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REPORT

Brain vital signs detect concussion-related neurophysiological impairments in ice hockey

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There is a growing demand for objective evaluations of concussion. We developed a portable evoked potential framework to extract 'brain vital signs' using electroencephalography. Brain vital signs were derived from well established evoked responses representing auditory sensation (N100), basic attention (P300), and cognitive processing (N400) amplitudes and latencies, converted to normative metrics (six total). The study evaluated whether concussion-related neurophysiological impairments were detected over the duration of ice hockey seasons using brain vital signs. Forty-seven Tier III, Junior A, male ice hockey players were monitored over two seasons. Twelve sustained concussions after baseline testing then completed post-injury and return-to-play assessments. Twenty-three were not diagnosed with a concussion during the season and completed both baseline and post-season testing. Scores were evaluated using a repeated-measures analysis of variance with *post hoc* two-tailed paired *t*-tests. Concussion resulted in significantly increased amplitude and delayed latency scores for all six brain vital signs ($P < 0.0001$). Importantly, significant changes at return-to-play were also detected in basic attention (P300) amplitude, indicating persistent subclinical impairment. In the non-concussed group, there was also a significant change between baseline and post-season ($P = 0.0047$), with specific decreases in cognitive processing (N400) speed ($P = 0.011$) and overall total score ($P = 0.002$).

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Abbreviation: ERP = event-related potential

Introduction

Background

Concussion in sport is a global public health issue. There are between 1.6 million and 3.8 million sport-related concussions per year in the USA alone (Langlois *et al.*, 2006). Concussions occur frequently in collision sports such as ice hockey, where players routinely sustain both direct head contact and indirect force transmission to the brain as a result of body checking, incidental or illegal collisions, and fighting (Smith *et al.*, 2017). There is a

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growing concern because a history of concussion is potentially associated with persistent mental health and cognitive impairments later in life in some athletes (Manley *et al.*, 2017) and may result in an increased risk of progressive neurodegenerative disease (Gavett *et al.*, 2012).

Subconcussive impacts

Recent evidence suggests that subconcussive impacts can accumulate over time to create functional and structural brain impairment, historically thought to occur only in acute concussive injuries (Talavage *et al.*, 2010; Bazarian *et al.*, 2012; Davenport *et al.*, 2014; Munce *et al.*, 2014). There is no known objective assessment designed specifically to measure the effects of subconcussive impacts. Indeed, current concussion protocols are based on an affirmative concern of injury.

Need for objective evaluations

Accurate clinical decision-making is important for sport-related concussion management to achieve the goal of safely returning an athlete to play as soon as possible. Neural tissue requires sufficient time to heal after injury and athletes are susceptible to potentially far more severe re-injury if cleared to return before fully recovered (Giza and Hovda, 2015). However, there is mounting evidence demonstrating that neurophysiological impairments persist even after the observable clinical signs and symptoms have subsided (Kamins *et al.*, 2017). Sports medicine professionals are currently limited by a lack of access to more sensitive, objective measurements to assist with evidence-based treatment decisions (McCrory *et al.*, 2017; Smith *et al.*, 2017). There is a growing urgency to develop practical approaches that use objective, physiological measures, which are also rapidly and easily deployable in both sport and clinical settings.

Cognitive evoked potentials

EEG is a non-invasive, electrophysiological measure of brain activity that is both affordable and portable. Event-related potentials (ERPs) are evoked potentials extended from sensory processing to include higher level processing and are a well established quantitative application of EEG. ERPs have been studied extensively in the literature since the 1960s and represent the brain's evoked neural responses to sensory and cognitive stimuli that provide objective, quantifiable information across a spectrum of brain function (Luck, 2005; Gawryluk and D'Arcy, 2010; Gawryluk *et al.*, 2010). ERPs are sensitive to cognitive dysfunction with established test-retest reliability, making them well suited and empirically validated as a sensitive measure of concussion-related impairments (Broglio *et al.*, 2011; Cassidy *et al.*, 2012).

Brain vital signs

ERP applications in concussion have been well studied, but have not yet been practically adapted to widespread implementation in sport or clinical venues (McCrory *et al.*, 2017). Accordingly, we developed a brain vital signs framework to translate well established ERP responses into a portable, rapid, automated, and easy-to-use evaluation method (Ghosh Hajra *et al.*, 2016). The brain vital signs approach preserves the essential ERP results and, importantly, incorporates a normative comparison framework analogous to existing vital sign metrics for heart rate and blood pressure. Conventional ERP methods and analysis are time consuming (hours/individual testing) and restricted to controlled laboratory settings. By contrast, brain vital signs are acquired and analysed in less than 10 min and fully deployable within a variety of sporting and clinical settings.

