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One season of head-to-ball impact exposure alters functional connectivity in a central autonomic network

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Abstract

Repetitive head impacts represent a risk factor for neurological impairment in team-sport athletes. In the absence of symptoms, a physiological basis for acute injury has not been elucidated. A basic brain function that is disrupted after mild traumatic brain injury is the regulation of homeostasis, instantiated by activity across a specific set of brain regions that comprise a central autonomic network. We sought to relate head-to-ball impact exposure to changes in functional connectivity in a core set of central autonomic regions and then to determine the relation between changes in brain and changes in behavior, specifically cognitive control. Thirteen collegiate men's soccer players and eleven control athletes (golf, cross-country) underwent resting-state fMRI and behavioral testing before and after the season, and a core group of cortical, subcortical, and brainstem regions was selected to represent the central autonomic network. Head-to-ball impacts were recorded for each soccer player. Cognitive control was assessed using a Dot Probe Expectancy task. We observed that head-to-ball impact exposure was associated with diffuse increases in functional connectivity across a core CAN subnetwork. Increased functional connectivity between the left insula and left medial orbitofrontal cortex was associated with diminished proactive cognitive

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CRediT authorship contribution statement

Derek C. Monroe: Conceptualization, Formal analysis, Software, Writing - original draft, Writing - review & editing, Visualization. **Robert S. Blumenfeld:** Conceptualization, Investigation, Project administration, Writing - review & editing. **David B. Keator:** Software, Validation, Writing - review & editing. **Ana Solodkin:** Conceptualization, Formal analysis, Writing - review & editing. **Steven L. Small:** Conceptualization, Project administration, Writing - review & editing, Funding acquisition.

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control after the season in those sustaining the greatest number of head-to-ball impacts. These findings encourage measures of autonomic physiology to monitor brain health in contact and collision sport athletes.

Keywords

Head impact; Concussion; Collegiate sports; Autonomic function; Cognitive control

1. Introduction

Approximately 1.4% of men competing in collegiate soccer sustain a concussion each season (Marshall et al., 2015), typically as a result of player-to-player or player-to-ground contact (Boden et al., 1998). Strategic use of the head to direct the ball contributes to this risk (Gessel et al., 2007). Although head-to-ball impacts rarely cause a concussion, chronic exposure is suggested to have neurological consequences for athletes many years later (Ling et al., 2017). This encourages active monitoring of soccer player brain health to prevent the long-term sequelae of these impacts. Attempts to inform soccer-specific protocols by relating repetitive head-to-ball impact exposure to symptoms and/or to performance on neuropsychological batteries has been largely unsuccessful (Caplan et al., 2016). Studies of other contact and collision sport athletes have revealed that subtle changes in cognitive function are strongly associated with physiological measures of injury (e.g., blood or neuroimaging biomarkers), but not with explicit measures of head impact exposure (Mainwaring, 2018). Thus, studies that take a psychobiological approach to understanding the effects of these impacts on the brain and on behavior have the potential to inform both a biological definition of these injuries and scientifically grounded methods for monitoring athlete brain health.

In contrast to the higher-order cognitive functions that are assessed by traditional neuropsychological tests, regulation of homeostasis via the autonomic nervous system (ANS) is a basic brain function that is also disrupted after concussion. Imbalance between sympathetically and parasympathetically mediated cardiac control is observed in concussed athletes compared to healthy controls (La Fountaine, 2018; La Fountaine et al., 2016). One study reports a negative association between heart rate variability, a surrogate measure of cardiovagal control (Berntson et al., 1997), and head impact exposure in asymptomatic football and hockey players across a single season (Smirl et al., 2017). Other work has suggested that a combination of buffering, negative feedback regulation, and feed-forward regulation in a central autonomic network (CAN) may be affected by mild brain injury, but these central adaptations may not be reflected in heart rate variability or other downstream measures of ANS function (Goldstein and Kopin, 2017).

Brain functions, including the autonomic regulation of homeostasis, arise from integrated activity across complex networks (Bassett and Sporns, 2017) that can be observed through correlated changes in the blood oxygen level dependent (BOLD) signals across spatially distinct brain regions. The CAN is a network of specific brainstem, subcortical, and cortical regions that integrates afferent visceral and environmental information and regulates efferent

