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A Resting State Functional Magnetic Resonance Imaging Study of Concussion in Collegiate Athletes

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Abstract

Sports-related concussions are currently diagnosed through multi-domain assessment by a medical professional and may utilize neurocognitive testing as an aide. However, these tests have only been able to detect differences in the days to week post-concussion. Here, we investigate a measure of brain function, namely resting state functional connectivity, which may detect residual brain differences in the weeks to months after concussion.

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Conflict of Interest Statement:

Suzanne Czerniak, Elif Sikoglu, Ana Liso Navarro, Joseph McCafferty, Jordan Eisenstock, J Herbert Stevenson, Jean King, and Constance Moore declare that they have no conflict of interest.

Informed Consent Statement:

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Twenty-one student athletes (9 concussed within 6 months of enrollment; 12 non-concussed; between ages 18 to 22 years) were recruited for this study. All participants completed the Wisconsin Card Sort Task and the Color-Word Interference Test. Neuroimaging data, specifically resting state functional Magnetic Resonance Imaging data, were acquired to examine resting state functional connectivity. Two sample t-tests were used to compare the neurocognitive scores and resting state functional connectivity patterns among concussed and non-concussed participants. Correlations between neurocognitive scores and resting state functional connectivity measures were also determined across all subjects.

There were no significant differences in neurocognitive performance between concussed and non-concussed groups. Concussed subjects had significantly increased connections between areas of the brain that underlie executive function. Across all subjects, better neurocognitive performance corresponded to stronger brain connectivity.

Even at rest, brains of concussed athletes may have to ‘work harder’ than their healthy peers to achieve similar neurocognitive results. Resting state brain connectivity may be able to detect prolonged brain differences in concussed athletes in a more quantitative manner than neurocognitive test scores.

Key Terms

concussion; fMRI; resting state; functional connectivity; neurocognition

Introduction

It is estimated that between 1.6 and 3.8 million sports-related injuries, including concussions, occur each year in the US (Langlois et al. 2006). The current standard of concussion diagnosis is through multi-domain clinical assessment by trained medical professionals, as concussed patients usually have no gross pathology or abnormalities that can be found by standard structural imaging techniques (e.g., CT or structural MRI) (Blennow et al. 2012; Duhaime et al. 2012; Grindel et al. 2001; McCrory et al. 2013). These assessments are multi-faceted in nature, and examine clinical symptoms (such as nausea, headaches, and difficulty thinking), physical signs (such as loss of consciousness), behavioral effects (such as irritability), problems with sleep, and/or cognitive difficulties (impaired ability to perform mental tasks) (McCrory et al. 2013). A detailed history and neurological exam therefore form the core of a concussion diagnosis (McCrory et al. 2013). However, several additional investigations can be utilized: neurocognitive (neuropsychological) testing, while not necessary for a concussion diagnosis, may be employed to evaluate memory, attention and concentration, problem solving, and other higher-order cognitive functioning (Grindel et al. 2001; McCrory et al. 2013).

Although neurocognitive testing has been shown to readily detect differences between recently-concussed (less than 1 week after concussion) and healthy patients in studies of collegiate athletes (Echemendia et al. 2001; Schatz and Sandel 2013), there are several challenges when using neurocognitive testing as an aide for tracking the recovery of brain function from a concussion. In many cases, athletes undergo pre-season neurocognitive

testing; these test results can be compared to those obtained post-concussion. There have been reports of athletes “gaming” the system by purposefully attempting a low score during baseline testing so that the cognitive effects of their concussion are not obvious (Hunt et al. 2007; Mahaffey 2012). It has also been shown that athletes’ concussion symptoms can persist even after neurocognitive testing scores have returned to normal levels (Tsushima et al. 2013). Such reports highlight the fact that neurocognitive testing may be a non-optimal indicator when assessing recovery status after concussion, and that a more sensitive long-term marker of brain deficits after a concussion may be useful as an element of clinical assessment and follow-up care.

