In-Clinic Event Related Potentials for Sports Concussion: A 4-Year Study

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ABSTRACT

Background: Numerous studies have reported changes in electrophysiological event-related potentials at various stages of recovery after concussion. While suggesting the possibility of use as a needed clinical adjunct for monitoring post concussive outcomes, questions remain about the transferability of this technology/paradigm to direct clinical application.

Objective: To determine if one of the simplest event-related potentials, the audio P300 amplitude as measured in a routine clinical setting, significantly changes from baseline after a concussive event (including a series of sub-concussive events) and if these changes persist at the beginning of return-to-play protocols when other standard measures have normalized.

Design: Cross sectional.

Participants: Three-hundred-sixty-four student athletes (17-23 years) were tracked over consecutive years, with forty-six concussion events.

Methods: P300 amplitudes and physical reaction times were analyzed for all students prior to contact sport participation, at various periods over the season, and during stages of post-injury recovery. The injury recovery values were then compared with symptom profiles, neuropsychological test results, and other clinical evaluations.

Group Results: After concussion, significant changes in P300 amplitude and physical reaction time from baseline were seen for the injured group compared to the non-injured group ($P<0.001$; Cohen's $d>1.1$). At the beginning of return to play protocols only the P300 amplitude changes remained significant ($P<0.001$, $d=1.3$), with reaction times changes no longer significant where both the neuropsychological and clinical evaluations had been deemed to have normalized.

Individual Results: All concussed players experienced a significant (>1.5SD) change in reaction time or P300 amplitude (sensitivity/specificity=100%/79%; or 88%/84% if P300 alone) and many of these players still showed large P300 amplitude changes when return to play protocols began even though reaction time had recovered (~40%>2SD P300 change in the concussion group compared to 5% in the reference group, with 20%>3SD). Most of these P300 changes had normalized by post season. Those who were slow to or did not normalize appeared to be more prone to repeat concussions and/or were part of the sub-acute group.

Conclusion: These data suggest significant changes in P300 amplitude after concussion and that these changes can normalize at a slower rate than other standard return-to-play assessments. More data are needed to determine if slow normalization relates to sub-concussive blows or repeated concussions.

Introduction

Concussion is a major source of sports injury. Because of the nature of the injury, often defined as a complex pathophysiological process, there currently exist no singular definitive, laboratory or imaging tests. [1-4] While symptoms seem to resolve within a few weeks after the event, around 10-15% of patients still report symptoms and cognitive deficits several months, to years, after the event. [5-9] To complicate matters for clinicians making return-to-play decisions,

symptom resolution may not be indicative of injury resolution, adding additional risk of injury if players return prematurely.[10] Neuropsychological assessment is one of the main clinical evaluation tools following concussion, though sometimes return to pre-concussion testing performance can take place when the subjects are still symptomatic and vice versa.[11-13] Studies have also demonstrated that some concussed players who passed clinical tests still displayed electrophysiological deficits, suggesting brain-network compensation to achieve normal functioning.[14] Similar results have recently been reported for fMRI studies where structural changes seemed to persist even as players were clinically cleared to play after concussion.[15]

To address these clinical issues, and to study the effects of concussion on cognitive brain processing, event-related potentials (ERP) have been used to assess cerebral activity following mild brain injuries (MTBI). ERPs are a measurement of the EEG signal time-locked to the onset of a given stimulus and consist of different components labeled by their polarity (P for positive or N for negative) and their time of occurrence after the stimulus in milliseconds (e.g. P300). Numerous studies have reported ERP and ERP-related differences between mTBI and control groups, even as some of these found no differences using neuropsychological measures.[16-26]

Because the variations of ERP protocols and corresponding hardware modifications are numerous, standard procedures are needed for these techniques to become clinically viable. This study, therefore, investigates one of the simplest techniques involving P300 during an audio oddball task. This technique is readily standardizable and can be implemented on a large scale, including for baseline screening.

The P300 parameters most commonly considered to be diagnostic include amplitude, latency, and peak habituation. The amplitude has been considered proportional to the amount of attentional resources devoted to a given task where latency suggested as a measure of stimulus classification speed.[27-31] While there is disagreement over the specific cognitive processes involved, shorter P300 latencies and larger amplitudes have been associated with superior information processing.[32-34] Because of wide variances and the influence of physical attributes such as skull shape or thickness, however, amplitudes may be most appropriate when used for longitudinal tracking.[34,35] Along with mTBI, P300 changes have also been reported for aging, dementia, and depressive disorders, among many others.[36] Because an increase in the P300 latency and a decrease in the P300 peak amplitude are observed in various diseases accompanied by cognitive impairment, these measurements are considered nonspecific (nosologically).

Our objective here is to test an auditory P300 protocol, using a two-tone odd-ball presentation, in a clinical setting alongside standard student athlete baseline and post-concussion evaluation procedures. The goal is to determine if the amplitude, as measured in-vivo, significantly changes from baseline after a sports concussion and if these changes persist at the beginning of return-to-play protocols when other standard measures have normalized. If so, can P300 tests help identify those who will be slow to recover?

Methods

The general analytical goal of this study was to understand the impact of concussion on measures of auditory p300 amplitudes, p300 latency, auditory response reaction time as well as assessments of visual attention and task switching. For those athletes that sustained a concussive event post-trauma, measures were compared to baseline (pre-season, no injury) assessments. In addition, stability of baseline measures was evaluated by comparison of pre- and post-season assessments in a subset of subjects without injury.

Subjects

The study followed 364 individuals aged 17-23 over the course of up to 4 sports seasons and at 5 different sites. These subjects are participants in NCAA Div. 1 men's football (172 players, representing all players from a single team), woman's soccer (29 NCAA Div. 1, representing all players from a single team), men's high school football (142 players, representing all seniors from a single team), and semipro men's ice hockey (20 players, representing all players from a single

team).

The study was approved by the Solutions Institutional Review Board and written informed consent was obtained from the participants before study intake.

Reference Subjects

Reference subjects were used to compare pre-contact to post-concussion and return-to-play groups. Here P300 voltages, along with reaction time and Trail Making measurements, were assessed during the course of other pre-contact clinical evaluations administered by sports medicine staff on 356 of the 364 players tracked. To follow the objectives of this study, which involves real clinical settings, and because the primary marker being studied is nonspecific, our exclusion criteria are minimal. The "control" group, therefore, is a reference group taken from all players participating on these teams and exclusions are limited to the 8 players who fell asleep during the first-year test (which was longer in duration as discussed later), leaving a total of 348 players comprising the baseline reference group of Table I.