neural and endocrine responses (Bennaroch, 2014; Critchley and Harrison, 2013). For the purposes of this study, we defined the CAN by a core set of regions that are most likely to be directly involved in cardiovascular regulation (Beissner et al., 2013): periaqueductal grey, hypothalamus, amygdala, ventral anterior insula, and medial prefrontal, medial orbitofrontal, and subgenual anterior cingulate cortices. We excluded regions that are part of an 'extended' CAN and likely important for the broader integration of autonomic function with nociceptive, sensorimotor, and emotional processing (e.g., posterior insula, thalamus, basal ganglia, supplementary motor area). The quality and quantity of the correlated signals that comprise the CAN are affected by endogenous and exogenous changes in milieu. In the athletic setting, for example, the CAN is sensitive to the sensorimotor demands of baseball training (Sie et al., 2019) and cardiorespiratory demands of aerobic training (Al-Khazraji and Shomaker, 2018) and has been associated with symptoms commonly reported after a sport-related concussion (Mayer et al., 2011; Thayer et al., 2012). Chronic disruptions in the circuitry underlying autonomic control are implicated in white matter loss (Galluzzi et al., 2009), decreased brain perfusion (Allen et al., 2015), and cerebrovascular dysfunction, which are collectively implicated in the development of neurological dysfunction (Goldstein et al., 2002).

Another important functional connectivity network, the "default mode" network (DMN), which becomes more salient when an individual is not focusing attention on a specific task, can also be modulated by repetitive head impact exposure (Abbas et al., 2015; Johnson et al., 2014). However, in these studies functional connectivity was based on bivariate correlations, which are biased by phase lags between BOLD time series (Goelman et al., 2014) that may be caused by different regional sensitivities to cerebral blood flow and volume that alter the hemodynamic response function (Buxton, 2004). Using measures which are sensitive to these lags may be particularly salient for the study of brain injury, as changes in cerebral blood flow and cerebrovascular reactivity have been observed after mild traumatic brain injuries (Len and Neary, 2011; Lin et al., 2016) and after a season of repeated head impact exposure in soccer players (Svaldi et al., 2020).

Ultimately, it is not known to what extent oscillatory activity in the CAN or DMN can impact development of a scalable monitoring protocol in athletics. Beyond cardiovascular measures of autonomic function, the regulatory capacity of the ANS is associated with cognitive control—the ability to coordinate cognitive resources and goal-directed behaviors (Braver, 2012)—via descending cortical projections that are responsible for parasympathetic control of the heart (Thayer and Lane, 2000). Importantly, ascending CAN projections to the cortex regulate sympathetic outflow and, as part of the ascending arousal network, are also implicated in cognitive control (Fang and Wang, 1962; Zamrini et al., 1990; Tops et al., 2010). After concussion, cognitive control is diminished acutely (Larson et al., 2011) and persistently (Moore, 2014), but more subtle impairments (as might be expected after head impact exposure in the absence of symptoms) may affect cognitive control strategies, or modes, without disrupting overall accuracy.

Two cognitive control modes have been proposed, proactive and reactive (Braver et al., 2009). Under proactive control, attention is maintained on the goal and interference from unrelated or distracting events are preempted, whereas reactive control is event-dependent,

with control processes only recruited when non-goal related events are detected. A shift from proactive to reactive control in healthy aging has been ascribed to abnormal recruitment of the prefrontal cortex during goal maintenance tasks (Paxton et al., 2007) and could be associated with cortical thinning (Schmidt et al., 2016). Diminished proactive control has also been observed weeks (Barlow et al., 2018) and months after concussion (Mayer et al., 2019), and, in healthy individuals, a tendency toward reactive control is associated with lower heartrate variability (Williams et al., 2016). If repetitive head impacts are capable of altering cortical-subcortical functional connectivity in the CAN, then it is plausible that athletes sustaining the most impacts will exhibit a shift from proactive control to reactive control.

In the present work, we aimed to elucidate the effects of head impacts on the CAN and the extent to which these effects provide predictive information about recovery. We monitored Division I soccer athletes for head-to-ball impacts sustained during a single season to address these two aims. First, we tested the hypothesis that soccer players sustaining the greatest head-to-ball impact exposure exhibit greater changes in cortico-subcortical functional connectivity within the CAN. Second, we sought to relate CAN functional connectivity and measures which can inform clinical decision making based on current standards (i.e., performance on neuropsychological tests), and quantify to what degree changes in a relationship between CAN functional connectivity and cognitive control over the season could be attributed to head-to-ball impact exposure.

2. Materials and methods

2.1. Participants and data collection

Thirty male NCAA Division I varsity athletes (age: 20.2 ± 1.5 years) agreed to participate. Eighteen soccer players were monitored by athletic training staff throughout one season for head-to-ball impacts. Four cross-country runners and eight golfers served as controls. Two athletes (one soccer, one control) reported symptomatic head impacts to the athletic trainers during the season, but these resolved spontaneously, and the athletes returned to competition prior to their post-season appointment. All participants provided written informed consent in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All procedures were approved by the Institutional Review Board at the University of California, Irvine. Data reported here are publicly available in the BIDS format on openneuro.org (10.18112/openneuro.ds002940.v1.0.1).