To this end, quantitative neuroimaging measures that go beyond standard structural MRI imaging offer a promising approach for the development of a diagnostic and recovery status aid for concussion. A growing body of sports-related concussion research examining changes in brain white matter tracts through the use of Diffusion Tensor Imaging (DTI) (Gardner et al. 2012) already exists; however, relatively few studies have looked at changes in functional brain networks due to concussion. Functional brain networks are determined through investigation of the Blood Oxygen Level Dependent (BOLD) signal synchrony among different brain regions. BOLD signal is thought to serve as an indirect measure for brain activity, and brain areas that show similar patterns of changes in BOLD signal are thought to work together as part of a larger brain network. This brain functional connectivity (FC) is a reflection of the central tenant of Hebbian theory that “cells that fire together, wire together” (Hebb 1949). When the FC is studied while a subject is “at rest”, that is, not performing an explicit task, it is referred to as resting state functional connectivity (rs-FC). rs-FC is advantageous as an imaging technique, as it is non-invasive with high spatial resolution and its task-independent nature provides a relatively fast measure comparable across different studies and sites.

The goal of the present study is to investigate changes in rs-FC, a quantitative marker of alterations in the brain, due to concussion in student athletes and associate the findings with established clinical and neurocognitive assessments that are commonly used in assessing severity of concussion. Specifically, we employed neurocognitive tests of execute function (Berg 1948; Delis et al. 2001; Stroop 1935) and for the rs-FC analysis we focused on the brain regions known to underlie executive function, i.e. the Anterior Cingulate Cortex (ACC), the Left DorsoLateral PreFrontal Cortex (LDLPFC), and the Right DorsoLateral PreFrontal Cortex (RDLDPFC) (Buchsbaum et al. 2005; Laird et al. 2005; Leung et al. 2000; Lie et al. 2006; MacDonald et al. 2000; Monchi et al. 2001). As we recruited participants in the subacute to chronic phase of injury (concussed 3 weeks to 6 months previous to study enrollment), we hypothesized neurocognitive measures would be similar between concussed and non-concussed groups. We further hypothesized that rs-FC measures would be abnormal in the concussed group, reflecting the longer-term impact of concussion on brain function. Finally, we aimed to understand how the relationship between neurocognitive performance and rs-FC changes after a concussion.

Materials and Methods

Participants

Participants in this study were all active collegiate athletes (male or female; between ages of 18–22 years old) (Table 1). Athletes were recruited from local colleges and universities with the help of team physicians (JHS). Head athletic trainers (ATs) from 5 institutions of higher learning in the central Massachusetts area were contacted by JHS and given information about this study; the ATs then referred team members they saw who met criteria for participation. Participants were subsequently screened to ensure they met all inclusion (aged 18–22 years old, currently an active member of one or more sports teams, and either no history of concussion OR a concussion experienced within the last 6 months) and exclusion (no medical illnesses or psychiatric disorders, no substance abuse or dependence, able to have MRI scanning done, and if female, not pregnant or nursing) criteria. All enrolled concussed participants experienced their concussion within the past 6 months, and were seen by their AT and subsequently a physician at the time of their concussion. All of the subjects provided written consent as approved by the University of Massachusetts Medical School (UMMS) Institutional Review Board (Docket #H00001821). All participants underwent a clinical interview, neurocognitive testing, and an MRI scanning session as part of the study.

Clinical Interview

The clinical interview was conducted by a psychiatrist and/or neurologist (AAL, JE). This interview assessed the subjects' demographics, medical/psychiatric history (including the administration of the Hamilton Rating Scale for Depression (HAM-D: (0–7)- no depression, (8–16)- mild depression, (17–23)- moderate depression, and (24) severe depression), and questions about the subjects' concussion history, including symptoms experienced at the time of concussion, number of prior diagnosed concussions, and the number of days elapsed between experiencing the most recent concussion and study enrollment (Table 1). All participants were free of neurological disorders and active major psychiatric illness, including Major Depressive Disorder, Bipolar Disorder, schizophrenia, Autism Spectrum Disorders and ADHD. None of the participants were taking psychotropic medications at the time of the study.

