January 2017

Residual Deficits Observed In Athletes Following Concussion: Combined Eeg And Cognitive Study

Tamanna Tabassum Khan Munia

Residual Deficits Observed in Athletes Following Concussion: Combined EEG and Cognitive Study

by

Tamanna Tabassum Khan Munia
Bachelor of Science, Khulna University of Engineering and Technology

A Thesis

Submitted to the Graduate Faculty

of the

University of North Dakota

in partial fulfillment of the requirements

for the degree of

Master of Science

Grand Forks, North Dakota

December
2017

This thesis, submitted by Tamanna Tabassum Khan Munia in partial fulfillment of the requirements for the Degree of Master of Science from the University of North Dakota, has been read by the Faculty Advisory Committee under whom the work has been done and is hereby approved.

Dr. Reza Fazel-Rezai

Dr. Kouhyar Tavakolian

Dr. Mark Romanick

Dr. Colin Combs

This thesis is being submitted by the appointed advisory committee as having met all of the requirements of the School of Graduate Studies at the University of North Dakota and is hereby approved.

Grant McGimpsey
Dean of the Graduate School

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Department	Electrical Engineering
Degree	Master of Science

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ACKNOWLEDGEMENTS

We gratefully acknowledge Dr. Naznin Virji-Babul and her team from University of British Columbia (Vancouver, Canada) for providing us a dataset for our analysis. We also gratefully acknowledge Md. Ali Haider, Charles Schneider and Jeffrey Gendreau, for their assistance in data collection and analysis. In addition, financial support from University of North Dakota Faculty and Collaborative Seed Money and Department of Electrical Engineering are gratefully appreciated.

ABSTRACT

The neurocognitive sequelae of a sport-related concussion and its management are poorly defined. Emerging evidence suggests that the residual deficits can persist one year or more following a brain injury. Detecting and quantifying the residual deficits are vital in making a decision about the treatment plan and may prevent further damage. For example, improper return to play (RTP) decisions in sports such as football have proven to be associated with the further chance of recurring injury, long-term neurophysiological impairments, and worsening of brain functional activity.

The reliability of traditional cognitive assessment tools is debatable, and thus attention has turned to assessments based on electroencephalogram (EEG) to evaluate subtle post-concussive alterations. In this study, we calculated neurocognitive deficits in two different datasets. One dataset contains a combination of EEG analysis with three standard post-concussive assessment tools. The data for this dataset were collected for all testing modalities from 21 adolescent athletes (seven concussive and fourteen healthy) in three different trials. Another dataset contains post-concussion eyes closed EEG signal for twenty concussed and twenty age-matched controls. For EEG assessment, along with linear frequency-based features, we introduced a set of time-frequency and nonlinear features for the first time to explore post-concussive deficits. In conjunction with traditional frequency band analysis, we also presented a new individual frequency based approach for EEG assessment. A set of linear, time-frequency and nonlinear EEG markers were found to be

significantly different in the concussed group compared to their matched peers in the healthy group. Although EEG analysis exhibited discrepancies, none of the cognitive assessment resulted in significant deficits. Therefore, the evidence from the study highlight that our proposed EEG analysis and markers are more efficient at deciphering post-concussion residual neurocognitive deficits and thus has a potential clinical utility of proper concussion assessment and management.

Moreover, a number of studies have clearly demonstrated the feasibility of supervised and unsupervised pattern recognition algorithms to classify patients with various health-related issues. Inspired by these studies, we hypothesized that a set of robust features would accurately differentiate concussed athletes from control athletes. To verify it, features such as power spectral, statistical, wavelet, and other nonlinear features were extracted from the EEG signal and were used as an input to various classification algorithms to classify the concussed individuals. Various techniques were applied to classify control and concussed athletes and the performance of the classifiers was compared to ensure the best accuracy. Finally, an automated approach based on meaningful feature detection and efficient classification algorithm were presented to systematically identify concussed athletes from healthy controls with a reasonable accuracy. Thus, the study provides sufficient evidence that the proposed analysis is useful in evaluating the post-concussion deficits and may be incorporated into clinical assessments for a standard evaluation of athletes after a concussion.

CHAPTER 1

INTRODUCTION

1.1 Motivation

A concussion is a complex pathophysiological procedure which is induced by a direct blow to the head, neck, face or any other part of the body that transmits an impulsive biomechanical force to the head, affecting the brain [1]. In the US alone, sport and physical activity cause nearly 4 million concussions each year [2], [3]. It is critical to assess concussion and mild traumatic brain injury (mTBI) with high accuracy to avoid anxiety, sensitivity and cognitive biases which appear as post-concussion syndrome. Moreover, insufficient follow-up and treatment can put the post-concussive person under the risk of neurobiological depression with anxiety resulting in a longer concussion recovery time. Therefore, proper understanding and measuring of concussions are essential to treat the psychological factors as a means of effective prevention, which, in turn, can lead to a rapid post-concussion recovery period. When examining performance metrics related to motor control, it is well established that individuals diagnosed with the post-concussion syndrome can show marked impairments in reaction times [4], visual motor processing [5], gait stability [6], postural balance [7] and dynamic gait analysis [8], [9]. More importantly, it is a primary concern for both amateur and professional athletes. Because the symptoms of concussions sometimes go unnoticed or are self-reported and tend to subside within 1-2 weeks [10], many athletes fail to seek immediate and proper medical care. Furthermore, high school athletes tend to purposely avoid reporting their concussions in order to prevent being “benched” during subsequent games [11].

Though almost all recreational participants express their concern about post-concussion syndrome, most competitive athletes keep quiet about their minor physical discomforts or even deny considerable pain for the sake of pursuing their career goals. Although athletes' willingness of accepting risks greatly varies with the competition stages, game completion levels and types of sports, it's more likely that many individuals will choose to continue to play with a concussion rather than remove themselves from competition [12]. However, such a decision can pose a risk to their health with the potential for repeated head trauma [13]. Athletes have been shown to suffer from cognitive deficits up to three years after their brain injury incidents, exhibiting lower performance on select neuropsychological tasks when compared to an age-matched non-concussed group [14].

Detecting and quantifying the residual deficits are vital in making a decision about the treatment plan and may prevent further damage. For example, improper return to play (RTP) decisions in sports such as football have proven to be associated with the further chance of recurring injury, long-term neurophysiological impairments, and worsening of brain functional activity. The reliability of traditional cognitive assessment tools is debatable, and thus attention has turned to assessments based on electroencephalogram (EEG) to evaluate subtle post-concussive alterations. These ongoing debates about the degree of impairment concussion inflicts on physiological systems motivated us to work to find out a potential measurement tool which can expose the long-term cognitive impairment after an analytical study of EEG signals and help us to better understand the truer neurophysiological status after a concussion, along with the presence of a more positive neurocognitive and clinical assessment. To test our hypothesis, we utilized visual (King-Devick (K-D) Test), postural (Balance Error Scoring System (BESS)) and neurological (Immediate Post-Concussion Assessment and Cognitive Testing battery (ImPACT)) tests, along with a novel EEG spectral analysis that computes the distinguishing features from each individual component of EEG, as well as from the set of conventional frequency bands.

1.2 Concussion

Sport-Related Concussion (SRC), is a type of traumatic brain injury that is initiated by a sudden blow to head, a fall or any other injury that shakes the brain inside the skull, and affects the brain function [15] . After the injury, sometimes the affected people will suffer from obvious symptoms of a concussion, like forgetting what happened immediately before the injury or passing out. But, it is also possible to have a concussion without realizing it. Concussions are particularly common in the contact sports, such as football, rugby, soccer, and hockey. Besides contact sports, other causes may include blows to the head, bumping your head when you fall, being violently shaken, and car accidents. Though usually most of the people recover fully after a concussion, for some people, symptoms may persist for days, weeks, or longer. The recovery after a concussive incident may be slower among teens, older adults or young children [16] . People with one or multiple concussion in the past are also at risk of having another one and may also find that it takes longer to recover with a concussion history [17].

According to Head Injury Hotline [18], a concussion is "A complex pathophysiological process affecting the brain, induced by a violent blow, shaking or other non-penetrating injury to the brain."

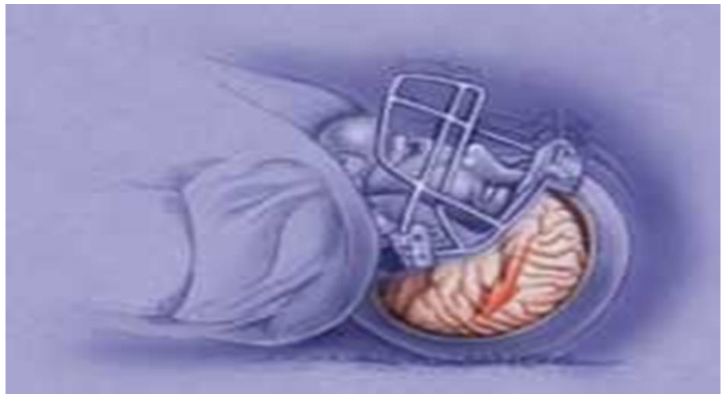


Figure 1. Concussion [18]

According to CDC Physicians Toolkit [19], the evolving definition of concussion is, **"**A concussion (or mild traumatic brain injury) is a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces secondary to direct or indirect forces to the head. **Disturbance of brain function is related to neurometabolic dysfunction, rather than structural brain injury**, and is typically associated with normal structural imaging findings (CT Scan, MRI) **"**[19].