Athletic training staff monitored soccer players during practices and intercollegiate games for the purpose of recording the number of head-to-ball impacts sustained by each player. Trainers used a sheet with player names and jersey numbers to tally, in real-time, the number of head-to-ball impacts sustained by each player during the practice or game (including warm-ups). Each member of the athletic training staff (which included 2 or more trainers) was accompanied by a member of the research team, who was not an athletic trainer and assumed head impact monitoring duties in the event that training staff were required to perform their other duties (e.g., attending to an injury).

Twenty-four athletes (13 soccer; 11 controls) completed two resting state functional MRI (rs-fMRI) scans, one before and one after the season, within 2 weeks of the beginning and end of potential exposure to head-to-ball impacts (mean ± SD: 117.3 ± 8.6 days between scans). A Dot Probe Expectancy task (DPX) was administered on the same day as the MRI scan. Data analysis was limited to those athletes who completed data collection activities at both time points.

2.2. Dot pattern expectancy task (DPX)

The DPX is a continuous performance task designed to assess the capacity for sustained attention and goal maintenance (Barch et al., 2008). It was developed as an alternative to other expectancy tasks which rely on letters (MacDonald et al., 2005). Though these other tasks have demonstrated sensitivity to cognitive control deficits arising after concussion (Zhao et al., 2018), the dot patterns used in the DPX increase the difficulty of the task. We viewed this as an advantage given our sample of healthy young adults. A target response was required when a configuration of dots representing the cue (typically defined as “A”) was followed by a configuration of dots representing the probe (“X”). In BX trials, when the X was not preceded by the A-cue, the B-cue should be used to inhibit the response to X. In AY trials, when the A-cue is not followed by the X-probe, the response to the Y-probe must be inhibited. Proactive control processes should result in better performance on BX trials, whereas reactive control processes should result in better performance on AY trials.

The dot stimuli (Braille dot patterns) were presented using PsychoPy (Peirce et al., 2019) in four blocks, each with 40 trials and a 4000 ms intertrial interval. Each block consisted of 28 (70%) AX ‘target’ trials, 5 (12.5%) AY trials, 5 (12.5%) BX trials, and 2 (5%) BY trials. The proactive behavior index (PBI) (Braver et al., 2009) was calculated [$PBI = (AY_{acc} - BX_{acc})/(AY_{acc} + BX_{acc})$] to represent a relative balance of interference between AY and BX trials. Positive PBI reflects higher interference on AY trials (proactive control), and negative PBI reflects higher interference on BX trials (reactive control). Goal maintenance was defined by d-prime, a measure of response accuracy calculated by subtracting the false alarm rate on BX trials from accuracy on AX trials [$d\text{-prime} = (zAX_{acc}) - (zBX_{err})$], where ‘z’ indicates a z-transformation of accuracy and error rates.

2.3. MR data acquisition

All functional and structural images were obtained using a 3T Philips Achieva MRI scanner (Best, the Netherlands) using a sensitivity encoding (SENSE) 32-channel head coil at the Neuroscience Imaging Center (NIC) at the University of California, Irvine. The anatomical scans were performed using a T1-weighted fluid attenuated inversion recovery (FLAIR) sequence (flip angle = 90°; matrix size = 240 × 240; number of slices = 180; slice thickness = 2 mm). Functional images were acquired using a T2-weighted EPI sequence (TE = 29 ms; TR = 2000 ms; matrix size = 64 × 64; number of slices = 51; flip angle = 71°).

2.4. Region of interest (ROI) creation

Using the nonlinear MNI152 template as implemented in FSLeyes (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes), masks were created (by D.C.M.) in regions that were selected for their putative core role in central autonomic regulation (Bennaroch, 2014) based

on previous empirical studies, meta-analyses, and probabilistic atlases reporting the location of these regions in MNI space. Bilateral ROIs, represented by 5 mm diameter spheres (volume = 65.4 mm^3), were placed in the ventral anterior insula (Cerliani et al., 2012; Mutschler et al., 2009), medial prefrontal and medial orbitofrontal cortices (Thayer et al., 2012), amygdala and subgenual anterior cingulate cortex (Critchley and Harrison, 2013), periaqueductal grey (Keuken et al., 2017), and hypothalamus (Seoane-Collazo et al., 2015). ROIs were represented with small spheres so that all ROIs were the same size, even those that are most proximal at the midline (i.e., periaqueductal grey and hypothalamus). The masks were reviewed by an expert neuroanatomist (A.S.) who advised changes where necessary in order to create the most theoretically accurate core CAN in standard (MNI) space. MNI coordinates representing the center of these spheres are similar to previous reports of these CAN regions, as cited above, and fall within the boundaries of their respective regions in the Harvard-Oxford and AAL atlases (Table 1). Data analysis was only performed after ROI masks were finalized.