Neurocognitive Assessments

Computer formatted Wisconsin Card Sorting Task (WCST) (to measure attention, flexibility of thinking, and working memory) (Berg 1948) and Delis-Kaplan Executive Functioning System (D-KEFS- Pearson, Inc, San Antonio, TX.) Color-Word Interference Test (CWIT) (to assess attention, inhibition, and reaction time) (Delis et al. 2001; Stroop 1935) were administered to each participant. Each subject's performance on the WCST was converted to an age-corrected standardized score on a scale with a mean of 50 points and standard deviation of 5 points. Participants with scores greater than 1 standard deviation from the mean (>55) were considered better than normal, and participants with scores less than 1 standard deviation from the mean (<45) were considered impaired. Similarly, each subject's score on the CWIT was scaled to correct for age so that standardized scores were on a scale with a mean of 10 points and a standard deviation of 3 points; after scaling higher scores reflected better CWIT performance.

Neuroimaging Data Acquisition

Data were acquired on a 3.0 Tesla Philips Achieva whole-body MR system (Philips Healthcare, Best, the Netherlands) with an 8 element phased-array head coil at the Advanced MRI Center, UMass Medical School. T1-weighted anatomical MRI (MPRAGE sequence, 256×256 voxels, TR: 6.985 msec, TE: 3.15 msec, FOV: $240 \text{ mm} \times 256 \text{ mm} \times 170 \text{ mm}$, 180 slices) were collected for diagnostic and localization purposes. All of the participants underwent the resting-state scan with open eyes and staring at a white cross sign superimposed on a black background, and were told to not think about anything in particular (Friston 1994). Resting-state scan images were obtained using an EPI sequence (84×81 voxels, FOV: $256 \text{ mm} \times 150 \text{ mm} \times 256 \text{ mm}$, TR: 2540 msec, TE: 30 msec, flip angle: 75° , slice thickness: 3 mm, 50 slices) lasting 406 sec. Diagnostic scans were evaluated by a board certified neuroradiologist and no anatomical brain abnormalities were identified.

Neuroimaging Data Analysis

Resting-state fMRI data analysis was carried out by using Data Processing Assistant for Resting-State fMRI (DPARSFA_V2.2_130309-<http://www.restfmri.net>) (Song et al. 2011). DPARSA is plug-in software that works with SPM8 (Statistical Parameter Mapping—Welcome Department of Imaging Neuroscience, London, UK; (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) and the Resting-State fMRI Data Analysis toolkit (REST_V1.8_130303). The visualization was done using xjView toolkit (<http://www.alivelearn.net/xjview8/>). Images were corrected for slice acquisition time differences, realigned, normalized, spatially smoothed with a 4 mm FWHM kernel, detrended, and temporally band-pass filtered to 0.01–0.08 Hz (Chai et al. 2011). An independent component-based noise correction method was used to regress-out physiological and other sources of noise such as white matter and cerebrospinal fluid signals and head motion related covariates. Functional connectivity analysis was performed using a hypothesis-driven seed-based approach. Seeds (i.e. ACC; left and right DLPFC) were chosen as these regions were associated with the above mentioned neurocognitive tests (Buchsbbaum et al. 2005; Laird et al. 2005; Leung et al. 2000; Lie et al. 2006; MacDonald et al. 2000; Monchi et al. 2001). The centers of the seed regions were determined based on the previous literature: the connectivity patterns from ACC (spherical seed with center located at MNI: 0,44,10 and radius 10mm) (Blakemore 2008; Chai et al. 2011; Conklin et al. 2007; Cullen et al. 2009; Kelly et al. 2009; Margulies et al. 2007) and left (spherical seed with center located at MNI: -34,42,20 and radius 10mm) and right DLPFC (spherical seed with center located at MNI: 34,42,20 and radius 10mm) (Hayama and Rugg 2009; Qin et al. 2009; Siltan et al. 2010; Staudinger et al. 2011) were investigated. First-level analysis consisted of extracting the average BOLD time courses from each seed and computing the Pearson's correlation coefficients between this average time course and the BOLD time course of every other voxel. These correlation coefficients were then converted to normally distributed z-scores using Fisher's z-transform. First-level analysis was separately performed for each participant. Through the second-level analysis, group functional connectivity maps, for concussed- and non-concussed participants, with each seed were formed. The two groups' resting-state functional connections with each seed were compared voxelwise using a 2-sample t-test and for this analysis we controlled for the gender effects of having fewer females in the concussed group ($n=2$) than in the non-concussed group ($n=6$).