While the P300 test is considered nonspecific it's still informative to compare normal changes to changes seen after a concussion event. Normal changes in the specificity tests to follow are taken from 2 groups of assorted test-retest samples, REF and ALL. The REF group comprises a convenience sample of 34 retests performed over a single season ($\Delta T=0.4\pm0.3$Yr from initial test), with a sampling of follow-up tests 1-2 weeks after the initial baseline as well as postseason tests. Exclusion criteria are again minimal where 4 tests with known changes in medication or condition (e.g. drowsiness) were excluded from the variance extraction, leaving a total 31 retests on 26 players for this group. The ALL reference group comprises a convenience sample of 70 tests from 57 players and includes the single-season tests above but also includes the excluded tests as well as other retests taken from the 348 players at various times over the course of up to 4 seasons with a sample of following-season baselines and post career tests ($\Delta T=1+-0.6$Yr from initial test). While these samples provide a reasonable real-life example of what to expect over the course of a season, or college career, for a player, it also includes multiple tests for single players so statistical caution is needed. Also, note that we have not separated out gender or age because there were not enough statistics to detect any differences between these categories and outside the scope of this study.

Concussion Subjects

Out of these 364 players, 56 concussion events occurred where a player was removed from a game or practice by a trainer or physician for a suspected concussion, including those from single events as well as repeated sub-acute events. These players were ideally tested at baseline (BASE), 24-48 hours after the event (CN, or NCN for non-qualified events), during graded return-to-play protocols (RTP), at post season (END) several months removed from the event, and at pre-contact for the following season when possible (NEXT). We use the word "ideally" here because one objective of this study is to perform these tests in real-life training room settings and so the ideal timeline could not always be followed. For example, 7 pre-contact baseline measurements were not made, leaving test-retest variability to be inferred either from post-season or the following season. Also, when the event occurred toward the end of the season there was no return to play, leaving only post-season tests in these instances.

For our purposes, establishing concussion criteria is important because relying on self-reported symptoms alone is not sufficient for the objective of this study. For example, motivations among players vary as some can mask symptoms hoping to get back into a game while others may do the opposite. Furthermore, conditions such as jaw or neck pain can also present with similar symptoms as concussion. A qualified event for this study, then, was defined as an event occurring followed by a clinical diagnosis of concussion made by a medical provider trained in the evaluation and management of concussion. These evaluations typically included deficits in one of the SCAT3 assessments such as balance or delayed recall. Out of these suspected events, 45 qualified concussion events occurred, which is consistent with the expected concussion rates for these sports. [37,38]

RTP for both the CN and NCN groups was then guided by the attending physician, utilizing an assessment and management system from the International Symposia on Concussion in Sport to evaluate return to play after concussion. [3,4] Team physicians for the University of Colorado include a performance-related psychometric exam, the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT™), administered both at baseline and post-symptom resolution. [39] For the purposes of this study, the attending physicians and players were blinded from the study results so that only current standards of care, and not the P300, were used in determining RTP. Table I summarizes the number of tests performed for each category.

Procedure

After completing a short 1-page intake form, participants were given an EEG test that included an oddball audio P300 component (discussed below). Reaction times were also measured by asking the participant to click the track pad or mouse upon hearing the oddball tone. Touch screen Trail Making Tests A and B were added in the second year. [40]

EEG acquisition and preprocessing

The electroencephalogram (EEG) was recorded using the WAVi ™ Collaborative Research Platform (WAVi Co., Boulder Co USA) and sampled at 250 Hz. The electrodes were placed according to the International 10– 20 system using caps with 19 tin electrodes (both with the WAVi Headset and Electro-cap International Inc., Eaton, Ohio, USA). Linked reference electrodes were placed at the earlobes.

To be consistent with the goal of testing a simplified platform, a 4 minute 2-tone audio oddball eyes-closed P300 protocol was used. Here, 200 common tones (1000 Hz) and 40 rare tones (2777 Hz) were delivered on a random order over the span of 4 minutes. The tone was delivered using Skullcandy™ over the ear headphones.

First Season Testing

For the first season, in order to collect other qEEG parameters in addition to the P300, an 18-min test was administered. Here three 20/100 rare/common tests were administered in succession, each separated by 3 min of eyes closed and 3 min eyes-open focused. The eyes closed qEEG data collected can be compared to those same parameters extracted during the eyes-closed P300 paradigm for further studies, including post-concussion qEEG spectral analysis. The three P300 portions of these tests can be combined into 60/300 common/rare test providing the subjects remained awake. As discussed above, documented sleeping portions of the test were discarded. For the following seasons, the testing was reduced to a single 4 min test using a 40/200 paradigm. No significant differences in the P300 parameters between the first year 18-min protocol and the 4-min protocol were observed once sleeping subjects were removed.

EEG extraction

While many methods exist for removing movement and other artifacts, we have chosen a technique of automatic artifacting that produces acceptable test-retest variance. Here EEG segments with excessive amplitude and/or frequency activities were automatically excluded from analysis on a channel-by-channel basis. Data were then visually inspected to eliminate other artifacts, such as blinks or movements synchronized with the delivery of the oddball tone. The WAVi platform is intended to be collaborative in nature and these data can be made available to qualified researchers for further analysis, including for spectral analysis discussed above or other machine-type learning techniques not investigated here. [41]

Likewise, the individual ERP features can be quantified by a variety of methods, including the extraction of P300 parameters at the extremum, taking voltage differences between common and rare at the extremum, and calculating areas under curves with some time window centered at the individual extremum. Here, again to be consistent with our goal of investigating the simplest

approaches that produce acceptable test-retest variance, the amplitudes of the P300 components reported here were measured by identifying the positive extremum in the latency range of 240–500 ms. The depth (P300V) is then extracted from the mean amplitude of all stimuli and the latency (P300T) is the delay recorded for that depth. These independent ERP epochs were baseline corrected using the 100 ms pre-stimulus period. Trials with omission or commission errors were excluded from averaging.

