereno@purdue.edu