The current brain vital signs approach consists of six measures representing auditory sensation [N100; (Davis, 1939)], basic attention [P300; (Sutton *et al.*, 1967)], and cognitive processing [N400; (Kutas and Hillyard, 1980)], and includes normative evaluations of amplitudes and latencies metrics for each of the three responses. The task is a 5-min auditory stimulus sequence with interlaced tones and spoken, word pair primes. Auditory tones are randomly distributed into 80% standard (75 dB) and 20% deviant (100 dB) conditions, to evoke the N100 and P300 ERPs. The N400 is derived from word pair primes that are either semantically congruent (e.g. bread-butter) or incongruent (e.g. bread-window). Ghosh Hajra *et al.* (2016, 2018) provided a detailed overview of the brain vital signs framework along with empirical validation in young and older healthy individuals.

Objectives and hypothesis

We hypothesized that (i) brain vital signs would be sensitive to the effects of concussion; and (ii) at least one of the brain vital signs metrics would not return to baseline values at return-to-play, indicating impairment undetected by current protocols. Because of the emerging concerns around sub-concussive impairment, a secondary analysis also examined pre-to-post season changes in non-concussed athletes.

Materials and methods

Participants

Each player provided informed, written consent obtained according to the Declaration of Helsinki and approved by the ethical committees of the Mayo Clinic Institutional Review Board and Simon Fraser University Research Ethics Board. For participants under the age of 18 enrolled in the study, parental consent and minor assent was obtained.

All individuals were required to be active players on the team, fluent in English, and with normal hearing. Team physicians were the primary healthcare providers. Brain vital signs data were recorded in parallel with routine clinical concussion management protocols, and results were not used to inform any clinical decisions.

Players were assessed within 24 h of their concussion, and again when they passed the concussion protocol for returning to play as determined by the medical staff. All athletes were also scanned at the end of the season. All scans were completed at the point of care either at local medical facilities or rink-side in the ice-hockey arena.

Data collection

EEG data were recorded from three midline scalp electrodes (Fz, Cz, and Pz) using a portable 8-channel g.Nautilus system (Gtec Medical Engineering) and a custom auditory stimulus delivery system (Ghosh Hajra *et al.*, 2016) running on a laptop (Hewlett-Packard). g.GAMMAsys gel was applied to each electrode location for conductivity. A reference electrode was attached to the right earlobe and three disposable Ag/AgCl electrodes were used for ground (forehead), and electro-oculogram recording from the supra-orbital ridge and outer canthus of the left eye. Skin-electrode impedances were maintained below 20 kΩ at each site. To reduce motor and ocular artefacts, participants were instructed to sit motionless, and maintain visual fixation on a crosshair positioned at eye-level 2 m away. One run of the stimulus sequence was collected per participant at each time point. The EEG system and consumables all fit in a portable carrying case (34 cm × 29 cm × 8 cm).

Event-related potential processing

Data were processed in MATLAB (Mathworks, USA). A fourth order Butterworth filter (0.1–10 Hz) and a custom Notch filter (60 Hz) were applied to the raw EEG data. Adaptive filtering was implemented to correct for ocular artefacts as recorded by the electro-oculogram electrodes (He *et al.*, 2004). ERPs were derived through segmentation (range: −100 ms pre-stimulus to 900 ms post stimulus), baseline correction, and conditional averaging (Luck, 2005). Template matching identified ERP features (N100, P300, N400) through the assessment of polarities within expected temporal ranges (Marchand *et al.*, 2002). ERP features were then evaluated for both peak latency and baseline-adjusted amplitude, for a total of six measures.

Normative translation to brain vital signs

The normative transformations were derived from the entire healthy baseline group ($n = 43$), using the group mean ± 3 standard deviations (SD) to generate the six brain vital sign scores on a scale of 0–100. Larger amplitudes and faster latencies equate to higher scores, decreased amplitudes and delayed latencies equate to lower scores, as described in Ghosh Hajra *et al.* (2016). Normality was checked using Shapiro-Wilk tests. To confirm that there were no significant differences between baseline scores of the concussed group ($n = 12$) and the normative comparison sample ($n = 43$), random samples of 12 datasets were extracted through a non-parametric bootstrapping comparison (1000 iterations) to verify no significant difference.