P300 parameters are typically extracted from the Cz, or Pz, or the average of various sites. Here we report a P300 μV that is the highest amplitude from the 6 C-P scalp sites (C3, Cz, C4, P3, Pz, P4), and the fastest P300 time (smallest latency) from these 6 C-P sites. These sites both produce an acceptable test-retest variance here but have also been noted as the most useful for mTBI identification in previous studies. [20]

Statistics

Categorical group comparisons were analyzed using paired-sample t-tests. While most studies suggest that P300 amplitude should decrease after trauma, amplitudes may increase in some cases. Because the direction is unclear, we use a 2-tailed t-test. In response to a concern over the lack of reproducibility of certain medical studies, we also set our p value cutoff to a more stringent alpha of 0.005. [42]

Successful group comparisons do not necessarily mean clinical utility. To understand potential clinical utility, it is common to report sensitivities and specificities for the ailments in question. If group comparisons are favorable we can turn our attention to sensitivities, using the expert- diagnoses as the standard, and specificities, with both the reference group and the reference group expanded to include multi-year and excluded players as the standards. Concussion studies, however, typically don't lend themselves to these kinds of neuro or biomarker studies because concussion itself is defined clinically and not physiologically (or electro-physically) and therefore the utility in development of a quantitative method of documenting post-injury electrophysiological change. Furthermore, the P300, as with most concussion assessments, is itself

a non-specific marker. Because one of our goals is to investigate changes in P300 parameters at RTP, our individual player studies will therefore also focus on comparing P300 normalization to reaction times as well as to neuropsychological and symptomatic normalization.

Results

Reference Group Test-Retest

Changes in P300 and timed performance after an event form the basis of this study and so variations in a non-concussed reference group from the same population need to be understood. Table II shows changes from baseline for this reference group as a standard deviation (SD, or 1 $\int$), into which 68% of the players fell. This creates a "normal" expectation where the statistical variation in P300 parameters here is consistent with previous studies for a normal population. [34,35,43] While it's not the purpose of this study to explore the Gaussian nature of P300 changes, these test-retest ranges provide useful endpoints for the Receiver Operator Characteristic (ROC) calculations to follow. Variations in reaction and Trail Making times include systematic errors from variations in posture, in computer interfaces (e.g. track pad vs mouse), and practice effects.

It should finally be noted that measuring change as a percentage change from baseline is one of many methods that can be employed. In this instance, information from players with lower baseline voltages can be overstated, for example a change of 50% for a player with a 3μV baseline is much less significant than a 50% change from a player at 30μV. Other methods include investigating the voltage change themselves. Using a Bland-Altman method, a change of approximately $\pm$7μV covers a 95% limit [44,45]. This method doesn't greatly change the results of this paper except that information from the lowest baselines is lost.

Between Group Results

To investigate the general performance of P300 in relation to concussion, Figure 1 shows average P300 amplitude and latency for 7 groups (BASE, NCN, and BASE, CN, RTP, END, and NEXT for the players who had a qualified concussion). Here significant differences from BASE are seen after the event at CN and RTP for P300 voltage ($P<0.001$, effect size Cohen's $d=1.1/0.8$ respectively) and these normalize by post season. No differences are seen for the NCN group and latency differences are not significant, as also shown in Figure 1.

Figure 2 plots changes from initial baseline in the P300 amplitude along with other performance measures for the various groups. These between-group statistics show significant P300 voltage, reaction time, and Trail A time changes after concussion ($P<0.001$, effect sizes Cohen's $d>1.1$ for all of these measures). Note that even though Figure 2 shows a large change at CN for Trail B, these changes were not significant at the $P<0.005$ level ($P<0.05$ $d=0.6$) partially due to the larger within-person variation for this test coupled with the fact that Trails were added in the second year, reducing the number of test subjects. Most importantly to this study, we see P300 recovery lingering at RTP ($P<0.001$, $d=1.3$) and possibly beyond, where reaction time and Trail Making changes were no longer significant. This shows a clear trend with P300V normalizing at a slower rate than performance measures, as will be discussed further with test-retest results.

Test-Retest Results on Concussed Individuals

The significant group differences seen between baseline and concussion normalize for all markers at RTP except P300V. The next question is how these translate on an individual basis. We explore this question below for the 2 strongest parameters: reaction time and voltage.

Figure 3 shows the ROC curve for the test-retests in these data for the following conditions: (i) reaction time changes from baseline for REF versus CN groups in bins of +12% change from baseline (AUC=0.80); (ii) P300 voltage changes from baseline for REF versus CN in bins of 10% change from baseline (AUC=0.92); (iii) a combined P300 voltage OR reaction time change from baseline for REF versus CN (AUC=0.95); (iv) a combined P300 voltage OR reaction time change for ALL (no exclusions) versus CN groups (AUC=0.91).

For reaction time, 68% of the concussed players slowed by more than +37% (slowed by $>1.5\sigma$ if we assume a Gaussian distribution for normal test-retest), compared to 23% in the non-concussed reference group. The resulting sensitivities and specificities are similar to that reported previously for reaction time, where the trading of a higher specificity for higher sensitivity was deemed appropriate for concussion screening.[46] Note that the 23% in the reference is higher than expectation because of a skew introduced by systematic errors associated with in-clinic use, for example a group of administrators choosing the track pad over the mouse even though the mouse was the suggested method.

Regarding P300 voltage, 88% of the concussed players showed a greater than ±30% change ($>1.5\sigma$ if Gaussian), compared to 16% in the reference group who unlike reaction time more closely followed expectation.

Adding reaction time with P300, we see that 100% of the players either had either a 1.5σ change in voltage OR reaction time at concussion, compared to 29% in the reference group, dropping to 88% true and 10% false at the 2σ level. If the clinician thinks the tradeoff of higher sensitivity is indeed appropriate in concussion screening, for example in youth sports, these markers can all provide significant screening information.

Injury Progression

While this study shows significant P300V and reaction time changes after concussion, as expected, another objective of this study is to test these parameters at the beginning of return to play protocols where clinical standards are less clear, particularly for the general practitioner often tasked with making these decisions. Evoked potentials can perhaps be most useful in providing additional

return-to-play insight, where a "when in doubt keep them out approach" may not warrant additional or more accurate tools in concussion diagnostics proper.

As with the group statistics, Figure 4 clearly shows P300V resolving slower than the standard symptom- and performance-based RTP assessments in some players, confirming expectations that electro-physical changes can linger after symptom resolution. It should be noted that of the players who had yet to normalize at RTP, roughly one half of those were from the subgroup of those who did not have a single event, rather experienced a series of sub-acute events typically associated with offensive linemen in football. These players also seemed more prone to multiple year concussions, though more statistics would be needed to confirm this result.