Statistical Analysis

Statistical analysis was performed using STATA 12 software (Stata Statistical Software: Release 12. (2011) College Station, TX: StataCorp LP). The connectivity coefficients between the seed regions and regions-of-interest (ROI) were compared across groups using t-tests. We also conducted a Pearson's correlation analysis to investigate the relationship between the rs-FC findings and clinical and neurocognitive assessments.

Results

Participant Demographics

A total of 21 young adults were recruited for this study: 9 concussed participants (2 females) and 12 participants never diagnosed with a concussion (6 females). Concussed participants all had experienced a concussion within the past 6 months prior to their enrollment in the study. All non-concussed participants had never been diagnosed with a concussion. For the concussed participants, the average time elapsed between experiencing the concussion and study enrollment was 112 days; the shortest time was 23 days and the longest time was 185 days. Of the 9 concussed participants, 6 had histories of previous concussions (n=3 for 1 previous concussion and n=1 for 2, 3, or 4 previous concussions). One concussed subject reported receiving a diagnosis of post-concussion syndrome (PCS). Concussed participants reported having the following symptoms at the time of their concussion: headaches (n=7), having a hard time thinking/concentrating (n=7), feeling confused/dizzy/dazed (n=5), memory loss (n=4), feeling excessively slow/tired (n=4), nausea (n=3), and experiencing sensitivity to light/blurred vision (n=3). None of the concussed participants reported loss of consciousness. All subjects were right-handed, with the exception of 2 left-handed concussed subjects and 1 concussed subject whose handedness was not recorded. Concussed and non-concussed participants' demographics, scores on the Hamilton Rating Scale for Depression (HAM-D), Body Mass Index (BMI) and sports played are presented in Table 1. There were no significant differences in any of these measures across the two groups.

Neurocognitive Assessments

There were no significant differences in neurocognitive test performance between the concussed and non-concussed groups on either the Wisconsin Card Sorting Task or the Color-Word Interference Task.

Resting State Functional Connectivity

The comparison of the connectivity maps between the concussed and the non-concussed participants revealed significant differences in the integrity of brain connections to all three seed regions (ACC, LDLPFC, and RDLPFC; Figure 1).

For the ACC seed (Figure 1a), areas of the frontal lobe (including parts of the left and right middle frontal gyrus, the left inferior frontal gyrus, and the left medial gyrus/paracentral lobule) and a portion of the parietal lobe (the left superior parietal lobule) showed stronger connectivity to the ACC in concussed subjects compared to non-concussed subjects. Increased connection to the LDLPFC (Figure 1b) was also found in concussed subjects, specifically between the LDLPFC and portions of the left middle and inferior temporal

gyrus, as well as two distinct parts of the right inferior parietal lobule. The RDLPFC (Figure 1c) also showed stronger correlations to parts of all lobes of the brain in concussed subjects: frontal (the left and right inferior frontal gyrus and the left middle frontal gyrus/precentral gyrus), parietal (the right superior parietal lobule), temporal (the left and right inferior temporal gyrus and the left superior temporal gyrus), and occipital (the left lingual gyrus).