2.5. rs-fMRI data analysis

Image pre-processing, functional connectivity estimation, and statistical analysis were done using the CONN functional connectivity toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012; RRID:SCR_009550) and SPM12 (Wellcome Department of Imaging Neuroscience, London, UK; RRID:SCR_007037), implemented in Matlab 2019a (MathWorks Inc., Natick, MA, USA), to preprocess images and perform functional connectivity statistical analyses.

Functional volumes were realigned and registered to each individual's T1-FLAIR images, resampled to a voxel size of 2 mm^3 , spatially normalized to standard space (Montreal Neurological Institute [MNI] template), and smoothed with a 4 mm^3 full-width at half-maximum (FWHM) Gaussian kernel. Conservative smoothing was selected to optimize signal-to-noise while maintaining anatomical accuracy of the core CAN regions across participants. The BOLD signal was bandpass filtered (0.008 Hz < f < 0.09 Hz) and a regression-based approach (aCompCor; Behzadi et al., 2007) was used to mitigate the effects of physiological and motion-related noise. The BOLD signal time series was averaged over individual cerebrospinal fluid (CSF) and white matter (WM) masks, and aCompCor identified eigenvectors of CSF (12 components), WM (5 components), and head motion (5 components) that served as nuisance variables in a general linear model (Whitfield-Gabrieli and Nieto-Castanon, 2012).

2.5.1. Functional connectivity—Functional connectivity within the core CAN for each participant at each time point (pre- and post-season) was defined using partial correlations, which represent linear relationships between two nodes conditioned on all other connections in the network. Partial correlations are well suited to estimating brain functional connectivity in real and simulated networks with various topologies, 'lags', and model orders (Smith et al., 2011; Wang et al., 2014). In this study partial correlations were inferred from the sparse inverse covariance matrix (precision matrix) using a graphical lasso (Friedman et al. 2008). To address the biases introduced through L1 penalized regularization we employed a smoothly clipped absolute deviation (SCAD) penalty (Fan and Li, 2001; Fan et al., 2009), effectively relaxing the rate of penalization as the absolute value of the lasso

regression coefficient increases. 10-fold cross-validation was performed to optimize selection of the tuning parameter and control model complexity. Off-diagonal elements less than 1.0×10^{-3} were set to '0'. To address the potential physiological relevance of negative covariances (i.e., regional differences in the relationship between the BOLD signal, blood volume, and blood flow) (Goelman et al., 2014), individual partial correlation matrices was squared. The resulting matrices were transformed (Fisher's-z) prior to statistical analysis.

2.6. Statistical analysis

The hypothesis that repeated head-to-ball impact exposure was associated with changes in a brain-behavior relationship was tested in two steps. First, to control univariate testing of the ROI-to-ROI connectivity matrix, the Z-transformed, squared covariance matrices were analyzed using the network-based statistic (NBS) (Zalesky et al., 2010) in conjunction with a GLM to determine whether head impact exposure (independent variable) was associated with changes in connectivity between each pair of CAN nodes (dependent variables), while controlling for two covariates, (i) concussions sustained during the season and (ii) group membership. The NBS uses a permutation approach to determine whether the relationship between head-to-ball exposure and CAN functional connectivity was greater than what would be expected due to chance. An arbitrary primary threshold (i.e., a critical *F*-statistic) ($F(3,20) = 13.43$, corresponding to $p < 5 \times 10^{-5}$, or $p < .005$ with Bonferroni correction for multiple comparisons) to limit the CAN to a network of supra-threshold functional connections ('edges') and the size of the resulting network was calculated as the number of all remaining edges. Suprathreshold functional connectivity matrices were shuffled between participants randomly (5000 permutations), the GLM was repeated and the same primary threshold was applied at each permutation. A non-parametric probability was computed for each subnetwork of suprathreshold edges based on the number of permutations which resulted in larger networks (i.e., networks with more edges). An association between head impact exposure and connectivity in a CAN subnetwork was considered to be statistically significant if there were fewer than 250 permutations (<5%) with stronger connections. Direction of change at each edge was interpreted from the t-statistic, representing the relationship between head-to-ball impact exposure while controlling for group, concussion incidence, and pre-season functional connectivity. To further examine the effects of head-to-ball impact exposure on this subnetwork, node degree (i.e., the number of edges at each node) and betweenness centrality (i.e., number of shortest paths in the network that pass through a node, normalized to the number of suprathreshold edges), graph theory metrics of nodal integration, were computed on the resulting binarized subnetwork using functions implemented in the Brain Connectivity Toolbox (Rubinov and Sporns, 2010; RRID:SCR_004841).