Case Studies

As shown, the addition of a 4-min P300 protocol that includes reaction time adds unique information to the existing protocols currently utilized in sports medicine. Topographic reports are a common way of heuristically reporting P300 amplitudes and are described in Figure 5. Here the P300 depth values (μV) are plotted in color values ranging from blue to red as given. This figure represents a player at baseline and then again after a qualified event. The raw voltage plots from which the topographic maps are derived are also shown.

Sample Test-Retest Reports

The topographs of Figure 6 illustrate a range of changes to be expected over the course of an NCAA football career for 3 players measured at BASE (pre-career) and post-career. These players were from three groups including one from a non-contact position, one from the CN group, and one from the NCN group in order of highest to least change. While the magnitude of the highest P300 voltage may vary, it appears that people retain the same general pattern (left-right or front-back) over time, particularly in the central-parietal region of interest. This finding reflects those of previous studies where a person's specific P300 morphology (waveforms of Figure 5) shows little variation over recording sessions or experiments.[34]

Sample Injury Progression Reports

The topographs of Figure 7 illustrate a range of changes seen after a concussion event for 3 players: one whose P300 voltage recovery matched that of the standard return protocols (symptom and performance), one whose P300 voltage recovery was delayed but normalized by pos season, and one whose voltage never returned to baseline. This latter player was a part of the sub-acute group, had concussions in three consecutive seasons, and never returned to initial baseline in any of these seasons.

Roughly 50% of the players showed the pattern seen in *player a* of Figure 7, with clear P300 changes at CN that had normalized to within 1.5 ∫ by the time the graded RTP protocol began. Roughly 40% of the players, however, showed patterns of *players b* or *c* who were clinically cleared by existing standards of care but still had lingering P300 deficits. Roughly 20% of these were clinically cleared with P300 anomalies that were sill >3SD reduced from initial baseline. Finally, there were six players who had CN events repeated in consecutive seasons, and four of these failed to return to less than 2 sigma of P300 voltage baseline the season before.

Discussion

Group comparisons showed significant changes from baseline in both the P300 depth, reaction time, and Trail Making times following concussion versus reference retests. By the beginning of return to play protocols, only the changes in P300 depth remained significant. Individual test-retest comparison, furthermore, showed all players at concussion had either a significant change in reaction time or P300 depth, where close to one half of these had P300 depths that had yet to recover at initiation of a graded return to play protocol. While previous studies showed attenuated P300 measures for previously concussed versus non-concussed groups, this study however is unique by adding baseline comparisons as well as being limited strictly to a younger age range

(17-23).

From these results, we can construct diagnostic measures with 100% sensitivities, but caution is needed because as is typical of concussion studies, these values are dependent on expert clinical opinions. For example, the physicians and trainers of this study knew the players well, both physically and sociologically. This greatly aided in determining if there were pre-post changes and what other factors were also involved, for example poor game performance, a history of jaw pain, etc. While we have good reason therefore to have excluded the NCN group, they were still removed from participation, albeit temporarily in most cases. The inclusion of these 12 cases would have resulted in 3 additional positives and 9 negatives, in line with our statistical expectations of normal but reducing our sensitivity of the combined P300 reaction time test from 100% to 80% (or from 88% to 71% in the case of P300 alone). Specificity claims may be even more problematic, given the multifaceted understanding of concussion. This is clearly illustrated in the SCAT3 where cognitive, balance, and neck tension assessments are included in the same test. Such are the problems associated with creating sensitivities and specificities on ill-defined ailments. (It should also be noted that there were more tests than patients, meaning in some cases a single player contributed more than one concussion or normal retest data point, thereby possible altering the statistical accuracy).

Another area for consideration is that clinical correlates of P300 amplitude attenuation after concussion are not clear. For example, if a player is deemed clinically ready for return to play but still has a p300 amplitude that is 3SD below baseline does that mean that they may be more susceptible to further injury (i.e. not yet fully recovered)? If subsequently injured, would their symptoms be more severe and longer lasting? Or, should they be held out until p300 amplitudes are more normalized? Given the current "when in doubt keep them out" approach to concussion management, perhaps a measure of ERP such as P300 at last stage of graded RTP protocol would be a next step before making the subsequent assertion of returning or holding out.

While the association between concussive traumatic events, P300 amplitudes and behavioral changes has yet to be clarified, these data lend strong support for those relationships. The value here likely will come from consideration of these data as an adjunct to good clinical histories and exams when making return to play decisions. Other diagnoses, clinical or recreational drug use, etc. can have an impact on the p300. In the end, the P300 likely will be most useful not in identifying a concussion, even though the predictive value is high, or even when it's safe to return, but rather in helping determine when it's not yet safe.

On a methodological note, this study was designed to test the P300 method in real-life clinical settings and this in-vivo data collection comes with necessary limitations. For example, the protocol was reduced from 18 to 4 min to better fit into busy schedules and keep players from falling asleep during baseline tests. Measurements at RTP were sometimes not preformed if the concussion occurred at end of the season when students disappear for the semester, and a few players failed to show up for their pre-contact baseline. Furthermore, the concussion assessment and management tools were limited to those practice standards and so these results may lack the granularity that may be achieved in a different type of study, for example a granularity that would allow focus on questions such as injury severity.

Finally, while this dataset is rich and could include other analysis methods such as spectral or machine-learning techniques, this analysis only focused on the P300 component. For that reason, we will make the raw data available to qualified researchers for further study.

Conclusions

The stability of p300 event-related potentials collected at baseline (without injury) across significant periods of time appear to remain stable with a known amount of inherent variability suggesting utility in serving as a reference for comparison with changes seen post-concussion. Using a simple 4-min procedure, our data from post baseline concussion events corresponds to significant changes in P300 amplitude, typically a reduction from baseline, with amplitudes

normalizing back to baseline at a rate slower than that observed for performance markers in many cases. Our data corroborate previous results suggesting that concussions cause measurable changes in the electrophysiological markers of brain activity, concussed participants often pass clinical tests while still displaying electrophysiological deficits, and that ERPs may constitute a useful adjunct in determining return to play for injured athletes thereby preventing early return that may be a cause for prolonged post-concussive symptomology. As more data are collected, this method may also be proven to have utility in managing more chronic mTBI cases or perhaps preventing early return that may be a cause of prolonged post-concussive symptomatology.