The seed regions (ACC, LDLPFC, and RDLPFC) were determined based on our hypothesis: rs-FC measures, related to the brain areas underlying the neurocognitive tests, would be abnormal in the concussed group, reflecting the longer-term impact of concussion on brain function. The finding from the cluster analysis illustrated these abnormalities and guided us to form ROIs. Based on this hypothesis-driven approach, we concentrated on investigating connectivity coefficients between the seed regions and ROIs for each subject using the time course information. The comparison of concussed and non-concussed groups based on these connectivity coefficients for each investigated seed-ROI pair is shown in Table 2. As expected, there were significant differences in connectivity coefficients across the two groups, with the concussed group showing stronger connections within most seed-ROI pairs except for the following: the LDLPFC-to-Left Inferior Temporal ROI, the RDLPFC-to-Left Inferior Temporal ROI, the RDLPFC-to-Right Inferior Frontal ROI, and the RDLPFC-to-Left Superior Temporal ROI.

Relationship between Clinical Measures and Resting State Functional Connectivity Findings

There were no significant ($p < 0.05$) correlations between the number of prior concussions experienced by a subject, the time elapsed since the most recent concussion, or total score on the HAM-D and any connectivity coefficient measures. However, the connectivity coefficients between LDLPFC and Left Middle Temporal ($r = 0.43$; $p = 0.052$) as well as between the RDLPFC-Right Inferior Temporal ($r = 0.37$; $p = 0.099$) showed significant correlation with HAM-D scores at a trend level. In other words, depression severity and brain connectivity are positively (although not significantly) correlated (Figure 2).

Relationship between Neurocognitive Assessments and Resting State Functional Connectivity Findings

While there were no significant correlations between WCST assessments and connectivity coefficient measures, there were several significant strong correlations between the inhibition/switching errors measure of the Color-Word Interference Test (CWIT) and connectivity coefficient measures (Table 3). In particular, the ACC-to-Right Middle Frontal ROI connectivity coefficient and all LDLPFC-to-ROI connectivity coefficients significantly correlated with the standardized inhibition/switching errors measure. After standardization, higher CWIT scores indicate better performance on task, so here task performance and brain connectivity are positively correlated (Figure 3). This positive association held true across all subjects, indicating that performance of higher-level executive tasks (flexibility of thinking, inhibition, problem solving, etc.) is associated with stronger resting brain connectivity.

Discussion

We investigated group-level differences in brain function and connections between college athletes who had experienced a concussion within the past 6 months (but not sooner than 3 weeks) and college athletes who had never experienced a concussion by examining differences in scores on neurocognitive tests of executive function as well as brain resting state functional connectivity (rs-FC) measures. We found that, consistent with our hypothesis, there were no differences between concussed and non-concussed athletes' neurocognitive performance. We also discovered that concussed athletes had significantly stronger connections between the ACC, LDLPFC, and RDLPFC and other areas of their brain than did non-concussed athletes. These increased connections led us to examine (1) the relationship between three clinical measures (the number of prior concussions experienced by a subject, the time elapsed since the most recent concussion, or total HAM-D score) and rs-FC measures and (2) the relationship between neurocognitive performance and rs-FC measures. While there were no significant correlations between clinical measures and brain connectivity, we found that across all subjects, better performance on the Inhibition/Switching Errors portion of the CWIT positively correlated with the strength of brain connections between the ACC and the Right Middle Frontal, as well as the LDLPFC and Left Inferior Temporal, and the LDLPFC and Left Middle Temporal, and the LDLPFC and Right Inferior Parietal regions.

Previous studies have already examined the effect of concussion on neurocognitive performance. In a 2005 meta-analysis of 21 studies addressing sports-related concussions, recently-concussed athletes clearly performed worse on neurocognitive assessments across six cognitive domains (Orientation, Attention, Executive Function, Acquisition Memory, Delayed Memory, and Global Cognitive Ability) (Belanger and Vanderploeg 2005). However, by 10 days post-injury, concussed subjects' performance was no longer significantly impaired in any of these domains (Belanger and Vanderploeg 2005). These findings were corroborated in a 2008 meta-analysis of 39 articles: again, concussed athletes' neurocognitive performance was significantly worse when assessed immediately post-injury, but by 2 weeks post injury this effect had largely disappeared (Broglia and Puetz 2008). In the present study, we recruited athletes who had experienced a concussion between 3 weeks and 6 months prior to study enrollment. We were therefore unsurprised when their neurocognitive performance on two tests of executive function – the WCST and CWIT – did not differ significantly from that of healthy controls.