Statistical analysis

Statistical analysis was performed using JMP (Version 13.1.0, SAS Institute Inc., Cary, NC, 1989-2017). Scores were compared using a repeated-measures ANOVA [full factorial standard least-squares mixed-model; fixed effects: brain vital signs and time; random effects: subject; false discovery rate (FDR) corrected] with *post hoc* two-tailed paired *t*-tests. Results are presented as mean (±SD). All six brain vital signs scores were plotted on standard radar plots to characterize changes across baseline, concussion, and return-to-play time points. $P < 0.05$ denotes significance.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because they contain information that could compromise the privacy of research participants.

Results

Participants

Forty-seven, Tier III Junior-A competitive ice hockey players (age 18.49 ± 1.03 years, height 1.82 ± 0.06 m, weight 80.91 ± 6.74 kg) were recruited over two seasons, including 27 forwards, 13 defenders, and seven goaltenders. Seventeen players self-reported zero previous concussions, 24 reported between one and five prior concussions (mean: 1.71 ± 1.02), and six did not report. During the season, participants played between one and 48 games (mean: 26.91 ± 14.8, median: 30).

Forty-three participants completed baseline testing. Baseline data were collected at rest, during the time of player physical examination. Ten of these players were clinically diagnosed subsequently with a single concussion during their season, one was diagnosed with two concussions, and one was diagnosed with three concussions. Only the first concussion of each player was included ($n = 12$) in the analysis. The player with three concussions was cleared for return-to-play but discontinued playing hockey after completing this evaluation. The time from concussion to return-to-play ranged from four to 70 days (mean: 16.67 ± 17.53, median: 11).

Thirty-one players were not diagnosed with a concussion during their respective seasons following baseline testing. Twenty-three completed post-season testing (age 18.74 ± 0.89 years, height 182.8 ± 6.01 cm, weight 79.97 ± 7.11 kg), including 15 forwards, five defenders, and three goaltenders, and played between two and 48 games (mean 30.65 ± 11.66, median 31). Six of the 31 were traded away mid-season and two were unable to complete post-season evaluations because of technical difficulties.

Concussion analysis

All group baseline scores passed the Shapiro-Wilk test for normality. Radar plots show profiles for brain vital signs depicting group mean changes across the test points (Fig. 1A). Point-line plots for corresponding test point comparisons indicate the changes for each individual brain vital signs component for each participant (Fig. 1B). Representative ERP waveforms from the tone (Fig. 2A) and incongruent semantic word-pair (Fig. 2B) stimuli demonstrate these changes on an individual, electrophysiological level.

The ANOVA showed significant interaction effects for brain vital signs and time [$F(10\,110) = 5.55$, FDR LogWorth = 5.457, FDR $P < 0.0001$]. *Post hoc* *t*-tests indicated significant differences between baseline and concussion in all six elemental brain scores: auditory sensation amplitude increased [$t(11) = 3.36$, $P = 0.0064$], auditory sensation latency decreased [$t(11) = -2.90$, $P = 0.0144$], basic attention amplitude increased [$t(11) = 3.32$, $P = 0.0069$], basic attention latency decreased [$t(11) = -3.32$, $P = 0.0069$], cognitive processing amplitude increased [$t(11) = 2.54$, $P = 0.0275$], and cognitive processing latency decreased [$t(11) = -2.28$, $P = 0.0435$]. There were significant differences from concussion to return-to-play in four: auditory sensation amplitude decreased [$t(11) = -3.23$, $P = 0.0080$], auditory sensation latency increased [$t(11) = 2.65$, $P = 0.0227$], basic attention latency increased [$t(11) = 2.63$, $P = 0.0236$], cognitive processing amplitude decreased [$t(11) = -2.29$, $P = 0.0429$]. Finally, a significant increase was observed from baseline to return-to-play in basic attention amplitude [$t(11) = 2.24$, $P = 0.0466$].

Subconcussion analysis

For the non-concussed group, radar plots show profiles for brain vital signs depicting group mean changes from baseline to post-season (Fig. 3A). The ANOVA showed a significant effect for time across all six brain vital signs [$F(1,22) = 13.042$, FDR LogWorth = 2.333, FDR $P = 0.0047$]. *Post hoc* *t*-tests identified a significant decrease in the cognitive processing index for latency [$t(22) = -2.788$, $P = 0.011$]. The total score was also significantly reduced in post-season [$t(22) = -3.611$, $P = 0.002$], as shown in Fig. 3B. Figure 4 demonstrates representative ERP waveforms of a single subject, showing the N100 (Fig. 4A), P300 (Fig. 4A), and N400 (Fig. 4B) responses.