Individual functional connectivity matrices were thresholded, based on the subnetwork deemed by NBS to be associated with head-to-ball impact exposure, such that sub-threshold edges were set to '0'. Post-season functional connectivity was residualized to group, concussion incidence, and pre-season functional connectivity. Post-season DPX scores (PBI, d-prime) were also residualized to group, concussion incidence, and pre-season DPX scores.

In the second step, a 'brain' matrix, representing thresholded and residualized post-season core CAN functional connectivity, and a 'behavior' matrix of residualized DPX scores (PBI, d-prime), as measures of cognitive control, served as inputs to a partial least squares (PLS) correlation analysis (http://www.rotman-baycrest.on.ca/pls, Version 6.1311050) (McIntosh and Lobaugh, 2004). PLS is a multivariate statistical method that employs permutation tests to compute statistical significance, thus controlling for multiple comparisons, and bootstrap resampling tests to quantify coefficient reliability. Each analysis resulted in a maximum of two latent variables (LV) and the statistical significance of each LV was quantified using a permutation test (5000 permutations). Significant latent variables are identified as those for which fewer than 250 permutations (<5%) resulted in a singular value greater than what was observed. Each LV represents a correlation, between CAN functional connectivity and behavior saliences, for which 95% confidence intervals were computed using bootstrap resampling (500 bootstraps) to estimate effect stability. CAN functional connections that contributed to the relationship represented by a significant LV were revealed by dividing each bootstrapped mean salience by its estimated standard error to obtain a normalized estimate of robustness, essentially a *z*-score given that the data are normally distributed. Edges that were found to have a bootstrap ratio > 2.576 and < −2.576 (a 99% confidence interval) were interpreted as reliably contributing to the observed brain-behavior relationship. CAN subnetworks were visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/; RRID:SCR_009446) (Xia et al., 2013).

This study was carried out on the members of a single sports team and a roughly equivalent number of control participants. A necessary sample size was not determined by an *a priori* power analysis. Therefore, we conducted a sensitivity analysis using G*Power (Faul et al., 2007) and determined that our sample was sufficient (power = 0.80, $\alpha = 0.05$) for detecting a large effect of head-to-ball impacts ($f^2 = 0.36$, Cohen's $d = 0.80$, $R^2 = 0.50$) using a regression analysis with two predictors of 'no interest'. A similar effect (Cohen's $d = 0.71$) was revealed by a meta-analysis of studies correlating neuropsychological performance and head impact exposure in boxers and soccer players (Belanger and Vanderploeg, 2005). Ultimately, the use of non-parametric permutation tests in the NBS and PLS steps greatly minimizes the potential for a failure to reject the null hypothesis (Type II error) that otherwise might be attributed to an insufficient sample size.

3. Results

In twenty-five practices and nineteen games, thirteen soccer players sustained a total of 1179 head-to-ball impacts (Range: 30–207 impacts per player; Median: 79 impacts per player; Fig. 1a). Head-to-ball impact exposure was associated with changes in functional connectivity within a subset of 40 edges between all 14 nodes of the core CAN ($p = .002$, FWE corrected) (Fig. 1b). The left insula (degree * normalized betweenness centrality = 6.958), left hypothalamus (6.660), and left amygdala (5.978) exhibited the greatest integration within this subnetwork, meaning they were most affected by head-to-ball impact exposure. The right amygdala (0.0) and left (0.0) and right (0.0) medial PFC exhibited the strongest segregation, meaning they were least affected by head-to-ball impact exposure.

PLS analysis revealed that a pattern of functional connectivity in this CAN subnetwork was also associated a decreased PBI (indicating a greater reliance on reactive cognitive control strategies), but not with a change in d-prime ($p = .028$) (Fig. 1c). This change in the brain-behavior relationship was uniquely driven by increased functional connectivity between the left medial orbitofrontal cortex and left insula (BSR = 3.99). This pattern of coupling explained 88.25% of the cross-block variance. Collectively, this means that changes in functional connectivity within a core CAN network after the season were associated with both head-to-ball impact exposure and a shift from proactive control (more positive PBI) to reactive control (more negative PBI).

4. Discussion

In the current study we sought to relate changes in a brain-behavior relationship with head-to-ball impacts in collegiate soccer players. CAN pathophysiology is associated with cardiovascular (Al-Khazraji and Shoemaker, 2018) and cerebrovascular (Allen et al., 2015) dysfunction in older adults and is predictive of later-life dysfunction in young adults (Wulsin et al., 2018). The patterns that were revealed through complementary, non-parametric analyses are discussed in the context of our hypothesis that repeated exposure to ‘sub-concussive’ impacts is capable of altering functional connectivity between a network of core CAN regions and CAN-related cognitive function.

