TITLE PAGE

TITLE: Decreased high-frequency center-of-pressure complexity in recently concussed asymptomatic athletes

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Abstract

Two experiments compared multiple methods of estimating postural stability entropy to address: 1) if postural complexity differences exist between concussed and healthy athletes immediately following return-to-play; 2) which methods best detect such differences; and 3) what is an appropriate interpretation of such differences. First, center of pressure (COP) data were collected from six concussed athletes over the six weeks immediately following their concussion and from 24 healthy athletes. Second, 25 healthy non-athletes performed four quiet standing tasks: normal, co-contracting their lower extremity muscles, performing a cognitive arithmetic task, and voluntarily manipulating their sway. Postural complexity was calculated using approximate, sample, multi-variate sample, and multi-variate composite multi-scale (MV-CompMSE) entropy methods for both high-pass filtered and low-pass filtered COP data. MV-CompMSE of the high-pass filtered COP signal identified the most consistent differences between groups, with concussed athletes exhibiting less complexity over the high frequency COP time-series. Among healthy non-athletes, high-pass filtered MV-CompMSE increased only in the co-contraction condition, suggesting the decrease in high frequency MV-CompMSE found in concussed athletes may be due to more relaxed muscles or less complex muscle contractions. This decrease in entropy may associate with reported increases in intra-cortical inhibition. Furthermore, a single-case study suggested high frequency MV-CompMSE may be a useful clinical tool for concussion management.

Key terms

mTBI; concussion; brain injury; postural stability; entropy

Introduction

Sport-related concussion has been recognized as a health concern, and balance assessments are an integral part of concussion assessments to ensure athletes with previously disrupted balance are fit to return-to-play (RTP) [1-3]. Compared with traditional clinical balance measures, nonlinear dynamic analysis of postural stability has shown greater sensitivity in identifying postural control differences post-concussion [4]. One example of nonlinear dynamic balance control is the complexity of postural control calculated by applying entropy algorithms to center-of-pressure (COP) time-series. Postural complexity characterizes the unconstrained patterns of postural sway, and theoretically more complexity (i.e. random fluctuations) represents a more robust control system capable of rapidly responding to perturbations [5].

Using approximate entropy (ApEn), which characterizes complexity by quantifying the repetition of patterns [6], Cavanaugh et al. [7] detected less postural complexity (lower ApEn values) in concussed athletes 48 hours and 96 hours [8] after injury despite normal clinical balance performance. These changes in complexity appear to be persistent; compared to individuals with no concussion history, less complexity in the COP time-series has been reported in athletes greater than nine months post-concussion [9, 10] and in adolescents with post-concussion symptoms an average of 49 days post-injury [11]. However, longitudinal information on postural complexity changes that may occur in the sub-acute period is lacking.

To date, only ApEn and SampEn have been reported to assess the complexity of postural stability post-concussion, but other entropy analyses may be more appropriate for COP complexity. Examining complexity over multiple timescales can improve the sensitivity to postural control changes [12]. Because COP data are multi-dimensional with anteroposterior

(AP) and mediolateral (ML) components, multivariate entropy methods may also be appropriate to account for potential correlations between the directions [13].

In addition to the variety of complexity measures, data processing techniques can influence the calculation and interpretation of COP entropy [14, 15]. Several studies have examined the entropy of low-frequency (<10 Hz) COP signals [4, 8, 9, 16-19]. However, this frequency spectrum is concentrated below 1 Hz [20], which can create non-stationarities and leave an insufficient number of cycles if the data length is short (e.g., <1 minute). Both of these technical issues can distort the entropy calculation [21, 22]. Thus, other studies have removed lower frequencies (<1 Hz) through filtering [22, 23] or increment differencing methods [15, 24]. The retained high frequency (>1 Hz) content provides enough cyclic repetitions and stationarity to provide valid entropy calculations. However, interpreting these high-frequency fluctuations is challenging. Past research has examined these approaches independently, but the efficacy of the low vs. high frequency approaches at differentiating tasks or populations remains unclear [25].

We addressed three questions pertinent to future concussion research specifically, and postural control in general: 1) Are there prolonged postural control complexity differences between recently concussed and healthy athletes during the timeframe immediately post-RTP?; 2) Which entropy methods can best detect such differences?; and 3) How do the interpretations of such complexity differences change when analyzing the different frequency content of a COP signal? We hypothesized that concussed athletes would persistently exhibit less postural complexity than controls and that multi-scale entropy methods would best detect such differences.