Discussion

Concussion

Brain vital signs detected significant changes in brain function after concussion in all six metrics (Hypothesis 1), as shown in Fig. 1A. Specifically, Fig. 1B shows increased

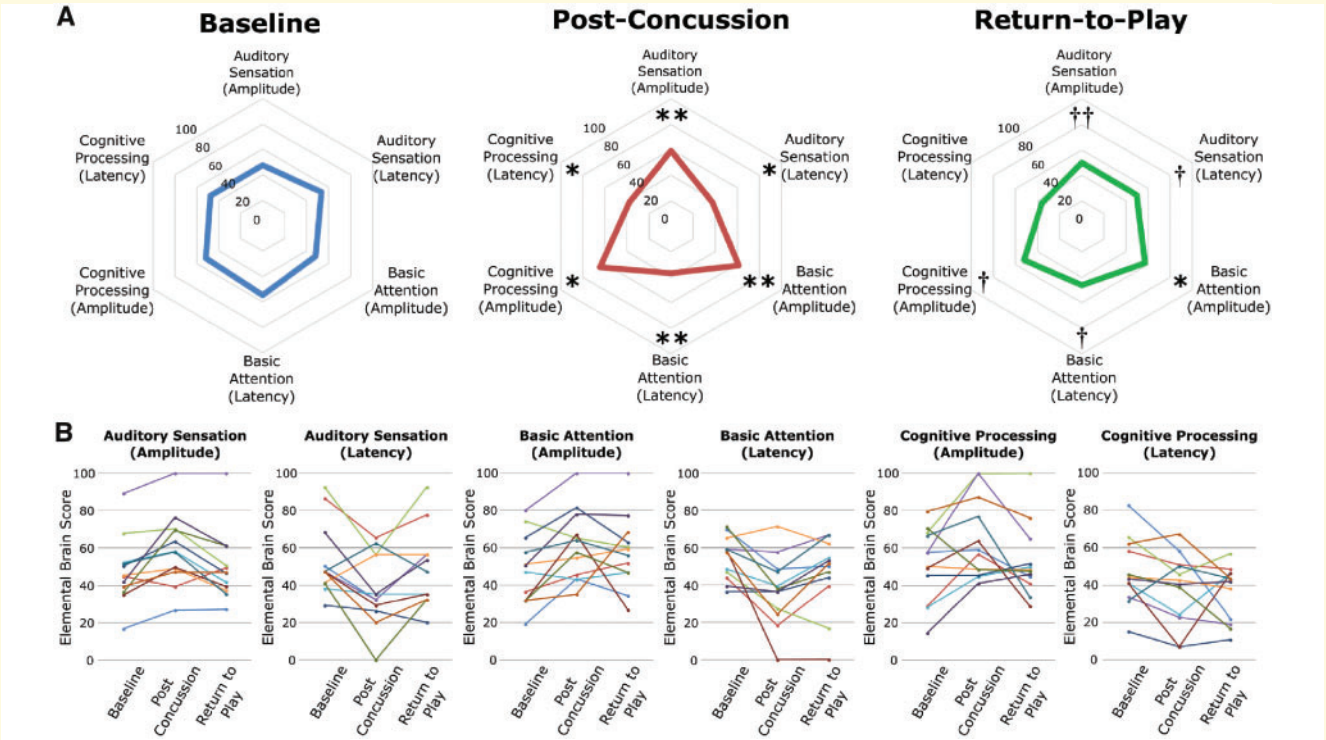

Figure 1 Brain vital signs results: concussion. (**A**) Radar profiles of brain vital signs scores at baseline, after concussion, and return-to-play time points. *$P < 0.05$, **$P < 0.01$, relative to baseline. †$P < 0.05$, ††$P < 0.01$, relative to post-concussion. (**B**) Test point comparisons for individual brain vital sign components for each participant.