Only a few studies have investigated the effect of a concussion on rs-FC measures and they have mainly focused on brain resting state networks (RSNs), which have been consistently found across many studies (Allen et al. 2011; Damoiseaux et al. 2006). The most common of these is ostensibly the Default Mode Network (DMN), which is involved in introspection and day-dreaming (Buckner et al. 2008; Raichle and Snyder 2007; Raichle et al. 2001) and is comprised of the medial prefrontal cortex (MPFC)/anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC)/precuneus, and the inferior parietal lobule (IPL). Attention networks, such as the Salience Network (SN) and the left and right Executive Control Networks (ECNs) are also present at rest, and underpin executive function by identifying decision-relevant stimuli (SN) and then preparing to react to those stimuli accordingly

(ECNs) (Seeley et al. 2007). The SN is comprised of the dorsal anterior cingulate (dACC) and orbitofrontal/insular cortices, while the ECNs are made up of dorsolateral prefrontal cortices (DLPFC) and portions of parietal cortex (Seeley et al. 2007). Previous work has shown overall decreases in the integrity of the connections within the DMN after concussion (Johnson et al. 2012; Marquez de la Plata, Carlos D et al. 2011; Mayer et al. 2011), although at least one study (Sharp et al. 2011) found increased connectivity within this network due to concussion. Several studies have also investigated concussion-related changes in attention networks: both increases and decreases in connectivity have been shown (Johnson et al. 2012; Mayer et al. 2011; Sharp et al. 2011; Slobounov et al. 2011). In this context, our results revealed the concussed group had no decreased connections to the ACC, which we chose as a node of the DMN. By contrast, we found increased connections between the ACC and frontal and parietal brain areas, consistent with Mayer et al. and Johnson et al.'s findings; we interpret this as potential increased connection within the SN (Johnson et al. 2012; Mayer et al. 2011). We also found increased connectivity in the concussed group to both Right and Left DLPFC, chosen as seeds of the ECNs. These findings are consistent with previous findings of concussion-related increased connection within attention networks (Johnson et al. 2012; Mayer et al. 2011; Sharp et al. 2011).

Our observations that concussed athletes did not perform differently than non-concussed athletes on assessments of executive function, yet exhibited significantly increased connectivity in resting brain networks known to underlie executive function led us to investigate the relationship between the two. While no WCST measures significantly correlated with brain connectivity, one section of the CWIT – the number of errors participants made during the inhibition/switching portion of the task – did. On this measure, across all subjects (concussed and non-concussed combined), increased brain connectivity was associated with better neurocognitive performance. This positive correlation between brain connectivity and neurocognitive scores held true not only for the strength of connectivity between the ACC and Right Middle Frontal ROI (shown as an example in Figure 3), but also between LDLPFC and 4 different regions-of-interest, namely Left Inferior Temporal, the Left Middle Temporal, and two regions within Right Inferior Parietal, which exhibited increased connections in concussed participants. The finding that neurocognitive performance correlates with the strength of the connection between the LDLPFC and areas of the Right Inferior Parietal lobule is particularly noteworthy, as these are two major areas that underlie executive function and are parts of the ECN. To the best of our knowledge, this is the first report of a significant relationship between measures of neurocognitive function and rs-FC in concussed and non-concussed student athletes. However, previous work has been done investigating the relationship between neurocognitive tests of executive function and rs-FC in the context of normal aging. In a study by Damoiseaux et al., it was shown that increased rs-FC measures in the DMN were associated with better performance (that is, faster completion times) on the Trail Making Test Part B, which is used to assess attention, concentration, and processing speed (Damoiseaux et al. 2008). This finding is in line with our own: in both cases, increased brain connectivity significantly correlated with improved neurocognitive performance. Given that the concussed participants exhibited increased brain connectivity, we speculate that concussed athletes may have to attain and maintain stronger connections within brain

networks that underlie executive function, even at rest, in order to achieve a similar neurocognitive performance as their non-concussed peers. Based on these findings, we also posit that resting brain connectivity may provide a more sensitive long-term measure of post-concussion recovery than tests of neurocognition, especially for follow-up care of the concussed patients.