Materials and Methods

Participants

Six Virginia Tech varsity athletes who had recently suffered a concussion participated in the first experiment, along with 25 varsity athletes with no concussion history (Table 1). All concussed athletes were clinically diagnosed by a Virginia Tech Sports Medicine physician and referred to this study by their athletic trainer. Healthy athletes were recruited from various sports. Exclusion criteria for both groups included any unresolved acute lower extremity injury, history of mental illness or diagnosed cognitive impairment. Recently concussed participants were tested weekly for six weeks, at means (SD, *n*) of 7 (0, 5), 16 (1, 3), 23 (2, 5), 29 (1, 5), 36 (2, 4), and 45 (3, 5) days post-concussion. Not all participants completed all six sessions because of scheduling conflicts. Healthy athletes were tested one time.

Insert Table 1

One healthy athlete was found, after testing had been completed, to have suffered a concussion 23 days prior to testing and was therefore excluded from the healthy group. However, this single athlete's data (H-C) was retained to investigate the use of entropy as a clinical predictor of recent concussions. A sample of 25 physically active young adults, who were not varsity athletes, were recruited from Virginia Tech and the surrounding community to participate in a companion experiment. Exclusion criteria remained unchanged. Non-athlete participants reported spending a mean of (SD) 3 (2.8) hours per week performing moderate exercise (e.g., running, biking) and 4 (3.6) hours per week doing intense physical activity (e.g., weight lifting, interval swimming / running). All participants gave informed written consent and all procedures and protocols were approved by the Virginia Tech Institutional Review Board.

Procedures

Concussed and healthy athlete participants were instructed to stand barefoot with their feet together on a force platform (Model #BP400600-2K, AMTI, Watertown, MA, USA) while

their postural stability was measured for two minutes. Participants were instructed to close their eyes and “stand still” with their arms at their sides for two minutes. Data was sampled at 1000 Hz.

Non-athlete participants performed the same quiet standing task described above for the concussed and athlete groups. Each of these participants also performed three additional quiet standing trials with additional task instructions in each, to: 1) “contract all your leg muscles as hard as possible for the full two minutes while standing still” (co-contraction); 2) “silently count down from 800 by sevens” (cognitive task); and 3) “randomly control your body sway” (random sway). Participants were given further clarification for the random sway condition, to sway in a manner that would be undetectable to an outside observer. The four conditions were chosen to address situations that may be undetectable using clinical balance metrics and represented greater muscle stiffness, a greater demand on attentional and cortical resources, and a larger voluntary contribution, respectively. All participants performed normal quiet standing first, with the following three tasks randomized in order across participants. Multiple practice attempts were allowed for each condition to ensure participants were accustomed to the tasks, and adequate rest was given for all participants following each condition.

Data Analysis

For each postural stability measurement, data were downsampled to 100 Hz and the AP and ML components of the COP displacement were computed. Each COP displacement data series was further processed to yield a low-frequency COP time-series (LF) to match previous concussion studies using COP complexity [8] and a high-frequency COP time-series (HF) to remove non-stationarities. First, raw COP data were low-pass filtered by removing intrinsic mode functions with frequencies above 10 Hz, using bivariate empirical mode decomposition

[26]. The resultant COP velocity and 95% ellipsoidal area were calculated from the LF COP time-series. Raw COP data were also high-pass filtered removing intrinsic mode functions with frequencies below 1 Hz. High-pass filtered COP displacement was chosen over other stationary COP time-series, such as COP velocity, to investigate how the presence of non-stationarities affects the inferences drawn from the results.

Complexities of both the HF and LF COP time-series were calculated using four distinct entropy methods. For entropy analyses, the LF COP signal was further downsampled to 10 Hz, as higher frequency content had been removed. For each HF and LF COP time-series, ApEn and SampEn were calculated for AP and ML components separately. Details on the ApEn [6] and SampEn [27, 28] methods can be found in previous literature. Multi-variate SampEn (MV-SampEn) [13] and multi-variate multi-scale composite SampEn (MV-CompMSE) [13, 29] were calculated using the two-dimensional (AP and ML) COP time-series. MV-CompMSE uses a coarse-graining procedure to calculate the SampEn over several time-scales within the signal [29], whereas ApEn, SampEn, and MV-SampEn only calculate complexity over one specific time-scale. For all analyses, a template length $m = 2$ and radius $r = 0.2$ times the standard deviation of the time-series were used. The areas under the complexity vs. scale curve were used as complexity indices for MV-CompMSE.