TABLES

Table I Assessments and mean timing of re-assessments.		
Group	***# assessments***	***timing of re-assessments (±SD)***
BASE *(initial pre-contact assessment upon enrollment into study)*	348	-
ALL *(all repeat assessments of non-injured players)*	70	310(227) days after BASE
REF *(subgroup of ALL taken within season, medication exclusions)*	31	146(110) days after BASE
CN *(initial assessment after qualified concussion event)*	33	1.6(1.2) days after event
NCN *(initial assessment after non-qualified event)*	12	1.1(0.4) days after event
RTP *(CN group at beginning of return to play)*	32	10(5) days after event
END *(CN group at postseason)*	24	94(35) days after event
NEXT *(CN group at following preseason)*	12	287(86) days after event

Table II Changes from first baseline for non-concussed groups.		
Indicator	***Change from Baseline (±SD)***	***% Change from Baseline (±SD)***
⊗P300V test-retest variation REF (within season, medication exclusion)	0(4) μV	2(20)%
⊗P300V test-retest variation ALL (multiyear, no exclusions)	0(4) μV	1(26)%
⊗P300T test-retest variation REF	9(29)ms	3(10)%
Reaction Time test-retest variation REF	37(69)ms	13(24)%
Trail A Time test-retest variation REF	-1(13)s	-2(30)%
Trail B Time test-retest variation REF	6(30)s	8(38)%

FIGURES

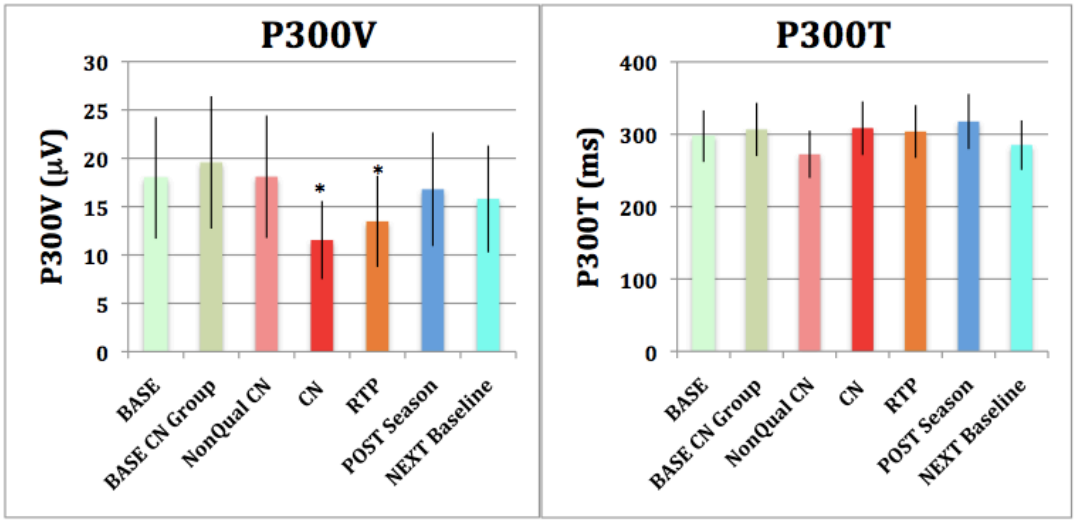

Figure 1: P300 voltage and latency for various groups, including BASE and NCN for the non- concussed players, and BASE, CN, RTP, END, and NEXT for the players who had a qualified concussion. Significant differences in P300V exist between BASE and CN/RTP (* P<0.001) with no significant differences in P300 latency for any group.

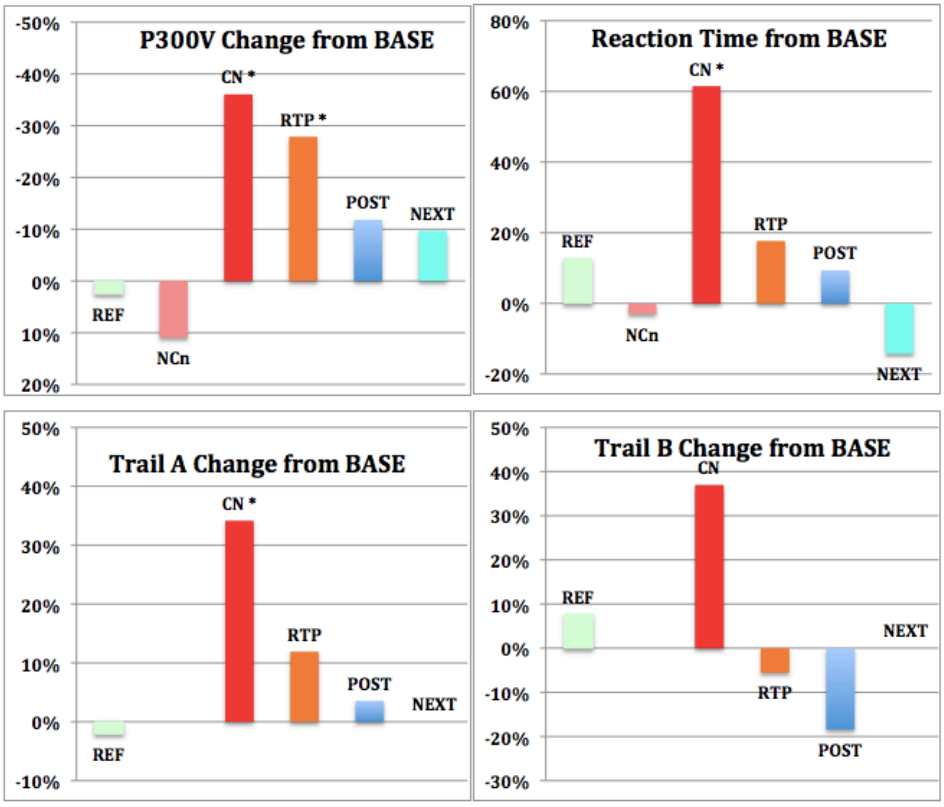

Figure 2: Changes in P300 voltage and performance parameters from initial baseline for various groups. Significant changes between baseline and CN are seen for all parameters (* P<0.001) except for Trail B. Only P300 changes remain significantly different at RTP.