Concussion may or may not result in a loss of consciousness. Concussion results in a collection of symptoms including physical, emotional, cognitive, and sleep-related disturbances. The recovery is a progressive process and the symptoms may persist for several minutes, hours to days, weeks, months, or even lengthier in few cases. The CDC physicians toolkit suggests physicians remember the following points immediately after a concussion [16]:

- **"** Following a concussion, there are metabolic chemical changes that take place in the brain.
- Brain injury can occur even if there is **NO** loss of consciousness.
- More than 90% of concussions **DO NOT** involve loss of consciousness.
- Memories of events **BEFORE** and **AFTER** the concussion are MORE accurate assessments of SEVERITY than the loss of consciousness. **"**

The definition of concussion defined by first and third international conference of concussion is “a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces” and recommended five conditions for concussion [19]:

1. Concussion can be initiated by a direct blow to the head, face, neck, or elsewhere in the body that transmits an impulsive or rotational force to the head.

2. A concussion usually results in the quick onset of short-lived neurologic impairment that resolves spontaneously.

3. Concussion may result in neuropathological deviations, but the acute clinical symptoms hardly reveal a functional disorder in lieu of structural injury.

4. Concussion results in a graded set of medical syndromes that may or may not involve loss of consciousness; determination of clinical and cognitive symptoms often follows a sequential course.

5. A concussion is normally associated with grossly normal structural neuroimaging studies.

According to CDC report, youths are at increased risk of concussion as 65% of the concussions occur in children between 5 to 18 years of age [20]. These children are at a larger risk for traumatic brain injury as the brain of a pediatric athlete is still young and developing and the tissue of this brain is not able to recover as rapidly as an adult brain [16]. This young population is more vulnerable to metabolic and neurochemical changes, their axons are not yet properly myelinated or insulated, their shoulder and cervical musculature are less developed causing in a reduced ability to absorb any mechanical energy through their bodies, and moreover, they are less likely to follow proper techniques to minimize risk [19]. Though majority will recover within the first 3-4 weeks, in some cases symptoms persist for much longer and 5-10% last a lifetime [21].

1.2.1 Concussion Pathophysiology

Our brain is one of the softest organs, encircled by spinal fluid and sheltered by the hard skull. Generally, the fluid, encircling the brain acts like a cushion that saves the brain from knocking the skull. But if the head or the body is hit hard, the brain can strike into the skull and thus cause injuries. There are numerous ways to sustain a concussion. The common methods include playground injuries, falls, fights, bike accidents and car crashes.

When the head strikes a hard object creating a concussion-type injury, it creates linear or rotational forces causing an acceleration and deceleration of the brain and thus results in a transient alteration of the brain function [19], [22].

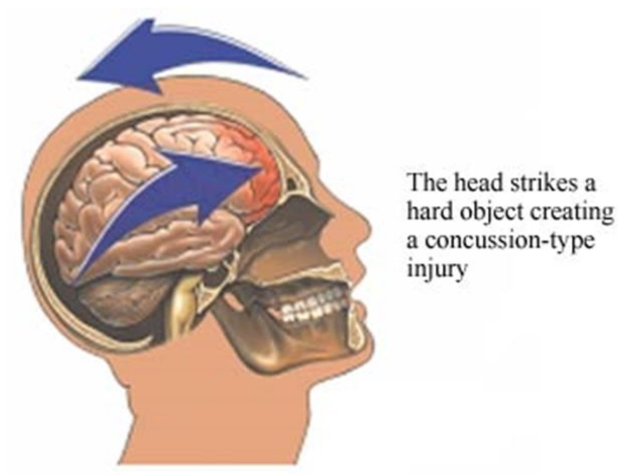


Figure 2. Concussion Pathomechanics [18]

The alteration in the brain can occur on the side of the force, or the opposite side of the force. Figure 3 shows a linear injury whereas Figure 4 shows a rotational injury.

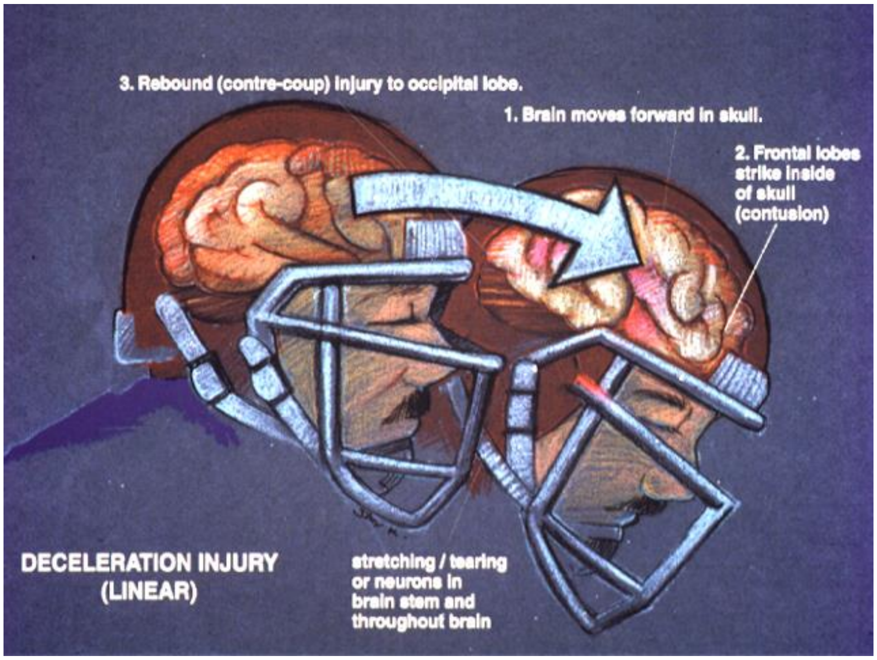


Figure 3. Linear injury [19]

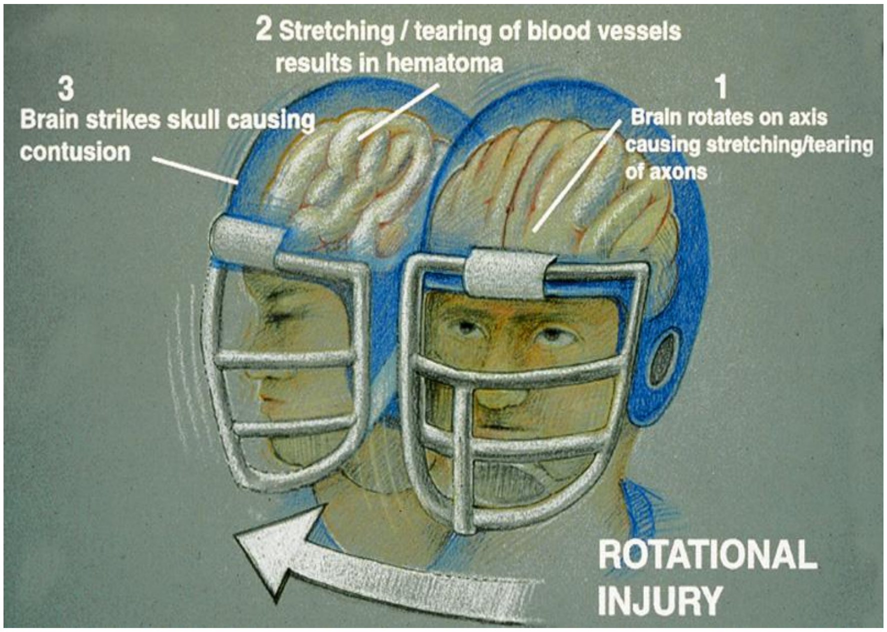
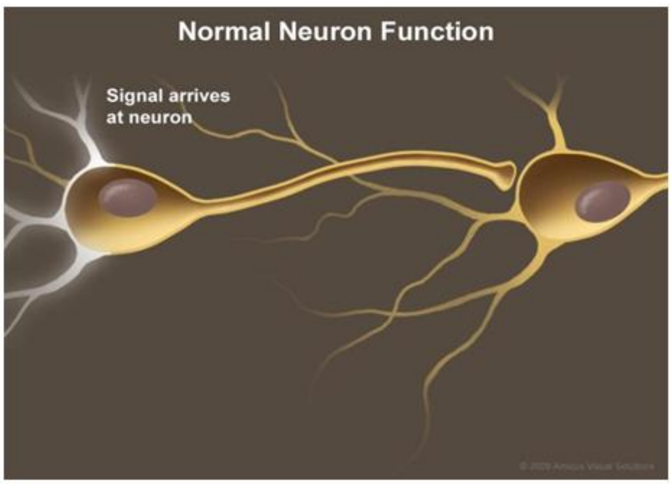
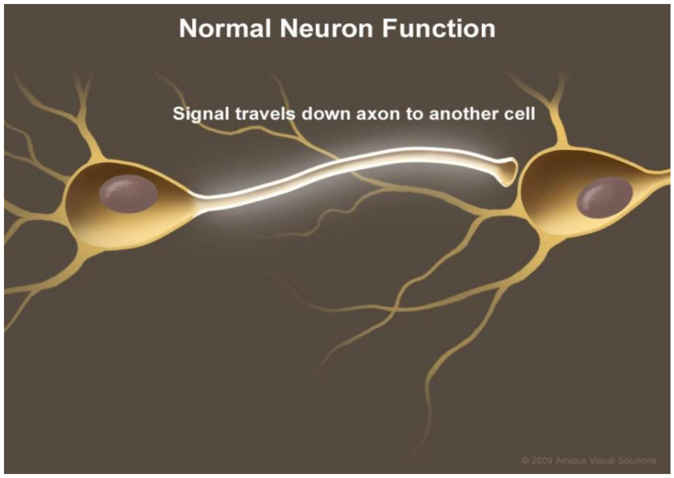


Figure 4. Rotational injury [19]

According to Dr. Micky Collins [19], Director UPMC Sports Medicine Concussion Program, the force creates a wave of energy that flows through the brain tissue to trigger neuronal dysfunctions. This includes a complex cascade of ionic, physiologic, and metabolic dysfunction, and sometimes is also referred to as a neurometabolic cascade of concussion. The concussion symptoms are generated due to this cascade and also because of microscopic axonal dysfunctions. In most cases, these dysfunctions are generally self-resolved itself and in most of the cases, the patients are fully recovered. However, while the brain is still in the recovering phase, a reduction in cerebral blood flow may result in cell dysfunction, eventually increasing the susceptibility of the cell to a second injury [16]. During normal neuron function**,** the components of the neuron including the dendrites, axon, nerve cell body, and synapse, work together in a process whereby the signal reaches the neuron and then the signal travels down the axon to the following cell through the synapse by means of neurotransmitters, triggers the subsequent cell with a particular message as shown in Figure 5 (a), (b) and (c).