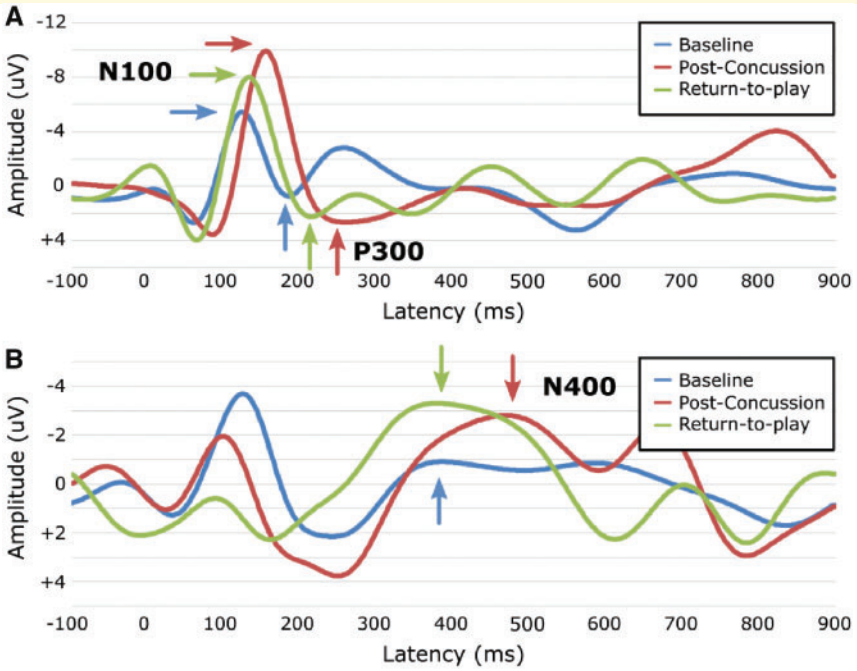

Figure 2 Representative ERP waveforms: concussion. Individual representative waveforms, showing raw ERP changes in N100, P300, and N400 ERPs resulting from Tones (**A**) and semantic word pairs (**B**) at baseline, post-concussion, and return-to-play time points.

scores for amplitude (larger voltage response) and decreased scores for latency (slower processing speed). Figure 2 demonstrates that these brain vital sign changes are present at the individual level. The directional changes in brain vital signs are closely associated with the diagnosis of injury as well as the clinical recovery and resolution of symptoms. Importantly, the basic attention amplitude (P300) measure remained significantly different from its baseline value at the return-to-play time point (Hypothesis 2). The continued impairment in basic attention suggests that concussed players who were cleared for return-to-play still had objective, physiological deficits as detected by brain vital sign assessment, with persistent attention impairments being a common symptom related to concussion (Kamins *et al.*, 2017). These results reinforce the notion that current clinical protocols should be supplemented with objective measures to more accurately assess the concussion injury spectrum and prevent players from returning to play ahead of full recovery.

Few longitudinal studies have looked at ERPs immediately post-concussion. To date, most of the literature has focused on longer-term effects of injury. The latency of the basic attention component (P300) has been shown to be delayed in the acute stage of injury (Gosselin *et al.*, 2006) as well as in athletes with a history of concussion (De Beaumont *et al.*, 2009). However, to our knowledge, the cognitive processing (N400) latency effects are novel. N400 latency delays represent a delay in semantic processing suggesting the initial demonstration of cognitive changes post-injury (Connolly and D'Arcy, 2000; Marchand *et al.*, 2002; D'Arcy *et al.*, 2003; Gawryluk *et al.*, 2010; Ghosh Hajra *et al.*, 2018).

The significant increase in response amplitudes in the acute stage of concussion also appears to be a noteworthy finding. While some studies have reported decreases in amplitude in the N100 and P300 components immediately after concussion (Gosselin *et al.*, 2006) and in athletes with a history of concussion (Moore *et al.*, 2017), Ledwidge and Molfese (2016) also reported an increase in P300 amplitude in athletes with at least one prior concussion. The authors attributed this increase to compensatory neural activity after injury to meet executive function demands. Amplitude increases have also been suggested to result from heightened sensitivity to noise or disrupted excitation/inhibition networks, both commonly reported symptoms of concussion (Giza and Hovda, 2015).

Subconcussion

We detected significant reductions in brain vital signs following a single season of ice hockey. In the absence of a diagnosed concussion, these changes underscore the importance of investigating subconcussive impairment caused by repetitive subclinical head impacts. Similar to the concussion results above, there was a significant reduction in cognitive processing latency scores, as measured by the N400 component (Connolly and D'Arcy, 2000; Marchand *et al.*, 2002; D'Arcy *et al.*, 2003; Gawryluk *et al.*, 2010). This result suggests that cognitive semantic processing may be a particularly sensitive indicator of concussion-related changes in neurophysiological processing.