To identify changes in the COP frequency spectrum, the power spectral densities of the raw COP series were computed using fast Fourier transforms. The power of the HF bandwidth (>1 Hz) was calculated relative to the overall power of the signal. All analyses were performed in MATLAB (MATLAB 2015a, The MathWorks, Inc., Natick, MA, USA).

Statistical Analysis

Concussed and Healthy Athletes

Univariate descriptive statistics of each outcome were calculated for healthy and for concussed groups at each point in time. Independent-sample t tests were used to compare the concussed group at each time to the single measurements from the healthy group. Methods that were unable to detect significant differences between concussed and healthy groups at least once were discarded from further analysis.

Logistic regression models were created for each retained outcome to classify concussed and healthy groups based on postural complexity. One combined regression model used all retained entropy outcomes as predictors. The logistic models were used to predict the probability that H-C (athlete whose concussion was discovered after data collection) had sustained a concussion. Since H-C had sustained a concussion, higher probabilities indicated more potential utility as a clinical assessment tool.

Non-athlete Healthy Adults

To compare the effect of standing condition on each outcome, generalized estimating equations (GEEs) were fit for all retained entropy outcomes. A compound symmetric covariance structure was used for all models, which assumes equal correlation between all within-subject measurements. Model assumptions were verified from residual analyses. A two-sided significance level of 0.05 was used throughout, and all statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Concussed and Healthy Athletes

No significant differences in any outcome were found between groups at week 1, though the concussed group had significantly less HF MV-CompMSE at weeks 2 ($p < 0.001$), 3 ($p = 0.043$), 4 ($p = 0.005$), and 6 ($p = 0.039$), with differences at week 5 approaching significance ($p =$

0.055) (Figure 1). The only LF outcomes that significantly differed between groups occurred at week 6 for AP ApEn ($p = 0.018$) (Figure 2) and SampEn ($p = 0.016$), with lower values of both among concussed athletes (Figure 3). No significant differences in COP area or resultant velocity were found at any time ($p > 0.09$). No significant differences in relative power were found between groups in weeks 1 through 5 ($p > 0.09$), but a significant increase in the relative power above 1 Hz was found in the AP direction at week 6 ($p = 0.014$).

Insert Figures 1-3

From fitting logistic regression models, HF MV-CompMSE was the best individual predictor with a probability of 0.75 that H-C had suffered a recent concussion. The other retained outcomes – LF AP ApEn, and LF AP SampEn – yielded probabilities of 0.61 and 0.59, respectively. The logistic regression model including HF MV-CompMSE, LF AP ApEn, and LF AP SampEn yielded a probability of 0.80, a slight improvement over the single predictor of HF MV-CompMSE.

Non-athlete Healthy Adults

Univariate descriptive statistics for all retained measures are presented in Table 4 in each condition. Compared to normal quiet standing, the co-contraction condition produced higher HF MV-CompMSE ($p < 0.001$), LF AP ApEn ($p = 0.001$), and LF AP SampEn ($p = 0.002$). No differences in complexity were found between normal standing and cognitive or random conditions. The co-contraction condition produced a significant increase in relative power >1 Hz in both the AP ($p < 0.001$) and ML ($p < 0.001$) directions compared to normal standing. The random sway condition decreased relative HF power in the ML direction only ($p < 0.001$), while the cognitive task condition did not produce any significant changes in the HF relative power.

Insert Table 4

Discussion

We evaluated the postural control complexity of recently concussed and healthy athletes and physically active non-athletes to identify and interpret postural control abnormalities that are present 1-6 weeks post-concussion. In agreement with previous evidence [7-10], concussed athletes exhibited less complexity compared to healthy athletes. Prior studies had identified decreased complexity among athletes 48-96 hours post-concussion [7, 8], and over nine months post-concussion [9, 10]. This study presents the first direct evidence that postural stability complexity remains affected by concussion in the timeframe surrounding RTP (1-6 weeks post-concussion). This result strengthens the growing body of evidence documenting post-concussion postural deficits that persist beyond the recovery of clinical signs and symptoms [9, 10, 30-33].