(a)



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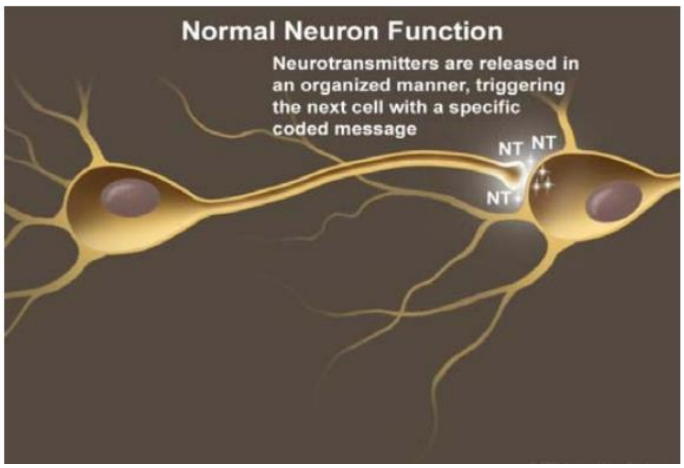
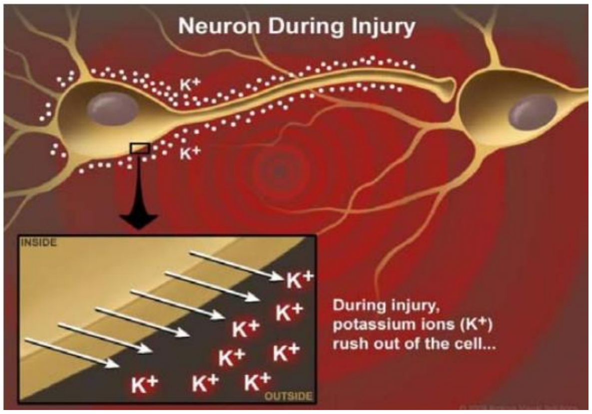


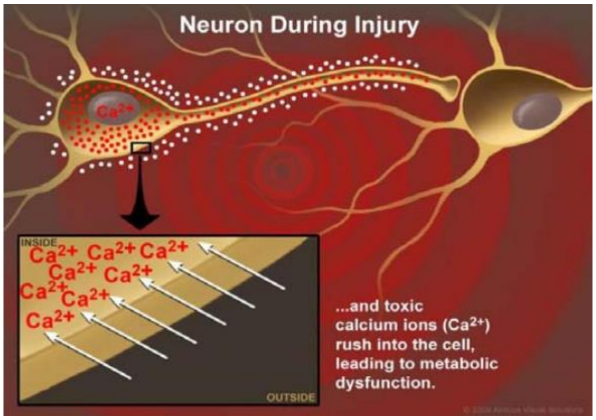
(c)

Figure 5. Neuronal function for a 'Normal Brain' [19]

However, during injury, the neuron discharges its K^+ (Potassium), which flares out of the cell body and toxic Ca^{2+} (Calcium) ions blast into the cell, leading to metabolic dysfunction as shown in Figure 6 (a), (b) and (c).



(a)



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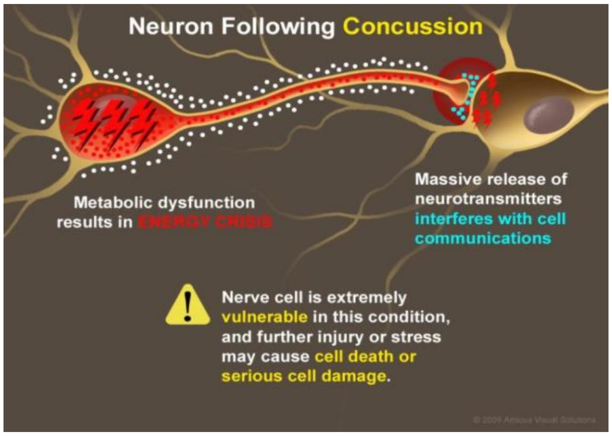

(c)

Figure 6. Neuronal function following a concussion [19]

These alterations of the brain develop some physical, cognitive and behavioral changes described as **concussion symptoms**.

1.2.2 Concussion Symptoms

The symptoms of a concussion are not fixed and may differ depending on the severity of the injury and also with the person injured. The concussion is also referred as a "mild" brain injury sometimes. It is important to comprehend that, concussions may not be a life-threatening injury, but they can still be very serious. The symptoms caused by concussion are subtle and sometimes may not be found right away; but they may start days or weeks following the incident. Rest is essential after a concussive injury as it helps the brain to reconcile the symptoms. It is suggested that, at the very beginning phase of recovery, a concussed person may limit their physical activities, as well as activities that require a lot of concentration, for example studying, playing video games or working on the computer [15]. These activities may worsen the already existed concussion symptoms like a headache or tiredness. Then, when the healthcare provider agrees, the concussed person can start to return to his/her normal activities slowly. All the cognitive, somatic and affective concussion symptoms are listed in Table 1 [16].

Table 1. Concussion symptoms [16]

COGNITIVE	SOMATIC	AFFECTIVE
1. Confusion 2. Post-traumatic amnesia 3. Retrograde amnesia 4. Loss of consciousness 5. Disorientation 6. Feeling "in a fog," "zoned out" 7. Vacant Stare 8. Inability to focus 9. Delayed verbal and motor responses 10. Slurred/incoherent speech 11. Excessive drowsiness 12. Balance problem	1. Headache 2. Fatigue 3. Disequilibrium, dizziness 4. Nausea/vomiting 5. Visual disturbances (photophobia, blurry/double vision) 6. Phonophobia 7. Balance problems 8. Sleeping more/less than usual 9. Trouble falling asleep	1. Emotional lability 2. Irritability 3. Sadness 4. Nervousness or anxiety

Table 2 highlights the most reported concussion symptoms based on a study conducted with 1438 concussed athletes (1-7 days following a concussion)[23].

Table 2. Most reported concussion symptoms (in percentage) [23]

Serial Number	Symptom	Percentage
1	Headache	75%
2	Difficulty Concentrating	57 %
3	Fatigue	52 %
4	Drowsiness	51 %
5	Dizziness	49 %
6	Foggy	47 %
7	Feeling Slowed Down	46 %
8	Light Sensitivity	45 %
9	Balance Problems	39 %
10	Difficulty with Memory	38 %

1.2.3 Concussion Diagnosis

For the diagnosis of concussion, normally the health care provider will do a physical exam and ask about the injury. The injured person most likely will have a neurological exam, which checks vision, balance, coordination and reflexes. The healthcare provider also conducts an examination to evaluate memory and cognition. In some severe injury cases, the concussed athletes may have a brain scan like MRI or a CT scan. A scan can check for a skull fracture or bleed, as well as inflammation in the brain. A various multifaceted approach which can capture the variability of deficits following an injury is proposed by several agencies for the assessment and management of concussion. Commonly used evaluation tools used for concussion are described as follows.

- **Physical Evaluation**

Physical evaluation normally takes place on the sideline within the first few minutes or immediately after an injury. A concussion management survey showed that more than 85% of physicians use this physical/clinical evaluation as the primary concussion assessment tool [24]. The physical evaluation includes questionnaires about the history and a complete testing of motor, nervous and sensory systems by the team medical staffs following an injury. The history questions provide information about the existence of previous concussion, symptoms that are unrelated to the current injury or any other post-concussive symptoms. The nervous evaluation mainly assesses the cranial nerves and give emphasis to the pupillary reflex.

- **Imaging**

Sport-related concussion mainly results in functional deficits rather than structural or physical deficits. That's why there is good evidence in the literature showing imaging techniques such as MRI, X-ray or CT scan unable to find out concussive deficits unless there was any structural change in the brain [25]. But newer techniques like functional MRI (fMRI) can provide neural function information and be used with a dual-task paradigm for concussion assessment [26]. Other techniques like magnetic source imaging (MSI), can track real-time brain activity by conducting through brain, skull and scalp without distorting [27].