We report a strong association between head-to-ball impact exposure and functional connectivity in a diffuse subnetwork comprising all 14 nodes and 40 of the 91 original edges of the core CAN. This means that soccer players sustaining the highest number of head-to-ball impacts exhibited greater increases in core CAN connectivity, a pattern which is broadly supported by a theory that enhanced functional connectivity is a compensatory response to structural damage or pathophysiological insult, and thus a fundamental marker of even mild brain injury (Hilary and Grafman, 2017, Iraji et al., 2016). Rapid acceleration or deacceleration of the head can disrupt resting membrane potential in neurons, leading to a metabolic crisis as ion channels work to re-establish homeostasis (Giza and Hovda, 2014). The acute dynamics of this cascade in humans remains elusive, but blood-based protein biomarkers of axonal damage are elevated hours and even weeks after exposure to head-to-ball impacts (Wallace et al., 2018; Wirsching et al., 2019), suggesting the impacts observed in this study are capable of disrupting brain microstructure which could elicit the observed state of CAN ‘hyperconnectivity’ as a compensatory response.

This effect may not have been consistent across hemispheres, as visual inspection suggested greater connectivity (more lateralized edges, nodes) in the left hemisphere of the CAN subnetwork associated with head-to-ball impacts than in the right hemisphere. Though parasympathetic regulation of the heart has generally been associated with left-lateralized CAN function (Ding et al., 2020; Macey et al., 2012), it is not possible to predict whether the observed pattern of functional connectivity is indicative of a shift in the balance between sympathetic and parasympthetic regulation (Goldstein and Kopin, 2017), particularly in the context of trauma wherein autonomic outflow may be uncoupled from central autonomic network connectivity (Thome et al., 2017).

Within the affected subnetwork, left-lateralized insular, amygdala, and hypothalamic nodes exhibited the greatest number of functional connections (degree) and incorporated the greatest relative number of shortest paths (betweenness centrality). This can be interpreted to mean that repeated head-to-ball impact exposure was most strongly associated with increased functional connectivity within a left-lateralized cortico-subcortical-hypothalamic circuit. At the subcortical level, the projections from the amygdala to the hypothalamus enhance glucocorticoid release and generate sympatho-excitatory responses along the hypothalamic-pituitary-adrenal axis (Herman et al., 2005). Chronic stress exposure stimulates this axis to promote a state of hypercortisolemia that may contribute to eventual cognitive decline in later life (Elgh et al., 2006).

At the cortex, the ventral anterior insula is responsible for integrating information from subcortical and cortical regions (Craig et al., 2009; Nagai et al., 2010), using that information to detect salient events, and facilitate resource allocation in other attentional networks to guide proper response (Menon and Uddin, 2010). Connectivity between the ventral anterior insula and medial orbitofrontal cortex has been directly associated with anxiety behaviors (Kim et al., 2012; Simmons et al., 2013; Yang et al., 2020), which are driven by enhanced error monitoring, likely mediated by the basolateral amygdala, and a tendency to rely on reactive control strategies (Braver, 2012; Moser et al., 2013). In this study, we observed increased functional connectivity in this circuit that was associated with greater head-to-ball impact exposure and diminished proactive control. Our findings extend reports of diminished cognitive control (Moore et al., 2014) and functional connectivity in a cognitive control network (Mayer et al., 2015) after concussion to include athletes sustaining asymptomatic head impacts. Although we focused on cognitive control as a specific CAN-related domain of cognitive function, a broader interpretation is that the CAN is responsible for integrating sensory and somatic information that in turn regulates simple and complex behaviors (Damasio, 1996). Thus, it is possible that robust changes in CAN functional connectivity, as we report in this study, could have broader, indirect effects on cognition and behavior.

The conclusions that can be drawn regarding the CAN ROIs in this study are ultimately limited by our a priori model of a core CAN in standard (MNI) space. Since the inception of this study, there have been a number of rigorous approaches to mapping complex, ‘physiological’ brain networks that interface with the autonomic nervous system to control peripheral physiology (de la Cruz et al., 2019; Chen et al., 2020; Valenza et al., 2019). Without these concomitant measures (e.g., pulse plethysmography, electrocardiography) to serve as regressors or covariates, we decided to use small spherical masks to seed highly specific regions of interest and perform conservative smoothing. Even though the patterns we report are consistent with relatively well studied brain-behavior patterns, the reported associations with functional connectivity in specific sub-regions (e.g., the anterior insula) must be interpreted with caution. The results from the current study should serve as an important first step to motivate the physiological measurement of autonomic outflow in the MRI for the purpose of studying mild traumatic brain injury. These techniques have the added benefit of mobility (outside the MRI) and could be useful in developing tests based on autonomic function that can be performed in the field for the purpose of monitoring athlete brain health.