The existence of several entropy [12] and data processing methods [14, 15] prompted a comparison to identify the most appropriate postural complexity method for concussion management. When analyzing the low-frequency COP signal, ApEn and SampEn were the only methods to detect significant differences between concussed and healthy groups, and these were only able to do so at week 6. Our LF ApEn results are partially supported by prior work using ApEn on LF COP signals post-concussion [7-10]. Here, however, LF ApEn only identified significant differences between groups at one point in time (week 6), suggesting LF ApEn may not be the most sensitive entropy method to use in concussion management. Conversely, HF MV-CompMSE identified significantly less complexity in concussed athletes over several points in time and provided the most consistent differentiation of the concussed and healthy groups.

This change in complexity over a HF spectrum (1.1-33.3 Hz) can be challenging to interpret as it is often associated with artificial noise when analyzing human movement [34]. However, ballistic muscle contractions in the soleus and gastrocnemius occur over a portion of

this relatively high frequency spectrum (1-3 Hz) [35, 36] and comprise a critical active component for maintaining upright stance [37, 38]. Additionally, COP spectral content up to 9 Hz can be affected by visual feedback, indicating postural control mechanisms at these higher frequencies [39]. The contribution of ballistic contractions to the HF COP complexity is further supported by the LF ApEn and SampEn results. The parameter selection of $m = 2$ resulted in an examination of patterns 3 points long to replicate the methods of prior investigations on post-concussion COP complexity [7, 8]. Thus, the single-scale LF entropy metrics actually quantified the complexity over 333 ms time scales (3.3 Hz), consistent with the time scale of unidirectional changes in muscle length [36].

While it is possible that the decreased complexity in concussed HF COP is due to more ordered ballistic muscle contractions, such movements only explain a small portion of the HF spectrum analyzed here. Monosynaptic reflex responses, which occur over faster timescales, 53 to 65 ms (15-18 Hz) [40, 41], also contribute to the regulation of ankle angle with short-latency torques opposing stretch [42]. Manor et al. [23] found multi-scale complexity changes in COP time-series over even shorter time scales of 8-33 ms (30-125 Hz), suggesting joint stiffness may also contribute to multi-scale complexity over HF bands. Postural control over these high frequency bands (11-33 Hz) has also been supported by the presence of an anti-persistent fractal scaling process, suggesting an “ON/OFF” intermittency model for the ballistic muscle contractions [43], and the presence of a “proprioceptive dead zone” [44]. Combined, this suggests that recently concussed athletes experience a decline in HF postural control complexity caused by a degradation of one or more multi-scale processes, or a change in the interaction between processes.

There is physiological evidence to support this decreased HF postural control complexity post-concussion. Increased intra-cortical inhibition in the motor cortex [45] and longer cortical silent periods following transcranial magnetic stimulation [46] are indicative of alterations to the corticospinal excitability and / or inhibitory capacity post-concussion [47]. This increased cortical inhibition has been associated with decreased muscle stiffness [48-50] and inhibition of prepared actions [51], which would be consistent with the present results. Though previous authors suggested that decreased COP complexity post-concussion may be due to increased co-contraction or stiffened musculature as an adaptation to decreased balance control [8, 52], we found an increase in complexity when non-athlete participants were instructed to co-contraction their lower extremity muscles. Thus, co-contraction and muscle stiffness appear positively correlated with HF multi-scale entropy and complexity. Based on these results, prior cortical excitability studies [9, 45-47], and increased postural complexity after trans-cranial direct current stimulation [53], the decrease in COP complexity post-concussion may be caused by decreased co-contraction, more relaxed musculature, and /or potentially more cortical inhibition / less excitability to initiate corrective ballistic contractions. However, future investigations that include measures of muscle activation and length and cortical excitability / inhibition are needed to confirm this result.

We did not find an effect of a cognitive task on postural complexity, contrary to other reports [23, 53]. However, the use of an unarticulated cognitive task [54] and the influence of different signal processing techniques and timescales of interest across the studies may have contributed to the different effects of cognitive tasks.