With the improvement of technology, the understanding of post concussive deficits should also improve. The use of newer techniques like MSI, PET and SPECT for concussion management is still limited to researchers only because of accessibility, cost and availability. Use of image techniques like MRI, X-ray and CT scan may be helpful for identifying life-threatening concussive injuries and can be used as a precaution if other more advanced techniques are not available. But most of the case, during sideline testing for mild concussions, imaging techniques are not available and so continuous monitoring of symptoms through another neurophysiological testing can provide immediate insights about the injury.

- **Self- Report Symptoms**

The interaction between athletes and their physician or medical staffs after a concussion are typically completed through some self-reported symptom checklist. Commonly used symptom scales to quantify the severity are the Post-Concussion Symptom Scale (PCSS), Head Injury Scale (HIS) and Graded Symptom Checklist (GSC). A survey with 2750 certified athletic trainer conducted by Notebaert *et al*. showed that about 85% of the athletic trainers use a self-reported symptom score list as a part of their evaluation battery [24]. The baseline assessment is important for self-reported evaluation as the symptoms reported by the athletes after an injury may be present at baseline [29]. The reliability of self-reported symptom evaluation is questionable as the evaluation results solely depend upon the interaction between the athletes and the medical professional and may vary with the desire of the athletes to return to play. So caution should be taken by clinicians while relying solely on self-reported symptoms and the use of a multifaceted assessment technique is highly recommended.

- **Sideline Assessments**

The athlete may display some changes in their cognitive, postural, and visual or symptom reports following a concussion. These deficits observed immediately after a concussion can be used to obtain a measure of concussion severity and can provide invaluable information for concussion management. Most commonly used sideline device for a concussion assessment includes King Davick (KD) test, Standardized Assessment of Concussion (SAC), and Sport Concussion Assessment Tool (SCAT).

The K-D test is a two-minute rapid number naming assessment in which an individual reads numbers aloud quickly from test cards total time required to complete the task is calculated to evaluate any visual processing deficits after a concussion [30].

The SAC is a neurocognitive examination that was specifically intended for the assessment of athletes who have concussions on the sideline of play. The test components include orientation, memory, concentration, and delayed recall. Athletes who had concussion scored significantly different than athletes who did not, with scores 48 hours post-injury returning to baseline values for the injured group [31]. A decline in SAC score at the time of injury is 95% sensitive and 76% specific in accurately classifying injured and uninjured subjects. Reliability analysis demonstrated a test-retest reliability of 0.53 [31].

- **Neuropsychological Tests**

Neuropsychological tests batteries have gathered a large attention from the athletic training as tools for a cognitive assessment of function before and following a concussion.. Several computerized neuropsychological platforms have recently been developed and include the Automated Neuropsychological Assessment Metrics, Cogsport, Headminder, and Immediate Post-Assessment of Concussion Test [4], [37]–[39]. These platforms increase higher sensitivity and more precise measures for the reaction time. Moreover, the computerized battery is easy to be administered in small groups without sacrificing the reliability. Evidence from a huge amount of liturature supports the use of neuropsychological testing for a concussion assessment. The suggestion from the literature suggests that the recovery patterns for collegiate and professional athletes following concussion lasts for hours [32], [40] up to 7 days [34], [41]. Following a concussive injury, individuals typically show transient deficits in cognitive functioning that can frequently be noticed through neuropsychological testing. These tests are measured to be the gold standard in concussion assessment sometimes, but they have never been assured for use with concussed athletes [42]. Further, there has been no consensus among researchers as to which neuropsychological tests within the battery are the most sensitive in identifying change following a concussion [43].

- **Posturography**

Following concussive injuries, athletes may have difficulty assimilating information from the three aspects of the balance mechanism. Though the somatosensory aspect seems to remain normal, incorporation between the visual and vestibular components have found to be not functioning accurately [34].

The two most frequently used postural assessment tools are the Balance Error Scoring System (BESS) and Neurocom Sensory Organization Test. The Sensory Organization Test (SOT) has a force plate that can measure angles and the forces that are produced at the ankle, hip and knee. The test systematically varies visual and somatosensory referencing in an attempt to individually evaluate the three components of the balance mechanism (visual, somatosensory and vestibular). The SOT is considered as the gold standard for the assessment of postural stability in concussion; however, the SOT is very expensive and it is not portable. The BESS was developed as an objective assessment tool to be used by clinicians with least training and cost for the sideline evaluation of the postural steadiness after a concussion incident. Athletes suffering from a concussion have found to expose deficits in postural balance while using the SOT and BESS assessment for up to 5 days postinjury in a collegiate population; the recovery to the pre-injury states typically occurring within 4 to 7 days. Postural evaluation within a concussion battery has been proven as postural deficits following injury were present after symptoms resolution and cognitive deficits dissipated [34], [44]. Concussion assessment tools are recommended in combination to obtain complete information regarding deficits post-concussion. Broglio and colleagues [45] found that neuropsychological testing in combination with self-reported symptoms produces a sensitivity of 89% to 96% following a concussion. As the discrepancies after a concussion carry the similar variability as the individuals who have a concussion, a multidimensional approach provides information regarding as many deficit areas as possible. Obtaining the most information possible will enable clinicians to offer quality care and management while providing good, reliable, and safe return-to-participation decisions.

1.3 Current Trends in Literature for Concussion Assessment and Management

With the advancement of concern about sports medicine, at present the clinicians and researchers have a variety of tools available for evaluating the post-concussion deficits and rehabilitating the athletic injuries. In most cases, these tools offer the clinicians evidence about the presence of the injury and the severity of the symptoms. But the clinicians need to recommend a timeframe for the rehabilitation and suggest the return to play timeline after a concussion incident. In the case of sport-related concussion, no simple tests are available that can be implemented in the brain to determine the actual severity of a head injury and assist the clinicians in establishing a goal for rehabilitation and a timeline for a return to play. Due to the complexity of concussion injuries, it is required that the clinicians use a variety of tools to gather as much information as possible, but most of the cases, the tendency is to determine the return-to-play decision based on the athlete's self-reported symptoms and their ability to perform some sport-specific tasks without a resurgence of concussive symptoms [46]–[48]. It can be dangerous to solely rely on this information for an important decision like a return to play timeline, since it can only provide a partial picture of the injury [24].

A multidimensional protocol has been suggested by various authors in the literature [25], [46], [47], [49]. The recent statement published by the National Athletic Trainers' Association (NATA) suggests to include the symptom checklists, postural stability assessment and neuropsychological testing together for concussion assessment [49]. A baseline testing is important on these measures for the athletes who are participating in contact sports with a high risk of concussion; however, it is also recommended that, if the resources are available, then all athletes should obtain the baseline assessment. If baseline testing is available, the follow-up testing should be performed to assist during the decision procedure for return to play. The use of all the available information about the post-injury condition may be the best method to ensure the safe return of an athlete to play after an injury.

1.3.1 Postural Stability Assessment:

Postural stability has become an integral part of the post-concussion assessment for many athletic trainers. Clinicians, however, sometimes question the viability of instituting preseason baseline testing and the value of these results in making return-to-play decisions. A lot of studies were performed to examine the efficacy of postural study and the course of recovery on various postural stability measures after sport-related concussion. The postural stability test conducted by Guskiewicz *et al.* with 36 concussed athletes at day 1, 3 and 5 post-injury using the Sensory Organization Test on the NeuroCom Smart Balance Master System and the Balance Error Scoring System revealed that the postural stability deficits were significantly poorer than both baseline scores and scores from matched control subjects' on post-injury day 1 [36]. Another study conducted by Guskiewicz *et al.* on 19 healthy and 19 concussed athletes on days 1, 3, 5 and 10 days postinjury using the Chattecx Balance System for three eye conditions and also for three surface conditions to measure sway index and center of balance suggested that the concussed group revealed increased postural sway compared with the control group on day 1 post-injury through all platform conditions, and for the foam platform condition on day 3 [50]. The center of balance analysis for the same subjects discovered that the injured athletes' center of balance was farther away from the baseline on day 1 post-injury in comparison with the subsequent tests ($p < .05$) [50]. Riemann *et al*. also investigated the efficacy of the clinical balance testing procedure in terms of BESS tests and the NeuroCom Smart Balance Master for Sensory Organization Testing for the detection of acute postural stability disruptions at 3 post-injury time intervals (days 1, 3, and 5) [51]. The statistical analysis resulted in significantly higher postural instability in the mild head injury subjects through BESS test battery, with the foam surface revealing significant differences at day 3 post-injury [51]. A Sensory Organization Test analysis also highlighted significant group variations on day 1 post-injury [52]. A retrospective cross-sectional study conducted by Sonsoff *et al*. with 224 individuals (among them 62 mTBI participants) to assess postural control associated with the history of concussion using the NeuroCom Sensory Organization Test (SOT) postural-assessment battery revealed minimal alterations in the SOT indices between individuals with and without a history of concussion or mTBI ($P > .05$) [53]. Unlike traditional measures of postural control, while author conducted nonlinear dynamical measures using approximate entropy on the 'center of pressure' time series data, individuals with a history of mTBI displayed different postural dynamics compared to the individuals with no history of mTBI [53]. So the author hypothesized that the lack of group differences in traditional SOT measures but the presence of deficits during in-depth nonlinear study raises questions about the ability of the traditional balance assessments tools to readily identify the deficits beyond the severe stage of injury [53]. Thus, it is required for the clinicians to be aware of these limitations of traditional measures and comprehends that more sensitive and accurate procedures of both static and dynamic balance may disclose the clinically significant changes in postural stability present due to the persistent effects of concussion [53]. The first approximate entropy based study conducted on the center of pressure data collected from 29 concussed athletes revealed that, the approximate entropy values of time series data decreased immediately at 48 to 96 hours after injury, compared with the healthy preseason state and, approximate entropy values remained significantly depressed even among athletes whose initial postural instability had resolved [54]. So the author concluded that the effects of the cerebral concussion might persist for longer than 3 to 4 days on postural stability control, even among the athletes who have no signs of unsteadiness. Slobounov *et al*. conducted a virtual time-to-contact (VTC) based study to measures of postural stability on 12 concussed athletes on 30 days post-injury along with traditional COP based measure (COP area, velocity and stability index) and reported that, though no significant differences were found for any of the standard COP-based measures of postural control, there were significant variations in the absolute values of VTC, mode and range of VTC at the deflection points, at the day 30 post-injury [55]. Shannon and Renyi Entropy-based study conducted by Cao *et al*. reported postural instability in athletes at least 10 days post-concussion through the calculation of the area of COP and fractal analysis of COP motion time courses and suggest that entropy analysis appears promising as a sensitive measure of effects of mTBI on postural sway [56].