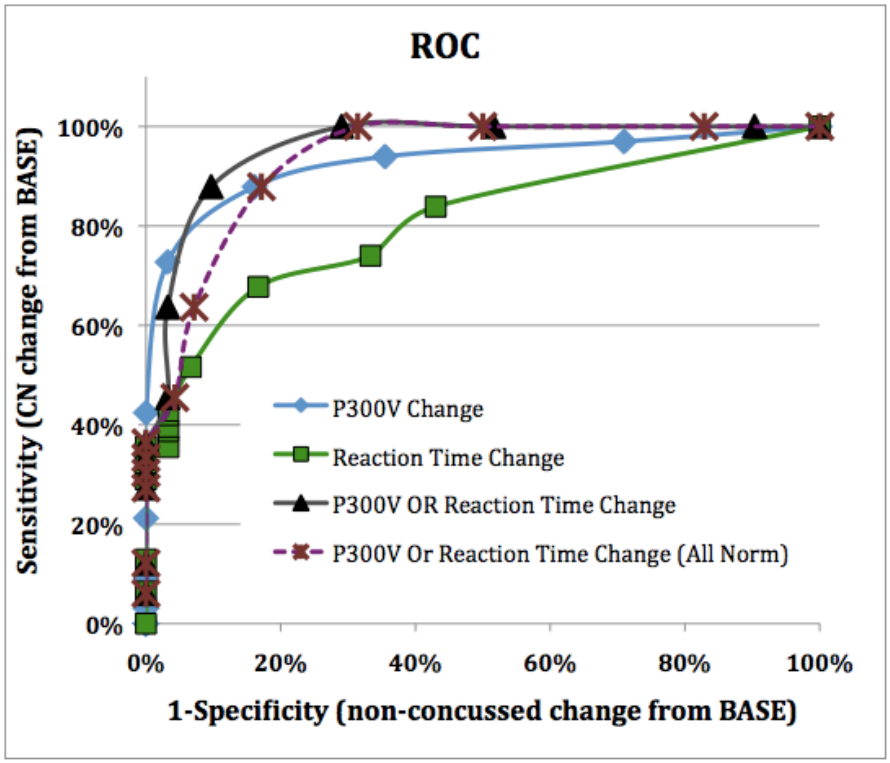

Figure 3: ROC curves comparing reaction time and/or P300 voltage changes from baseline for concussed group versus non-concussed reference groups. Specificities for the REF group (retests taken within season and with medication exclusions) are shown in the blue, green, and black curves. Specificities for the ALL group (all retests with no exclusions) are in red.

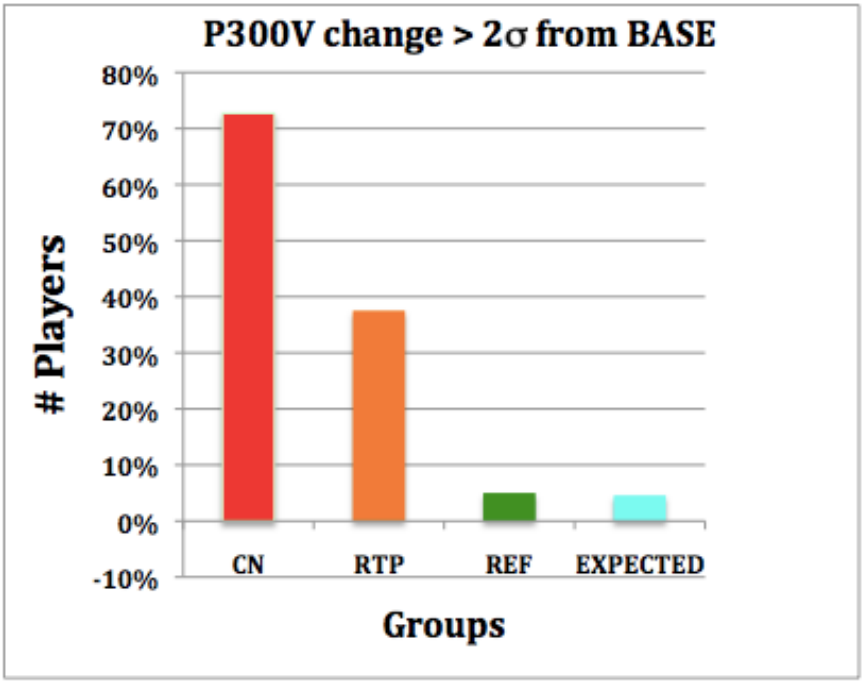

Figure 4: Number of players showing greater than ±40% (>2ó) P300 voltage change from baseline for CN, RTP, and non-concussed REF groups. Figure shows lingering P300 changes at RTP.

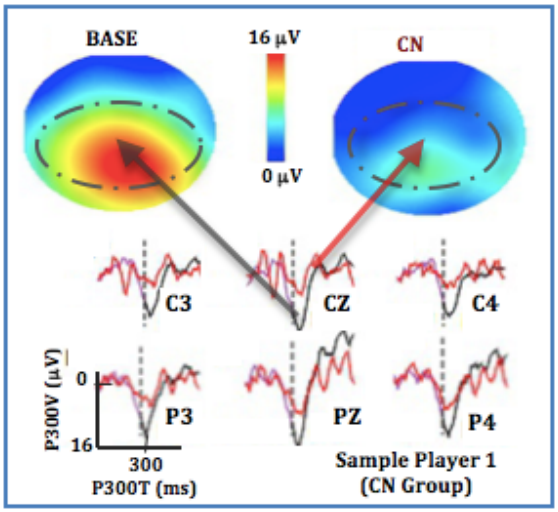

Figure 5: P300 rare tone depths for a player at BASE and CN displayed as topographs (top, with color scale as shown) and as voltage plots for the C-P region of interest (below, with black at BASE and red at CN). Vertical dotted lines are at 300msec post stimulus.

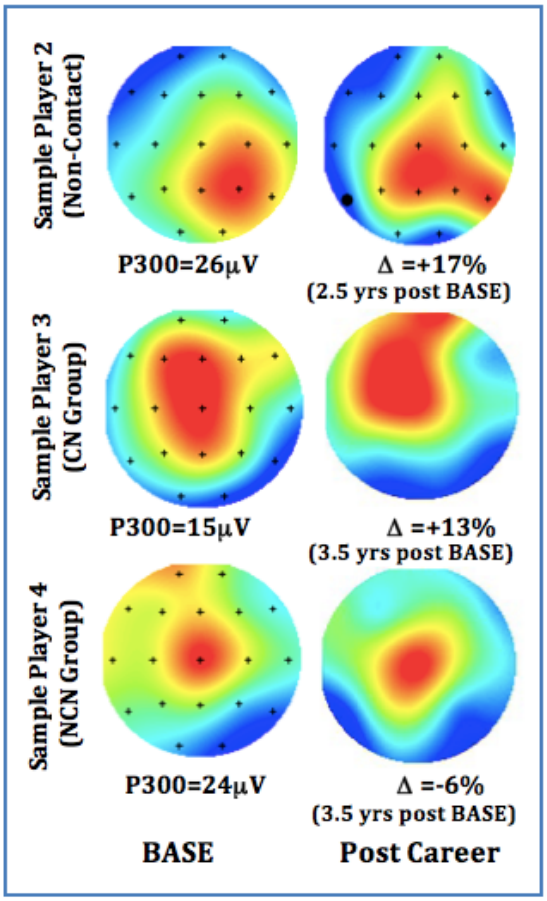

Figure 6: Sample P300 depth reports showing changes over the course of an NCAA football career for 3 players. Player 2 played a non-contact position, Player 3 was in the CN group, and Player 4 was in the NCN group.