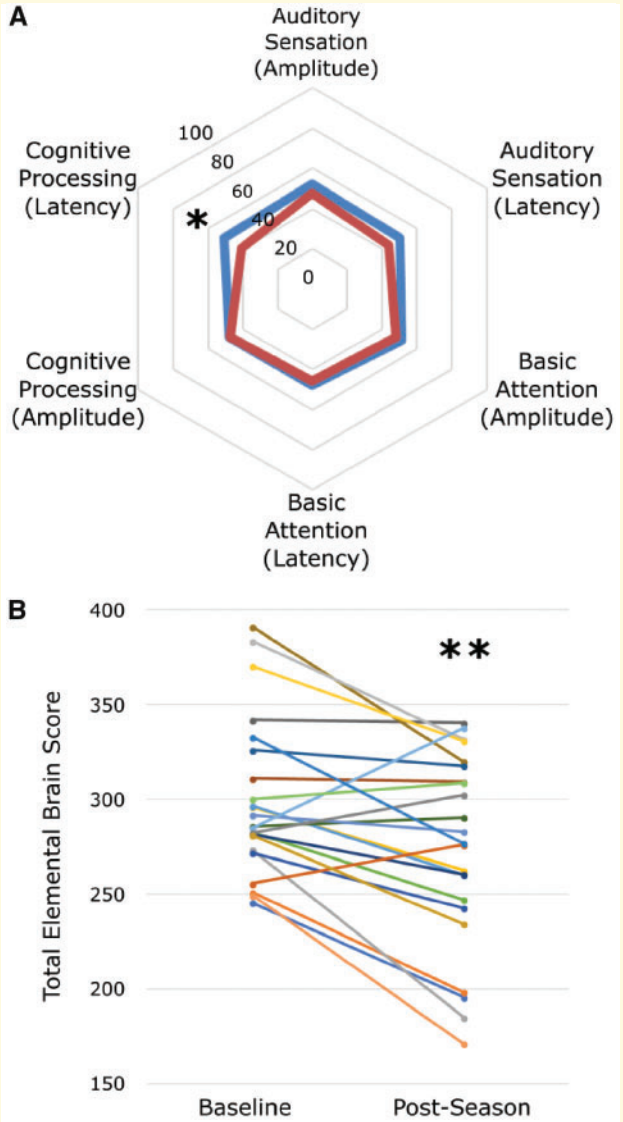

Figure 3 Brain vital signs results: subconcussion. (**A**) Radar profiles of brain vital signs scores at baseline and post-season for the non-concussed group. *$P < 0.05$. (**B**) Test point comparisons for the total (sum of) brain vital signs scores for each participant in the non-concussed group. **$P < 0.01$.

The brain vital sign changes from baseline to post-season are consistent with MRI assessments of subconcussive accumulation in athletes (Talavage *et al.*, 2010; Bazarian *et al.*, 2012). In the only similar study found using EEG and ERPs, Wilson *et al.* (2015) reported no difference between pre- and post-season in the P3b ERP. The observed effects are thus novel. As such, it will be important to understand whether this subconcussive impairment reflects a general reduction in cognitive information processing or a specific reduction in semantic processing.

Radar profiles

The radar profiles present a unique method of visualizing changes in brain vital signs over time. Baseline brain vital signs showed a hexagonal profile, with all six metrics in healthy normative ranges. Immediately following concussion, it is quite noteworthy that the systematic amplitude increases and latency decreases across all three responses resulted in a triangular profile associated with concussion. The profile largely reverted to a hexagonal shape at the return-to-play time point, but still displayed some of the persisting score impairments in relation to baseline values. This pattern of results may have significant potential as a clinical visualization tool. Current work is examining integration of the shape profiles with machine learning methods to provide further classification at the individual level.

Limitations

Some caveats to this study should be considered. A larger sample of male hockey players completed baseline testing ($n = 43$), but our findings are based on a smaller group ($n = 12$) of players who sustained a concussion, with evidence of individual variability. Larger sample sizes will be used to confirm these results through our continued research programme. Furthermore, additional time points will be collected to better characterize recovery patterns and timelines.