1.3.2 Neuropsychological Testing

The practice of neuropsychological testing for the management of sport-related concussion is gradually becoming more familiar among the sports medicine clinicians and researchers. Recent research suggests that, the practice of using these comprehensive approaches may benefit the team physicians and the athletic trainers to identify the signs of a concussion that is not identified through the routine clinical examination [33], [50], [52]. Moreover, the use of these tests can reduce some of the presumptions from the return-to-play (RTP) decision following a concussion, as the subjective nature of the post-concussion symptoms makes this assessment very challenging [36]. Even though the consequences of an athlete's premature RTP after a concussion can be potentially catastrophic, often the RTP decisions are taken based on assumption rather than certainty [36]. The life-threatening consequences of a second-time syndrome are well documented in the literature [57]–[61] and should be an important concern for all sports-medicine personnel.

Recent research has established that even in case of a mildly concussed athletes, there can be a noticeable memory decline, enduring for at least 7 days after the injury [62], [63]. These data have led to a reexamination of previous return-to-play guidelines and a reconsideration of return-to-play standards that were heavily symptom-based. The Vienna Concussion Centre has recently endorsed neurocognitive testing as a “cornerstone” for concussion management and identified this test as a cooperative piece of information to assist the diagnosis and management of concussions [25]. This position was reassured by the second international conference held in Prague in 2004 [64]. The role of neurocognitive testing in the diagnosis and management of concussion has been emphasized because of the potential unreliability of the athletes’ self-reported symptoms. The minimization of post-concussion symptoms (PCS) is a well-known phenomenon at all levels of competition [65], [66]. An athlete’s apparent fear of elimination from a game or the anxiety of losing his/her position on the team may tempt the athlete to deny or underreport postconcussive symptoms [67]. Moreover, previous research has hypothesized that premature RTP may be a dangerous practice, particularly in children, as there is a probability of heightened degree of vulnerability present in this group [17], [68].

The most popular test battery designed specifically for sports-related concussion is Immediate Postconcussion Assessment and Cognitive Testing (ImPACT), which is a computer-aided neurocognitive test battery [67]. This is a widely used program, allowing completion of neurocognitive testing in an expeditious and standardized manner. The ImPACT test battery has endured widespread validation over multiple studies and is presently used throughout all professional and amateur sports [63], [69]–[71].

In one study, Iverson used the ImPACT to evaluate post-concussion recovery [71]. Findings highlighted that the athletes who exhibited 3 of 4 reliable deficits, relative to their baseline levels of functioning, were 94.6% likely to necessitate at least 10 days to recover to be asymptomatic at rest and also while demonstrating intact neurocognitive functioning [71]. Furthermore, the study also suggested that the summation of the Post-Concussion Symptom Scale (PCSS) score was higher for the protracted recovery group, presenting that athletes with more symptoms require a longer time to recover [71].

Current large-population outcome studies using symptom- and neurocognitive-dependent measures after sports concussion highlight that typical recovery from sports concussion occurs within 10 to 14 days of injury [71]–[73]. Guskiewicz *et al*. examined the course of recovery with 36 concussed athletes (at postinjury days 1, 3, and 5) and 36 matched control by measuring their neurocognitive functioning using a combination of neuropsychological tests including Trail-Making Test, Stroop Color Word Test, Wechsler Digit Span Test and Hopkins Verbal Learning Test [36]. The analysis conducted for the 'Trail-Making Test' and 'Wechsler Digit Span Test Backward' resulted in a reasonable recovery curve that was able to link the lowered neuropsychological performance to the concussive injury [36]. Another ImPACT based neurocognitive testing conducted by Kampen *et al*. involving 122 concussed athletes at 2 days post-injury along with 70 healthy matched control resulted into significantly different "Abnormal" test performance for statistical analysis with reliable change index scores [67]. More than 280 peer-reviewed studies and 145 independent studies used ImPACT as a concussion management tool [74].

Another important neurophysiological test battery is Standardized Assessment of Concussion (SAC), which is a brief neurologic screening instrument initially developed to provide sports medicine personnel with a standardized technique of assessing athletes within minutes of sustaining MTBI during competition [75], [76]. Earlier studies have demonstrated the SAC's utility as a sensitive and accurate method of detecting mental status and neurologic abnormalities immediately following sports-related concussion, but did not scientifically observe the reliability of alteration in SAC performance as an indicator to reveal the clinically meaningful variations in neurocognitive status due to injury [31], [75]. The study conducted by Barr *et al.* to test the sensitivity and specificity of SAC on 50 concussed and 68 non-injured athletes resulted in 94% sensitivity and 76% specificity and thus provided supports indicating that the SAC is a valid instrument for detecting the immediate effects of mild traumatic brain injury [77].

A prospective cohort study where 94 concussed and 56 noninjured controls underwent assessment of symptoms, cognitive functioning, and postural stability by using Graded Symptom Checklist (GSC), Balance Error Scoring System (BESS), Standardized Assessment of Concussion (SAC), and a combination of neuropsychological test batteries (detailed in [41], immediately after the concussion, 3 hours after the injury, and 1, 2, 3, 5, 7, and 90 days post-injury provided a valuable insight to develop the clinical management system for the athletes recovering from concussion [41]. The study revealed that athletes with concussion displayed more severe symptoms that gradually resolved by day 7; immediate post-concussion balance deficits, that dissipated within 3 to 5 days after injury; and cognitive impairment that improved to baseline levels within 5 to 7 days post injury on average [41]. There were no significant differences revealed in terms of symptoms or functional impairments between the concussed and control groups 90 days after the injury [41].

Although numerous studies have used neuropsychological tests to document cognitive impairment following MTBI, there is a debate about the role of injury-related and non-injury related factors contributing to neuropsychological test performance in this population [78], [79]. Additionally, cognitive functions such as attention, processing speed, and working memory, which seem to be the most sensitive to variation after MTBI, are considered to transmit the least "hold" worth in test-retest conditions. Specifically, these functions are not only reported to be affected by MTBI, but are also likely to be sensitive to the effects of various factors comprising anxiety, physical pain and fatigue [80]. Consequently, the neuropsychologist assessing a patient with a concussion after a period of days, weeks, or months following an injury is frequently faced with the challenging task of separating the effects of cognitive deficiencies from other potential confounding influences.

1.3.3 Electrophysiological Assessment

A concussion is a complex pathophysiological procedure affecting the brain [81] and it is critical to assess concussion with high accuracy to avoid anxiety, sensitivity and cognitive biases, which appear as post-concussion syndrome. Moreover, insufficient follow-up and treatment can put the post-concussive person at the risk of neurobiological depression with anxiety resulting in a longer concussion recovery time. Therefore, proper understanding and measuring of concussions are essential to treat the psychological factors as a means of effective prevention, which, in turn, can lead to a rapid post-concussion recovery period. Despite a large number of assessment tools and studies, the reliability of these tests needs to be validated because most of these tools are designed to estimate a subject's performance while performing simple tasks that can reflect individual judgment. Evidently, the challenges in concussion assessment have led to the studies exploiting the sensitivity of EEG spectral features to mild, moderate, and severe traumatic brain injury over the time span as short as 15 days to four years post-concussion. Researchers have accomplished the quantitative analysis of the EEG signals collected from the concussed subject to evaluate the post-concussion physical and clinical recovery. Additional studies suggest that the EEG spectral profile varies with acute mTBI due to the change in the cognitive state during the resting stage [82], [83]. In essence, the spectral profile of EEG is also altered in acute mTBI and during any anomaly of consciousness. However, researchers argue whether mTBI can evoke long-term variations in spectral information. In addition, identification of any long-term change is sometimes controversially attributed to psychiatric comorbidity such as posttraumatic stress disorder (PTSD). So far, long-term neurological changes have remained indistinct. Nevertheless, many findings support that brain volume and white matter can be affected by mTBI [84]. Likewise, the resting state activation stage can be sensitive to mTBI. Another study found that EEG measurement was able to predict the return to play better than other measurement types [85]. Notably, one study examined EEG and showed that frequency information changes for as long as six months after the mTBI occurrence [86]. All these findings underscore the fact that the power of each frequency component of EEG can reveal significant physiological and clinical findings. Though there is a necessity to examine the details of spectral patterns after a mTBI incident, only a relatively small number of studies compared the spectral profiles just with a group of frequencies bounded under specific bands.