The effects of sport-related concussion on the sympathetic nervous system have been inconsistent, in part because of a reliance on heart rate variability, a commonly employed measure of autonomic function in athletes that is poorly suited for quantifying sympathetic activity (Berntson et al., 1997). Investigations using approaches better suited to assess sympathetic outflow have reported impaired cerebral autoregulation (Wright et al., 2018) and electrodermal and cardiovascular reactivity to laboratory stress (Johnson et al., 2018; van Noordt and Good, 2011), suggestive of a blunted regulatory capacity of the sympathetic nervous system after concussion. Others have reported transient increases in arterial stiffness, interpreted as hyperactivation of the sympathetic nervous system, which may be predictive of symptomatic recovery (La Fountaine et al., 2016). Our findings encourage concomitant measurement of central nervous system activity, particularly in the CAN, and peripheral markers of autonomic outflow, both sympathetic and parasympthetic, to resolve these discrepancies.

Though the patterns reported in this study were measured across the season, others have reported cognitive and motor deficits within one hour of a head impact exposure (Di Virgilio et al., 2016, 2019). Thus, it is possible head-to-ball impact exposure could result in a progressive deterioration of executive and sensorimotor function, increasing the risk of a symptomatic brain injury, via a sport-related concussion, or a musculoskeletal injury. In those studies, the effects abated after 24 h, but former soccer players have exhibited greater cortical thinning (Koerte et al., 2015) and altered brain neurochemistry (Koerte et al., 2016) relative to age-matched controls from non-contact sports, leaving open the possibility that the pattern we observed represents an accumulated effect of head-impact exposure over many seasons and a trend toward diminished proactive cognitive control and autonomic function later in life (Sturm et al, 2018). Collectively, our findings can inform the development of a biological definition of brain injury caused by repetitive head impacts.

Using multiple, single observers to record head-to-ball impacts, without recording video for offline corroboration, is a limitation of the current study and prevented us from discerning impact magnitude or impact location. Our laboratory (Cecchi et al., 2019) and others (Campbell et al., 2020; Cortes et al., 2017) have demonstrated the value of using independent review of video recordings to validate head impact data, even when field-based collection is performed using wearable impact sensors. We can assume that our measure contains some degree of human error, but these inaccuracies are not likely to be systematic. We also chose to explicitly measure head-to-ball impacts, which are common in soccer. In limiting our hypothesis to head-to-ball impacts, which are common and a central focus of concussion prevention strategies (Caccese and Kaminski, 2016), we did not measure other impact events (e.g., collisions with the ground or other players) that may also cause minor brain injuries. If head-to-ball impacts as defined in this study is viewed as a relative metric, that those sustaining the greatest number of head-to-ball impacts are those sustaining the greatest exposure to all head accelerative events, then it is unlikely that these omissions would greatly affect our conclusions. However, some of the variance in the pattern we report could be attributed to the athletes playing certain positions may experience more non ball-related head impacts than others. The use of head impact monitoring devices, in conjunction with video recordings, to more accurately quantify exposure in soccer is warranted (Caccese and Kaminski, 2016).

Considering that most collegiate athletes have competed and sustained impacts for many years prior to college, it is difficult to conclude that a pre-season measure of CAN functional connectivity or cognitive control is a true ‘baseline’. Thus, a strength of our study was the inclusion of control athletes that allowed for statistical correction of differences that might exist at baseline and also for natural changes that might occur over the course of a competitive season independent of head impact exposure. Our group recently reported a similar dose-response relationship between head impact exposure sustained by collegiate water polo players, increased coupling in whole-brain slow-rhythm oscillations, and a reduction in inhibitory control that was also suggestive of a shift away from proactive cognitive control strategies (Monroe et al., 2020). Slow (delta rhythm) oscillations measured by electroencephalography are associated with basic homeostatic processes (Knyazev, 2012), which means that the findings of the current study may corroborate those observations and support that repeated, sport-related head impact exposure is capable of disrupting the interface of central and autonomic nervous systems. At present, the natural remediation of these effects remains unknown. Understanding the time-course of recovery between seasons of head-impact exposure carries substantial clinical implications given the need to balance the benefits of regular exercise (i.e., continued sport participation) and the risks of later-life neurologic sequelae of repetitive head impact exposure.