It cannot be assumed that the observed brain vital sign changes, while significant, fall outside normal ranges without an empirical definition of normal versus abnormal ranges for healthy controls. Furthermore, in the absence of a control group or validated test-retest reliability of the brain vital signs stimulus sequence, it cannot be assumed that the changes seen in the non-injured group are exclusively due to accumulated subconcussive impacts.

Future directions

This study represents the brain vital signs component of a larger collaborative effort to develop an objective battery of concussion assessments (Smith *et al.*, 2017). Future studies should also verify the current concussion profile across various factors such as longer-term recovery, different sports, age ranges, sex differences, and levels of participation as well as non-athlete control populations for comparison. Concussed athletes could be randomly paired with a non-concussed player from the same game for comparison with 'rink-side' normative profiles. It will also be important to characterize individual differences along with concussion frequency and symptom-related variables to better understand variations in individual, heterogeneous recovery processes post-injury. Future studies should compare brain vital signs changes to head impact exposure from video or accelerometry, as well as other structural imaging modalities such as diffusion tensor imaging.

Continuing work is assessing normative variance of healthy populations to better contextualize the extent of impairment with respect to the degree of deviations from baseline. Work is also ongoing to better characterize test-

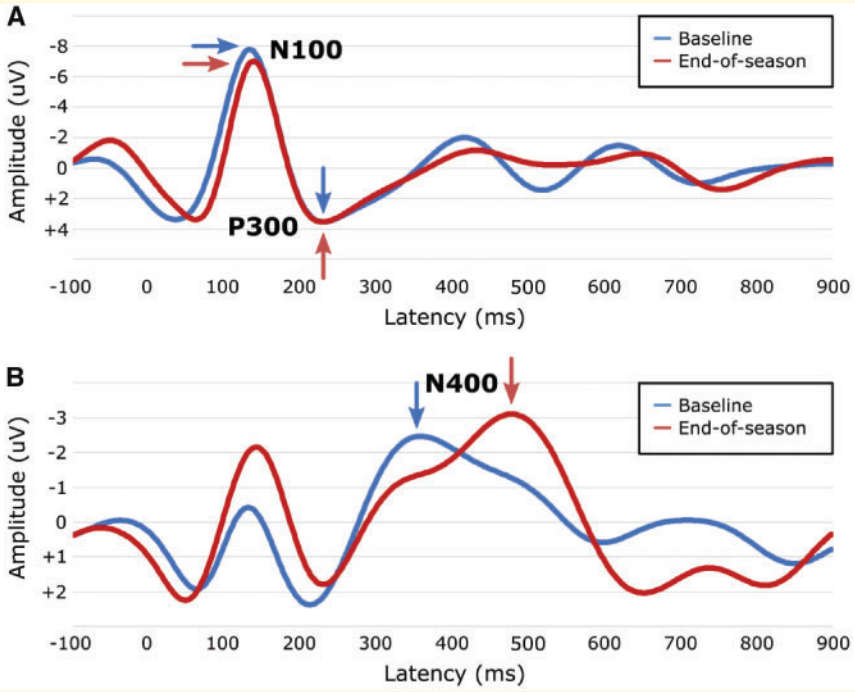

Figure 4 Representative ERP waveforms: subconcussion. Individual representative waveforms for a participant in the non-concussed group, showing raw ERP changes in N100, P300, and N400 ERPs resulting from Tones (**A**) and semantic word pairs (**B**) at baseline, and post-season.

retest reliability of the brain vital signs stimulus sequence in uninjured populations.

Clinical relevance

The results demonstrate the importance of an objective physiological evaluation of potential concussion effects over time. They address a major challenge faced by practitioners—the lack of practical, objective, evidence-based approaches deployed at the point of care to inform critical decisions for concussion management on sports. This emphasizes the need for continued implementation of the brain vital signs framework, as deployable at the point-of-care to better enable the evaluations of concussive and subconcussive impacts on brain function.

Conclusion

Brain vital signs were sensitive to the effects of concussion in hockey players, specifically detecting significantly increased amplitude and delayed latency scores for all six measures after injury. Significant changes remained in basic attention (P300) amplitude at return-to-play, indicating persistent impairment undetected by current protocols. In the non-concussed group, there was also a significant change between baseline and post-season with specific decreases in cognitive processing (N400) speed and overall total score.

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Competing interests

Some of the authors are associated with HealthTech Connex Inc. which may qualify them to financially benefit from the commercialization of a platform capable of measuring brain vital signs.

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