One of the most challenging problems associated with concussion is that currently there are no standardized, objective measures that can discern whether an individual has sustained a concussion or not [87]. This is particularly problematic given the wide heterogeneity of the mechanism of injury, the potential severity of the brain injury, and the resulting symptoms [87]–[89]. Thus, efforts to identify concussions from predictable symptoms collected upon preliminary examination may lead to inaccurate conclusions about the nature of the brain injury. Moreover, a study on sports concussions showed that common concussion symptoms, such as loss of consciousness and amnesia, are not very good predictors of outcome and severity of concussion [81]. Frequently used concussion assessment tools, like Balance Error Scoring System (BESS), Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT), and King-Devick (K-D) test, depend on some common postural stability and neurological measures [90], [91]. It should be noted that the symptoms associated with a concussion can be very subtle and some previous studies have shown that the physical and neurological symptoms of concussion are usually resolved within a one-week period [32], [92]. Consequently, the reliability of these traditional measures is questionable and can provide erroneous athletes' return-to-play (RTP) decisions [87].

Since the symptomatology at the time of concussion has proven not very useful in predicting outcome and severity, the hope is that EEG might be useful in this regard. EEG analysis has been used for concussion assessment over the last thirty years. Geets *et al.* tested 300 patients with concussion and reported a decrease in power in major EEG frequency bands and focal abnormalities within 48 hours of a concussive incident [93]. Tebano *et al.* showed an overall decrease in the beta frequency band and a shift in mean frequency in the alpha band towards lower power [94]. The reduction of theta power [95] accompanying a transient increase of alpha-theta ratios was identified as a residual symptom in concussion patients [96], [97]. The most comprehensive EEG study, using a database of 608 mTBI patients up to eight years post-injury, revealed: i) an increased coherence in frontal-temporal regions; ii) a decreased power differences between anterior and posterior cortical regions; and iii) a reduced alpha power in the posterior cortical region, all of which were attributed to mechanical head injury [98]. Our previous study involving adolescent athletes revealed an increase in the delta frequency band along with a decrease in the beta and gamma frequency band power spectral densities in previously concussed athletes [91]. Although several studies have provided substantial evidence of alteration in EEG patterns in concussed individuals [44], [90], [98], a controversial report indicating no unique EEG features associated with concussion, especially post-injury, was also reported [99].

CHAPTER 2

RESIDUAL DEFICITS: COMBINED EEG AND COGNITIVE STUDY

Concussion assessment is a challenge as many athletes show a tendency to underreport their symptoms. Moreover, no single approach appears sufficient for a sensitive and concrete concussion assessment. Our current study hypothesized that combining evaluations of multiple modalities such as brain alteration recordings and neurocognitive assessment can provide a set of characteristic “signatures”. We believe that this collective approach will better determine not only injury severity and recovery timeline but it will also allow coaches to make sensible RTP decisions. In this work, a comparison of the neurocognitive and electrophysiological performance of athletes with no history of concussion to those athletes with previous concussion history was made. The goal of this comparison was to highlight any potential differences between these athletes 8 to 12 months post-injury.

The goal of the current research is to look into the spectral profiles as a potential measurement tool which can expose the long-term cognitive impairment after an analytical study of EEG signals. To test our hypothesis, we utilized visual (King-Devick (K-D) Test), postural (BESS) and neurological (mPACT) tests, along with a novel EEG spectral analysis that computes the distinguishing features from each individual component of EEG, as well as from the set of conventional frequency bands. We also utilized novel time and nonlinear feature-based analysis to evaluate the EEG of injured and healthy athletes that provide unique and complementary measures of post-concussion deficiencies.

2.1 Methodology

2.1.1 Participants

The study was performed following the experimental protocol approved by the Institutional Review Board (IRB) of the University of North Dakota. The study included a total of 21 male participants between 14 to 17 years of age who were recruited from the Grand Forks area high schools. The participation was voluntary, and the participants had the right to withdraw any time from the study. Written consent for participation was collected from the athletes and also from their parents or guardians. Each participant had to complete a demographic information form with previous concussion history before data collection.

Individuals who met our protocol inclusion criteria were recruited for this concussion analysis study and assigned to a particular group based on the history of concussion. The healthy group consists of 14 subjects (Age 15.86 ± 0.67 years, Height: 1.75 ± 0.09 m, Weight: 72.82 ± 10.03 Kg) with no history of concussion while the concussed group has 7 subjects (Age 15.97 ± 0.74 years, Height: 1.77 ± 0.09 m, Weight: 73.20 ± 12.56 Kg) who suffered from one or multiple previous concussions. Following the established criteria of American Academy of Neurology [100] and state law of North Dakota [101], concussions were identified and diagnosed by a physician, who was assigned by the concussion management team of the school.

All participants were actively participating in sport and athletes with concussion history made a complete return to play within four weeks of injury. All athletes with a history of concussion (12 days to 15 months from injury) reported being symptom-free at the time of testing. Control participants were teammates who had never suffered a sport or non-sport related brain injury. Concussed participants' post-concussion status is shown in Table 3.

Table 3. Concussed participants demographic information

Concussed Participants	Number of concussion	Loss of consciousness	Confusion	Amnesia	Post-concussion RTP days	Days from concussion incident to data collection		
						From incident 1	From incident 2	From incident 3
1	2	No	Yes	Yes	14	263	216	-
2	1	No	Yes	Yes	21	118	-	-
3	1	No	No	No	7	267	-	-
4	3	No	Yes	Yes	10	462	297	162
5	2	No	Yes	Yes	25	92	65	-
6	1	No	No	No	10	127	-	-
7	1	No	No	Yes	15	12	-	-

From each subject, the traditional assessment data and EEG signals were collected in three different trials with 30-days' time difference between the trials. Therefore, the total number of data collection trials for the healthy group was three multiplied by fourteen (total 42 trials) and for the concussed subject was three multiplied by seven (total 21 trials).

2.1.2 Postural Data Collection Protocol

For postural stability assessment, we used BESS. This test was done based on the phenomena that postural stability deficits occur after a concussion. An objective recording of postural sway was introduced to overcome individual data acquisition error during data collection. A Wii Balance Board was used to record COP (center of pressure) data during BESS (Fig. 7).

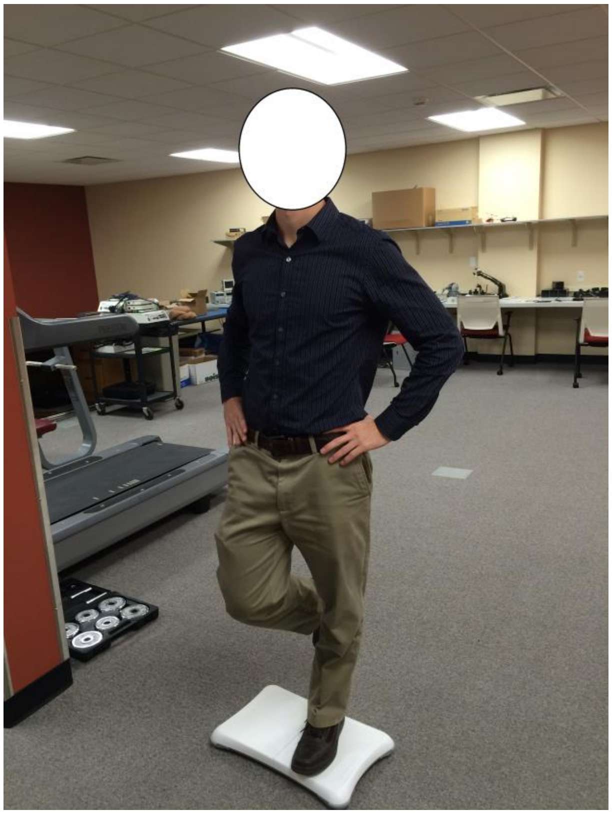

Figure 7. Experimental setup for postural data collection during BESS single leg stance.

2.1.2.1 Balance Error Scoring System (BESS)

The BESS is one of the most popular tests used to find balance deficit in concussed and fatigued athletes [102]. The BESS offers a portable, objective and cost-effective method of assessing static postural stability and control. If expensive and sophisticated postural stability assessment tools are unavailable, the BESS can be used to evaluate the effects of mild head injury or concussion on static postural stability/control. Information obtained through this clinical balance tool can be used to assist the clinicians in making RTP decisions following mild head injury.

Two testing surfaces need to complete the BESS test: floor/ground and foam pad. The purpose of using the foam pad is to generate an unstable surface that will eventually create a more challenging balance task, and will vary based on body weight. It has been theorized that, with the increase of body weight, the foam will deform more around the foot and therefore, the weightier the person, the foam will deform more [103]. As the foam distorts around the foot, there is an increase in the support on the lateral planes of the foot. Moreover, the increased contact area between the foam surface and the foot has also been hypothesized to raise the tactile sense of the foot, consequently helping to increase the postural stability [104]. The increase in the tactile sense is reported to cause further sensory information to be directed to the CNS and as the brain processes this additional information, it can develop better decisions while responding to the unsteady foam surface [104].

Twenty seconds of COP data were collected from each subject for six trials while performing three different tasks for two different surfaces described in Table 4 [103]. Types of errors recorded during a test are listed in Table 5 [103].