5. Conclusions

We report that the frequency of head-to-ball impacts sustained during a single season of men’s collegiate soccer is directly associated with increased functional connectivity in a core central autonomic network, a pattern which was associated with a shift from proactive to reactive cognitive control strategies. Our findings encourage future studies of athlete brain health that utilize (a) tasks capable of distinguishing between modes of cognitive control, and (b) the concomitant measurement of autonomically-mediated physiology in human imaging studies of mild traumatic brain injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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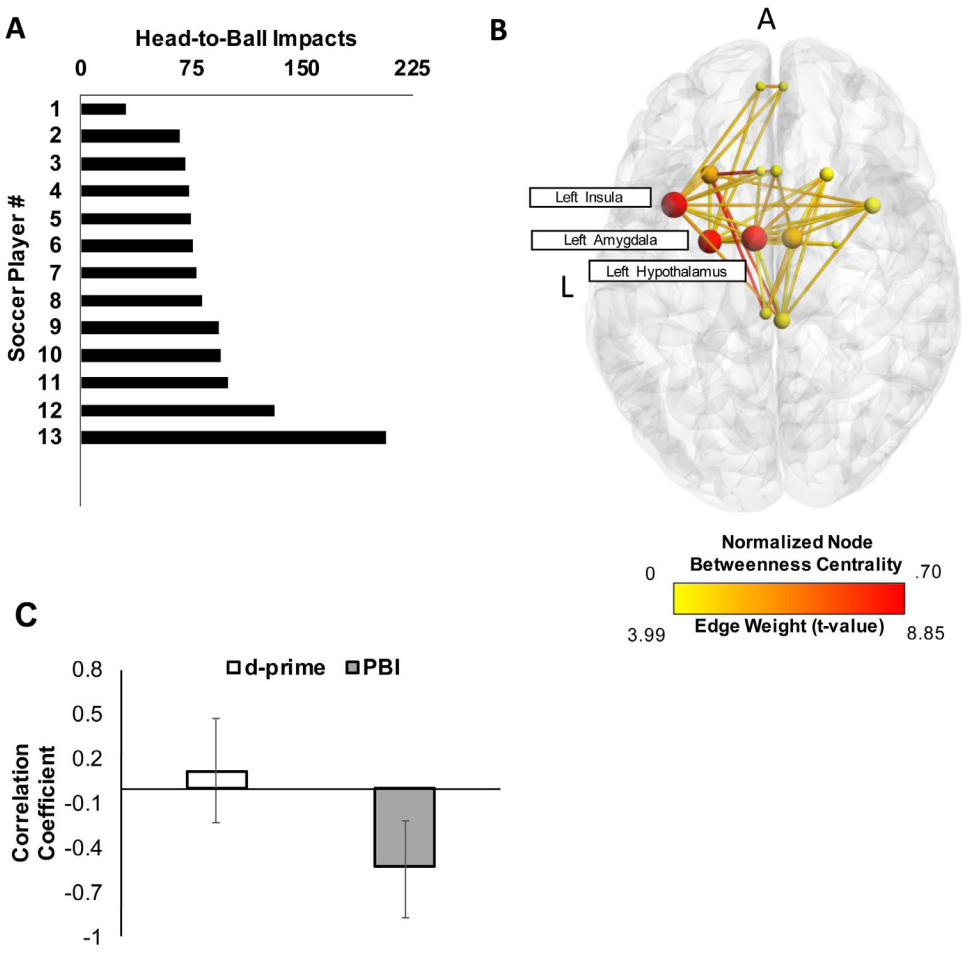

Fig. 1.

(A) The total number of head-to-ball impacts sustained by 13 male collegiate soccer players in practices and games over a single season. (B) The edges comprising a core CAN subnetwork that was positively associated with head-to-ball impacts. Edge colors represent edge weight (*t*-values). Larger nodes have greater degree (number of edges). Darker nodes have greater betweenness centrality. Labeled nodes (largest, darkest) were most strongly integrated in this network, which was interpreted to mean that functional connectivity with those nodes most strongly associated with head-to-ball impact exposure. (C) The first latent variable reveals a pattern of CAN functional connectivity that was inversely correlated with the proactive behavior index (PBI; negative PBI = reactive cognitive control) measured after the season, but not with response accuracy (d-prime).

Table 1

Montreal Neurological Institute (MNI) coordinates for a core set of autonomic regions defining the central autonomic network in this study.

MNI coordinates (in mm)	***X***	***Y***	***Z***
Right ventral anterior insula	38.4	10.8	−9.5
Left ventral anterior insula	−36.5	11	−12.9
Right medial prefrontal cortex	4.7	55.5	−17.3
Right medial orbitofrontal cortex	21.1	22.4	−20
Left medial prefrontal cortex	−3.9	55.5	−17.7
Left medial orbitofrontal cortex	−23	22.4	−20.3
Right amygdala	24.4	−3.9	−18.9
Left amygdala	−23	−2.8	−17.3
Right periaqueductal grey	4.2	−32.5	−10.2
Left periaqueductal grey	−2	−29.9	−7.9
Right hypothalamus	8.1	−1.5	−12.5
Left hypothalamus	−6.2	−1.6	−12.9
Right subgenual anterior cingulate cortex	2	23.7	−6.5
Left subgenual anterior cingulate cortex	−3.9	23.7	−6.1