This study had several limitations. First, the small sample size limits the generalizability of this study to broader populations. However, the current results are the first evidence of

persistent decreases in complexity over the subacute timeframe post-concussion in asymptomatic athletes. Second, while data from clinical assessments, such as the Sport Concussion Assessment Tool 3 (SCAT3), were collected as part of the standard concussion protocol at Virginia Tech, those data were not presented here as the majority of differences in postural complexity occurred after all athletes were asymptomatic and clinically healthy. The initial severity of clinical symptoms may be associated with the duration of time that postural complexity remains abnormal [55]. However, the small sample size in this study prevented any exploratory analysis in this regard. Additionally, pre-concussion measurements were not obtained from the concussed group. It is possible that lower complexities in the concussed group were natural differences in those individuals.

While we drew conclusions from prior evidence regarding muscle contraction, stiffness, and cortical excitability, such outcomes were not measured here. Therefore, greater muscle co-contraction and stiffness could only be speculated based on the non-athlete co-contraction condition. The combined results from the two experiments provide insight into potential mechanisms for postural changes, but do not directly explain why concussed athletes exhibited abnormal complexity values. Further, this insight is restricted to the specific entropy methods described here, mainly HF MV-CompMSE of the COP displacement; other entropy methods or time-series (e.g., COP velocity) may have different interpretations. Future studies should examine a direct connection between electrophysiological measures and postural complexity.

While the clinical implications of decreased HF postural complexity post-concussion are unclear, these results encourage further study of HF postural complexity as a potential clinical test in RTP decisions. A single case-study presented here supported this utility, with postural complexity offering moderate utility in identifying an athlete with a previous concussion,

without the use of any other clinical tools. These results indicate that postural complexity presents promise and is worthy of inclusion in future longitudinal studies.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Figure Captions:

Figure 1. Longitudinal results of HF MV-CompMSE. Solid black bars show means and one SD error bars of concussed athletes as each week. The dotted black line indicates the mean of the healthy athletes. The athlete H-C is represented with a gray bar. Significant differences between the healthy group are shown with an asterisk (*). Significant differences ($p < 0.05$) between groups were found at weeks 2, 3, 4, and 6.

Figure 2. Longitudinal results of LF AP ApEn. Solid black bars show means and one SD error bars of concussed athletes as each week. The dotted black line indicates the mean of the healthy athletes. The athlete H-C is represented with a gray bar. Significant differences between the healthy group are shown with an asterisk (*). Significant differences ($p < 0.05$) between groups were found at week 6 only.

Figure 3. Longitudinal results of LF AP SampEn. Solid black bars show means and one SD error bars of concussed athletes as each week. The dotted black line indicates the mean of the healthy athletes. The athlete H-C is represented with a gray bar. Significant differences between the healthy group are shown with an asterisk (*). Significant differences ($p < 0.05$) between groups were found at week 6 only.

Table 1. Demographic information of each participant group; values are means (SD). Concussed athletes were cleared for full RTP after complete resolution of clinical symptoms and after completing the graduated RTP protocol [56]. Full RTP here refers to full medical clearance to participate in games and practices.

Group	Gender	Height (cm)	Mass (kg)	Cleared Full RTP (days)
Concussed	2M / 4F	167.6 (6.5)	65.6 (8.3)	11 (4)
Healthy Athletes	1M / 23F	164.9 (10.3)	68.8 (9.0)	-
Healthy Non- Athletes	17M / 8F	173.7 (9.0)	71.7 (15.0)	-
H-C	1F	170.2	75.1	18

Table 2. Means (SD) for select entropy outcomes for each standing condition in healthy non-athletes, including the relative power of the HF bandwidth. Conditions significantly different ($p < 0.05$) than normal are shown in bold.

	Normal	Co-contraction	Random Sway	Cognitive Task
LF AP ApEn	0.71 (0.11)	0.83 (0.21)	0.72 (0.15)	0.72 (0.14)
LF AP SampEn	0.63 (0.12)	0.76 (0.23)	0.64 (0.16)	0.65 (0.14)
HF MV-CompMSE	7.76 (2.43)	10.44 (2.76)	8.69 (2.04)	7.72 (2.53)
HF AP Relative Power (%)	2.91 (1.38)	5.16 (3.91)	3.28 (2.81)	3.21 (2.00)
HF ML Relative Power (%)	5.66 (3.02)	9.06 (5.31)	3.63 (2.12)	5.94 (3.29)