Table 4. BESS data collection protocol [103]

Record errors, max of 10 errors each stance/surface	Firm Surface	Foam Surface
Double Leg Stance: Standing with feet side by side (touching), hands on the hips and eyes closed	20 Seconds	20 Seconds
Single Leg Stance: Standing on the non-dominant foot, the hip is bent to approximately 30° and the knee is flexed to approximately 45°. Hands are placed on the hips and eyes are kept closed.	20 Seconds	20 Seconds
Tandem Stance: Standing heel to toe on a firm/foam surface by placing the non-dominate foot in the back. The heel of the dominant foot should be in touch with the toe of the non-dominant foot.Hands are placed on the hips and eyes are kept closed.	20 Seconds	20 Seconds

Table 5. BESS error types [103]

BESS Errors
1. If hands are moved off iliac crest **2. Opening eyes during data collection** **3. Step off, stumble or fall from the surface** **4. Moving hip for more than 30 degrees from fixed position** **5. Lifting heel or forefoot** **6. To be out of test position for more than 5 seconds**
The BESS test error is calculated by adding one error point for each error during the 6, 20-second trials for both firm and foam surface.

Figure 8 shows all the six stances on firm and foam surface for BESS data collection.

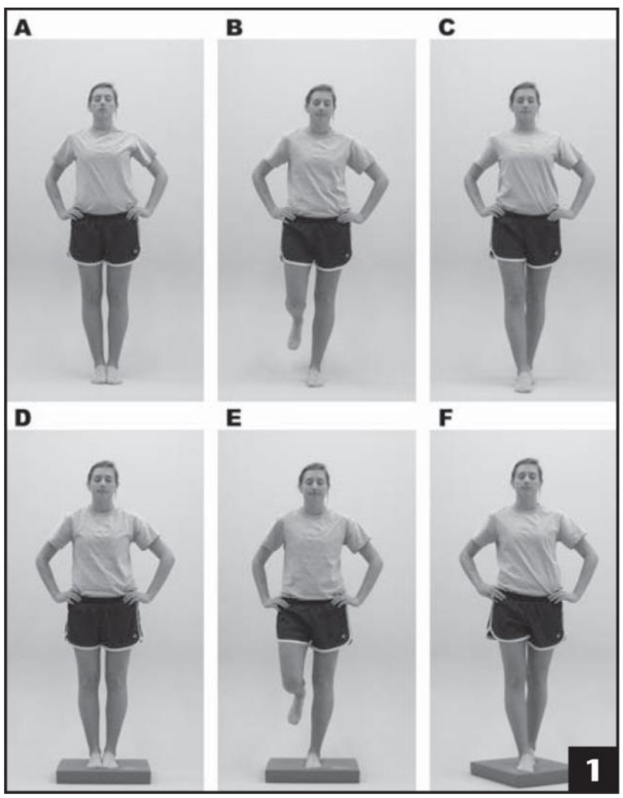

Figure 8. BESS data collection stances [103]

Each of these six subtests is performed for 20 seconds. Deviation from proper stance is referred to an error, and the total number of errors during the subtests are counted. Other performance measures include the resultant sway per second, resultant sway, sway along the x- and y-axis, and maximum displacement along x- and y-axis for each trail of the BESS test for all three sessions of data collection.

2.1.3 Visual Data Collection Protocol

The deficiencies of attention and visual movements due to a concussion were measured using King Davick (KD) test.

2.1.3.1 King-Devick (K-D) Test

The K-D test is a test of the visual system and is based on measurement of the speed of rapid number naming [105]. The K-D test is faster than other standardized tests like ImPACT, Military Acute Concussion Evaluation (MACE) and the sports concussion assessment tool (SCAT 3) as it takes just two minutes to complete the testing and thus is more practical in case of sideline application [105]. K-D test performance has been shown to correlate with suboptimal brain function in concussion [106], [107]. The test procedure included one demonstration card with three test cards, as shown in Fig. 9.

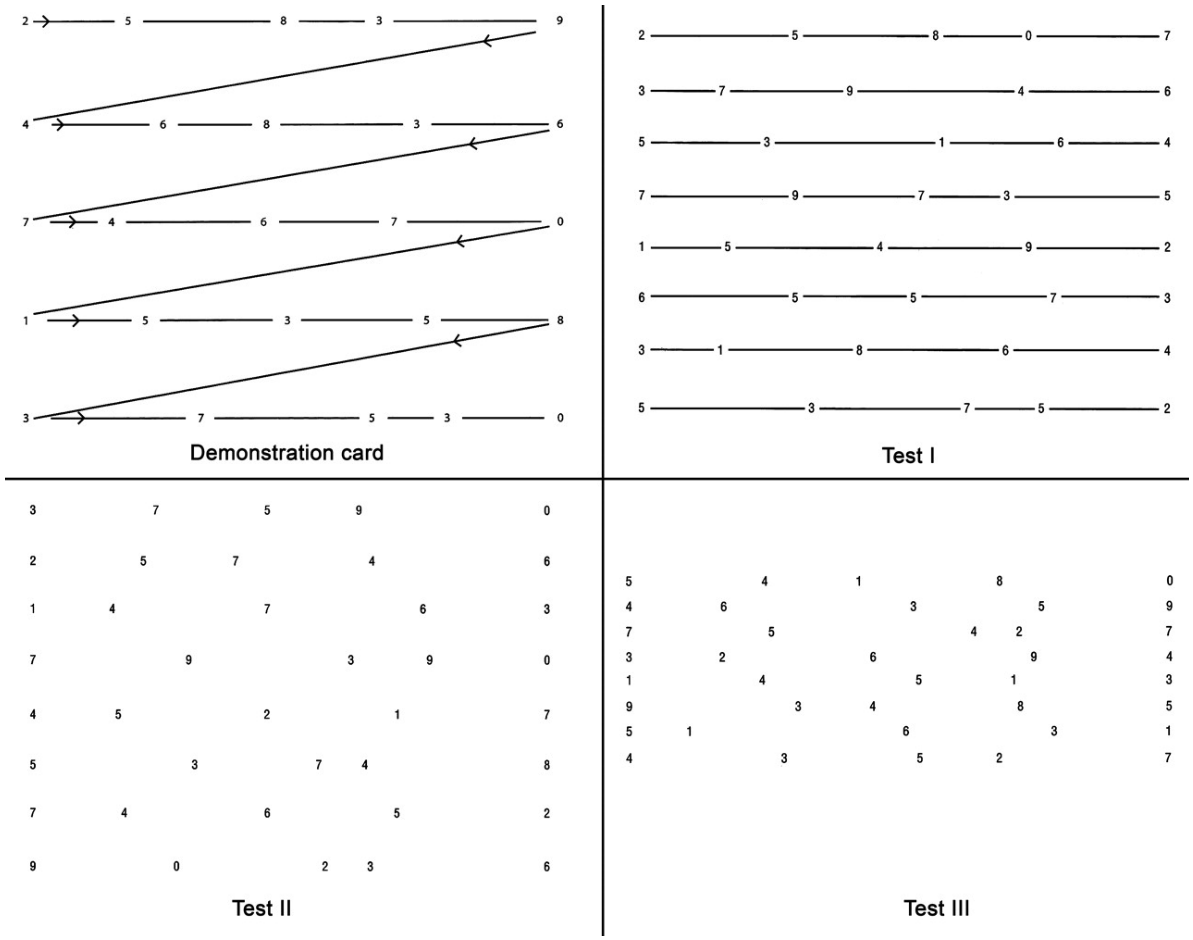

Figure 9. Demonstration card and test cards used during the K-D Test [106]

The athletes need to name the numbers from the three test cards rapidly without any error. The score for the test is calculated by combining the amount of the three times, in seconds, required to read the three cards. The test involves attention, rapid eye movements as well as language operation. These three functions may be adversely affected, resulting in a poor K-D test performance. The test purports to measure any suboptimal brain functional deficits after a concussion incident, as well as sometimes reflects deficits due to sleep deprivation, Parkinson's disease, hypoxia and multiple sclerosis.

2.1.4 Neuropsychological Data Collection Protocol

For neuropsychological data collection we have used ImPACT as More than 280 peer-reviewed studies and 145 independent studies used ImPACT as a concussion management tool [74].

2.1.4.1 Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

The ImPACT battery is the most common computerized test that can be used in cognitive concussion assessment [63]. The test battery consists of three different measures: Demographic data, neuropsychological tests, and the Post-Concussion Symptom Scale (PCSS). The assessment results from these three sections are combined to assist in accurate evaluation and management of concussion [108]. The demographic data section mainly consists of all the important sport, medical, and concussion history related information.

For the neuropsychological test sections, ImPACT (version 3.0) contains six different neuropsychological tests, and each of these tests is intended to target different parts of cognitive functioning comprising attention, verbal and visual memory, control, reaction time and processing speed. Neurocognitive tests were used to evaluate various aspects of cognitive functioning such as working memory, attention span, attention time, problem solving ability, response variability, and reaction time for both the healthy and concussed group of athletes by conducting six neurophysiological tests called word memory, symbol match, design memory, color match, X’s and O’s, and three letter memory test. Five composite scores were generated from these subtests (Table 6) [109]. Combining the results from these six different tests, a set of composite scores are produced containing separate measures named verbal memory, visual memory, motor speed, reaction time and impulse control. The detailed description of these tests can be found at [63], [69], [110].