There are several limitations to the present study. First, the small number of subjects recruited for this study (9 concussed and 12 non-concussed) may have reduced our ability to see group differences that would be more obvious with a larger sample. For example, we did not find decreased connectivity within the DMN, which is inconsistent with previous literature. Second, two-thirds of our concussed subjects had a history of experiencing at least one other concussion, which may have contributed to our findings. With such a small number of subjects in our concussed group it would be difficult to conduct any sub-analyses based on concussion history; however, in future, larger studies, this would be a worthwhile pursuit. Along with this, we did not gather participants' histories of sub-concussive blows, which may have an effect on correlation coefficient measures even in the non-concussed group. Within the larger groups, it would be possible to control for clinical measures such as previous concussive or sub-concussive blows. Third, this study is cross-sectional in nature, which restricts the extent of the conclusions we may draw about any individual subject's recovery from concussion over time. A longitudinal study designed to assess both neurocognitive and rs-FC measures in athletes before concussion, immediately post-concussion, and at several weeks and several months follow-up may be considered. In addition to multiple, specific time points for assessment, future studies may also enroll a larger number of subjects, all of whom have never experienced a concussion. Future work may also include investigations into connectivity differences in other resting state networks; for example, the motor network.

Conclusion

We measured neurocognitive performance on tests of executive function as well as resting state functional brain connectivity in concussed and non-concussed participant groups. Based on our findings, neurocognitive measures may not reflect functional brain deficits several weeks after a concussion; however, during this time we found significantly increased connections within areas of the brain underlying executive function in the concussed group. rs-FC may therefore represent a more sensitive long-term measure of recovery after a concussion, and may be a useful aide for clinical assessment and follow-up care if investigated further longitudinally.

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Figure 1.

Statistical difference maps illustrating alterations between concussed and non-concussed participant groups for connections between **A.)** ACC, **B.)** LDLPFC, **C.)** RDLPFC, and other brain regions. Seed locations are indicated in green. ROIs are labeled in yellow. The colorbar represents t-values. Maps were thresholded at $p < 0.001$ (ACC seed) or $p < 0.005$ (LDLPFC and RDLPFC seeds) and cluster size > 25 .

Figure 2.

Relationship between total score on the Hamilton Depression Rating Scale (HAM-D) and the connectivity coefficient between the LDLPFC and Left Middle Temporal ROI for all subjects. Higher scores on the HAM-D indicate a more severe level of depression.

Figure 3.

Relationship between performance on the Inhibition/Switching portion of the Color-Word Interference Test and the connectivity coefficient between the ACC and Right Middle Frontal ROI for all subjects. Higher standardized Inhibition/Switching Errors Score indicates better neurocognitive performance.

Table 1

Subject Demographics

	<u>Mean Concussed Group (SE) (n=9)</u>	<u>Mean Non-Concussed Group (SE) (n=12)</u>	<u>p-value</u>
Age	20.3 (0.4) years	20.0 (0.4) years	0.57
Gender	7 males, 2 females	6 males, 6 females	--
HAM-D	2.4 (0.8)	1.6 (0.9)	0.49
BMI	26.0 (0.9)	26.6 (1.5)	0.76
Sports Played	Lacrosse(n=3), football(n=1), softball(n=1), basketball(n=1), ice hockey(n=3)	Lacrosse(n=3), swimming(n=1), track and field(n=1), football(n=2), field hockey(n=2), volleyball (n=1), ice hockey(n=1), gymnastics(n=1)	
Days Post-Concussion	112 (22)	--	--
Prior Concussions	1.33 (0.5)	--	--