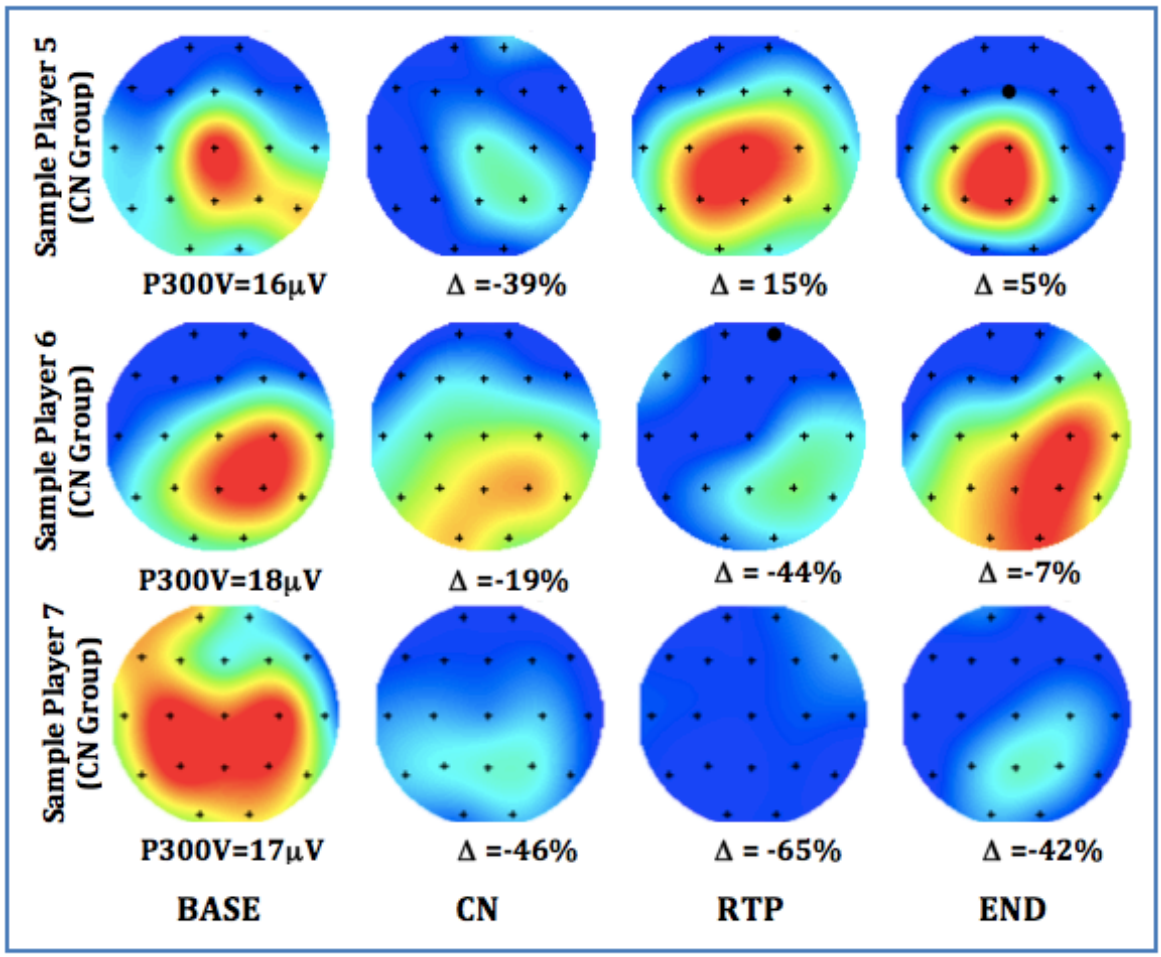

Figure 7: P300 depth reports for 3 sample players. Player 5 normalized at RTP, Player 6 did not normalize until post season (END), and Player 7 never fully normalized. Note: Player 7 had concussion events in 3 successive years.

References:

1. (GAO), U.G.A.O. VA Health Care, Mild Traumatic Brain Injury Screening and Evalluation Implemented for OEF/OIF Veterand, but Challenges Remain. (2008).
2. McCrory, P.*, et al.* Consensus statement on concussion in sport-the 5(th) international conference on concussion in sport held in Berlin, October 2016. *British journal of sports medicine* **51**, 838-847 (2017).
3. McCrory, P.*, et al.* Consensus statement on concussion in sport: the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *Journal of athletic training* **44**, 434-448 (2009).
4. McCrory, P.*, et al.* Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport, Zurich, November 2012. *Journal of athletic training* **48**, 554-575 (2013).
5. Makdissi, M.*, et al.* Natural history of concussion in sport: markers of severity and implications for management. *The American journal of sports medicine* **38**, 464-471 (2010).
6. McCrea, M.*, et al.* Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *Jama* **290**, 2556-2563 (2003).
7. Sosin, D.M., Sniezek, J.E. & Thurman, D.J. Incidence of mild and moderate brain injury in the United States, 1991. *Brain injury* **10**, 47-54 (1996).
8. Thompson, J., Sebastianelli, W. & Slobounov, S. EEG and postural correlates of mild traumatic brain injury in athletes. *Neurosci Lett* **377**, 158-163 (2005).
9. Williams, W.H., Potter, S. & Ryland, H. Mild traumatic brain injury and Postconcussion Syndrome: a neuropsychological perspective. *Journal of neurology, neurosurgery, and psychiatry* **81**, 1116-1122 (2010).
10. Cantu, R.C. Second-impact syndrome. *Clinics in sports medicine* **17**, 37-44 (1998).
11. Bigler, E.D. Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *Journal of the International Neuropsychological Society : JINS* **14**, 1-22 (2008).
12. Collins, M.W.*, et al.* Relationship between concussion and neuropsychological performance in college football players. *Jama* **282**, 964-970 (1999).
13. Maruta, J., Lee, S.W., Jacobs, E.F. & Ghajar, J. A unified science of concussion. *Annals of the New York Academy of Sciences* **1208**, 58-66 (2010).
14. Teel, E.F., Ray, W.J., Geronimo, A.M. & Slobounov, S.M. Residual alterations of brain electrical activity in clinically asymptomatic concussed individuals: an EEG study. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* **125**, 703-707 (2014).
15. Churchill, N.W.*, et al.* Neuroimaging of sport concussion: persistent alterations in brain structure and function at medical clearance. *Scientific reports* **7**, 8297 (2017).
16. Andelinovic, M., Titlic, M. & Andelinovic, D. Functional Changes of P300 Values among Young Football Players as a Measure of a Cognitive Function. *Collegium antropologicum* **39**, 641-645 (2015).
17. Baillargeon, A., Lassonde, M., Leclerc, S. & Ellemberg, D. Neuropsychological and neurophysiological assessment of sport concussion in children, adolescents and adults. *Brain injury* **26**, 211-220 (2012).
18. Broglio, S.P., Pontifex, M.B., O'Connor, P. & Hillman, C.H. The persistent effects of concussion on neuroelectric indices of attention. *Journal of neurotrauma* **26**, 1463-1470 (2009).
19. De Beaumont, L.*, et al.* Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. *Brain* **132**, 695-708 (2009).
20. Dupuis, F., Johnston, K.M., Lavoie, M., Lepore, F. & Lassonde, M. Concussions in athletes produce brain dysfunction as revealed by event-related potentials. *Neuroreport* **11**, 4087-

4092 (2000).
21. Kraus, N.*, et al.* Auditory biological marker of concussion in children. *Scientific reports* **6**, 39009 (2016).
22. Muller, A.*, et al.* Altered cognitive processes in the acute phase of mTBI: an analysis of independent components of event-related potentials. *Neuroreport* **26**, 952-957 (2015).
23. Rapp, P.E.*, et al.* Traumatic brain injury detection using electrophysiological methods. *Frontiers in human neuroscience* **9**, 11 (2015).
24. Reches, A.*, et al.* Preliminary investigation of Brain Network Activation (BNA) and its clinical utility in sport-related concussion. *Brain injury* **31**, 237-246 (2017).
25. Rousseff, R.T., Tzvetanov, P., Atanassova, P.A., Volkov, I. & Hristova, I. Correlation between cognitive P300 changes and the grade of closed head injury. *Electromyography and clinical neurophysiology* **46**, 275-277 (2006).
26. Witt, S.T., Lovejoy, D.W., Pearlson, G.D. & Stevens, M.C. Decreased prefrontal cortex activity in mild traumatic brain injury during performance of an auditory oddball task. *Brain Imaging Behav* **4**, 232-247 (2010).
27. Kramer, A.F. & Strayer, D.L. Assessing the development of automatic processing: an application of dual-task and event-related brain potential methodologies. *Biological psychology* **26**, 231-267 (1988).
28. Kutas, M., McCarthy, G. & Donchin, E. Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science* **197**, 792-795 (1977).
29. McCarthy, G. & Donchin, E. A metric for thought: a comparison of P300 latency and reaction time. *Science* **211**, 77-80 (1981).
30. Polich, J. Attention, probability, and task demands as determinants of P300 latency from auditory stimuli. *Electroencephalography and clinical neurophysiology* **63**, 251-259 (1986).
31. Wickens, C., Kramer, A., Vanasse, L. & Donchin, E. Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. *Science* **221**, 1080-1082 (1983).
32. Polich, J. Meta-analysis of P300 normative aging studies. *Psychophysiology* **33**, 334-353 (1996).
33. Polich, J. Clinical application of the P300 event-related brain potential. *Physical medicine and rehabilitation clinics of North America* **15**, 133-161 (2004).
34. van Dinteren, R., Arns, M., Jongsma, M.L. & Kessels, R.P. P300 development across the lifespan: a systematic review and meta-analysis. *PloS one* **9**, e87347 (2014).
35. Williams, L.M.*, et al.* The test-retest reliability of a standardized neurocognitive and neurophysiological test battery: "neuromarker". *The International journal of neuroscience* **115**, 1605-1630 (2005).
36. Gordeev, S.A. The Use of Endogenous p300 event-related potentials of the brain for assessing cognitive functions in healthy subjects and in clinical practice. *Human physiology* **33**, 121-133 (2007).
37. Gosselin, N.*, et al.* Brain functions after sports-related concussion: insights from event-related potentials and functional MRI. *The Physician and sportsmedicine* **38**, 27-37 (2010).
38. Zuckerman, S.L.*, et al.* Epidemiology of Sports-Related Concussion in NCAA Athletes From 2009-2010 to 2013-2014: Incidence, Recurrence, and Mechanisms. *The American journal of sports medicine* **43**, 2654-2662 (2015).
39. Iverson, G.L., Lovell, M.R. & Collins, M.W. Interpreting change on ImPACT following sport concussion. *Clin Neuropsychol* **17**, 460-467 (2003).
40. Tombaugh, T.N. Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol* **19**, 203-214 (2004).
41. Jash, A. & Oakley, D. A Low Dimensional Parameterization of Electroencephalograms

Towards the Detection of Mild Traumatic Brain Injury. *Proc 2011 Big Sky Athletic Training Sports Medicine Conference* **2011**(2011).
42. benjamin, D., berger, J., johannesson, M., Johnson, V. & al, e. Redefine Statistical significance. *nathumanbehav* **2**, 6-10 (2018).
43. Polich, J. & Herbst, K.L. P300 as a clinical assay: rationale, evaluation, and findings. *Int J Psychophysiol* **38**, 3-19 (2000).
44. Altman, D. & Bland, J. Measurement in Medicine: The Analysis of Method Comparison Studies. *Journal of the Royal Statistical Society. Series D (The Statistician)* **32**, 307-317 (1983).
45. Giavarina, D. Understanding Bland Altman analysis. *Biochem Med (Zagreb)* **25**, 141-151 (2015).
46. Eckner, J.T., Kutcher, J.S., Broglio, S.P. & Richardson, J.K. Effect of sport-related concussion on clinically measured simple reaction time. *British journal of sports medicine* **48**, 112-118 (2014).