BMI: Body Mass Index; HAM-D: Hamilton Rating Scale for Depression; SE: Standard Error

Table 2

Connectivity Coefficients

Seed-to-ROI	Mean Concussed Group CC (SE)	Mean Non-Concussed Group CC (SE)	p-value
ACC-Right Middle Frontal	0.24 (0.05)	0.06 (0.04)	0.02 [*]
ACC-Left Inferior Frontal	0.23 (0.07)	0.02 (0.04)	0.009 ^{**}
ACC-Left Superior Parietal	0.16 (0.03)	0.06 (0.03)	0.02 [*]
ACC-Left Medial Frontal	0.35 (0.05)	0.16 (0.05)	0.01 [*]
ACC-Left Middle Frontal	0.24 (0.04)	0.05 (0.03)	0.002 [*]
LDLPFC-Left Inferior Temporal	0.10 (0.03)	0.04 (0.02)	0.06
LDLPFC-Left Middle Temporal	0.23 (0.04)	0.11 (0.03)	0.02 [*]
LDLPFC-Right Inferior Parietal 1	0.20 (0.04)	0.07 (0.03)	0.01 [*]
LDLPFC-Right Inferior Parietal 2	0.31 (0.05)	0.20 (0.02)	0.03 [*]
RDLPFC-Right Inferior Temporal	0.14 (0.03)	0.05 (0.02)	0.01 [*]
RDLPFC-Left Inferior Temporal	0.08 (0.02)	0.05 (0.01)	0.13
RDLPFC-Left Lingual	0.14 (0.03)	0.04 (0.22)	0.01 [*]
RDLPFC-Right Inferior Frontal	0.22 (0.03)	0.16 (0.02)	0.07
RDLPFC-Left Superior Temporal	0.13 (0.03)	0.03 (0.04)	0.05
RDLPFC-Left Inferior Frontal	0.21 (0.03)	0.10 (0.02)	0.008 ^{**}
RDLPFC-Left Middle Frontal	0.20 (0.04)	0.09 (0.03)	0.03 [*]
RDLPFC-Right Superior Parietal	0.20 (0.03)	0.11 (0.02)	0.03 [*]

p-values:

^{*}
p<0.05^{**}
p<0.01

ACC: Anterior Cingulate Cortex; CC: Connectivity Coefficient; LDLPFC: Left DorsoLateral PreFrontal Cortex; RDLPFC: Right DorsoLateral PreFrontal Cortex; SE: Standard Error

Table 3

Color-Word Interference Test Measure-to-Connectivity Coefficient Correlations

<u>Seed-to-ROI</u>	<u>Correlation to Inhibition/Switching Errors on CWIT</u>	<u>Correlation p-value</u>
ACC-Right Middle Frontal	0.53	0.01 [*]
ACC-Left Inferior Frontal	0.38	0.09
ACC-Left Superior Parietal	0.37	0.10
ACC-Left Medial Frontal	0.30	0.19
ACC-Left Middle Frontal	0.24	0.29
LDLPFC-Left Inferior Temporal	0.52	0.02 [*]
LDLPFC-Left Middle Temporal	0.56	0.009 ^{**}
LDLPFC-Right Inferior Parietal 1	0.45	0.04 [*]
LDLPFC-Right Inferior Parietal 2	0.50	0.02 [*]
RDLPFC-Right Inferior Temporal	0.30	0.18
RDLPFC-Left Inferior Temporal	0.43	0.05
RDLPFC-Left Lingual	0.14	0.54
RDLPFC-Right Inferior Frontal	0.26	0.25
RDLPFC-Left Superior Temporal	0.42	0.06
RDLPFC-Left Inferior Frontal	0.37	0.10
RDLPFC-Left Middle Frontal	0.35	0.12
RDLPFC-Right Superior Parietal	0.33	0.15

p-values:

*
p<0.05**
p<0.01

ACC: Anterior Cingulate Cortex; LDLPFC: Left Dorsolateral PreFrontal Cortex; RDLPFC: Right Dorsolateral PreFrontal Cortex