Table 6. ImPACT composite scores [63]

Composite Scores	Neurocognitive Domain Measured	Better Performance Indicator
Verbal Memory	Word Memory + Symbol Match memory score.	Higher score
Visual Memory	Design Memory + X's and O's percent correct.	Higher score
Processing Speed	Weighted Average of Response to 3 interference tasks.	Higher score
Reaction Time	Average weighted reaction time for correct responses.	Lower score
Impulse Control	Number of incorrect distractors + Number of Errors.	Lower score
Total Symptom Scores	22 symptoms (headache, dizziness, balance problem, etc.): 0-7 for each symptom.	Lower score

The last section named PCSS is also utilized in the ImPACT battery study [69]. The scale is reported by various sports organizations to manage and track post-concussion symptoms [63], [70]. This section has a 21-symptom checklist which mainly asks the athlete to specify a rate for each symptom on a scale of one to seven, with zero representing no presence of a symptom and six representing a severe symptom.

An ImPACT test was performed by all participants during all three trials.

2.1.5 EEG Data Collection Protocol

EEG data analysis was used for electrophysiological assessment since it is one of the most used tools to evaluate dysfunctions associated with brain signals. Advantages of EEG also include its availability, effectiveness of analyzing these types of data and its noninvasive nature. Moreover, existing evidence indicates that EEG recordings can detect abnormal brain activities in asymptomatic concussed athletes, demonstrating superior sensitivity over neuropsychological assessments [111].

EEG activities were measured using a 9-lead wireless B-Alert headset [112]. Electrode impedance was kept below 50 kΩ. During data collection, the left mastoid was used as a reference, and the right mastoid was used as a ground. The sampling rate for data collection was 256 Hz, and data were acquired by placing nine electrodes at F3, F4, Fz, C3, C4, Cz, P3, P4 and POZ locations as shown in Fig. 10.

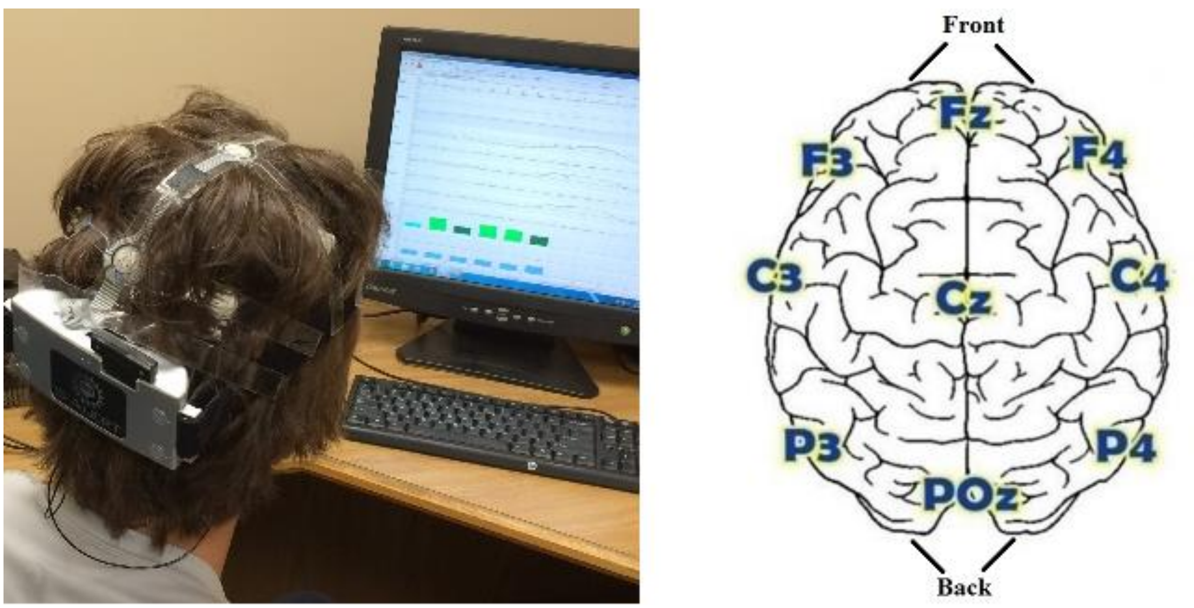

Figure 10. Experimental setup for EEG data collection with brain map of 9 electrode locations [112]

The data were collected for 5 minutes from all 21 subjects during different trial sessions each under three conditions: vigilant task (VT), eyes open (EO), and eyes closed (EC). These were done to create high engagement, low engagement, and distraction status for both healthy and concussed subjects. Details of this protocol are shown in Table 7.

Table 7. EEG data collection tasks

Tasks	Action	Status
Vigilance Task	Choose between primary vs. secondary or tertiary task every 1.5 to 3 seconds.	High Engagement
Eyes Open	Respond to visual probe every 2 seconds.	Low Engagement
Eyes Closed	Respond to audio tone every 2 seconds.	Distraction

The same procedure was followed at all different trials for all subjects.

2.2 Data Analysis

ImPACT data were analyzed from five composite scores called verbal memory score, visual memory score, processing speed score, reaction time score and impulse control score for both healthy and concussed athletes.

For the K-D test, the total time required to complete the task was calculated for each healthy and concussed subject. The average times for healthy and concussed athletes were compared to assess the performance.

The BESS test analysis was done by calculating the average x and y-axis sway (cm) in addition to the total number of balance errors for each healthy and concussed subjects to measure their postural performance.

In order to verify the deficits between healthy and concussed groups for these three test batteries, statistical analysis was performed without knowledge of groups. EEG data were analyzed to find out the linear, nonlinear and time domain deficits between healthy and concussed groups.

2.2.1 Statistical Analysis

The deficits between healthy and concussed groups were verified using statistical analysis, and the measurements were performed without knowledge of groups. The Shapiro-Wilk test was applied to ascertain the normality of the data. For normally distributed data, a two-tailed Student t-test, followed by Bonferroni's post hoc test when applicable was implemented; otherwise, Wilcoxon rank sum test was considered. The values in the manuscript are presented as mean ± standard deviation format with statistical significance set at ($p<0.05$). The test of significance was performed using the MATLAB Statistical Toolbox[113].

2.2.2 EEG Data Analysis

High-pass and low-pass filters were applied to the digitized data, forming a 1–40 Hz (24 dB/octave) bandpass filter. The first and last 10 s of each 5-min recording during EO, EC, and VT conditions were rejected to eliminate state transitions. Randomly occurring large amplitude with power ≥ 3 standard deviations with respect to clean EEG was removed. Then, the stereotypical noise like eye movements, eye blinks, muscular activity, line noise, motion related signal, and heart signals was cleaned by using well-established Independent Component Analysis procedure of EEGLAB detailed previously [114], [115]. Any other nonstereotyped or residual artifact was removed through visual inspection of the raw data.

The clean EEG data was then segmented into 1-second epochs containing 256 data points. Power spectral density (PSD) was determined by computing Fast Fourier Transformations (FFT) with a 10% Hanning window on each segment to determine spectral power (μV2) for 1 to 40 Hz frequency bins of each EEG channels. The PSD of the individual bins were then averaged and logged to calculate PSD of conventional EEG frequency bands named delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (30-40 Hz). After calculating the PSD for each channel and bands, overall PSD was calculated by calculating the mean PSD across all nine referential channels for both individual frequency bins and five frequency bands. Linear and nonlinear features were then extracted from the five frequency bands and also from each of 1 to 40 Hz EEG frequency bins.

This innovative analysis achieved a new range of frequencies with significant differences between healthy and concussed groups even when the band base analysis was not adequate to reveal the deficits. Moreover, in this paper, we present an exploration of the usefulness of several features for use in concussion detection, which aims at providing accurate feedback as early as possible. Along with the traditionally used band power estimates, we computed some time domain as well as nonlinear features from each EEG frequency band and then again computed all the features from each individual frequency bins. The parameters extracted from EEG signal are explained as follows.

2.2.2.1 Linear Features

Power spectral density analysis was performed to extract the linear features from the signal. The extracted features were; (i) average spectral power for five frequency bands and (ii) the spectral power for each of the individual frequency from 1 Hz to 40 Hz.

2.2.2.2 Time domain Feature

Most popular features used for concussion analysis are EEG band based power spectral density. In this paper, we introduce new features for concussion assessment called Time Domain Parameters that are also known as Hjorth parameters. The features are inspired by the fact that they have been previously used in EEG based experiments like Vidaurre *et al*. used Hjorth parameters, in their brain-computer interface (BCI) study [116] whereas Cecchin *et al*. used Hjorth parameters for seizure assessment from raw scalp EEG signals [117]. The parameters introduced by Hjorth [118] are three features defined as follows:

$$Activity\big(x(t)\big) = var\big(x(t)\big) \quad (1)$$

$$Mobility(x(t)) = \sqrt{\frac{var\left(\frac{dx(t)}{dt}\right)}{var\big(x(t)\big)}} \quad (2)$$

$$Complexity\big(x(t)\big) = \frac{Mobility\left(\frac{dx(t)}{dt}\right)}{Mobility\big(x(t)\big)} \quad (3)$$

The first parameter, Activity, calculates the alteration of time signal and characterizes the signal power. Mobility is computed by calculating the square root of the variance of the first derivative of the signal divided by the activity and thus specifies the average frequency or proportion of standard deviation of the spectral power. Complexity describes the change in frequency by comparing the Mobility of the first derivative of the signal with the signal's mobility, and for more resemblance between the signals, the value converges to one. These three parameters consider the frequency component of the signal itself and thus remain more robust against the errors due to overfitting or non-stationarities of the signal [117]. To reduce the complexity of calculation, these three parameters were calculated in a stationary mode of signal separately for each EEG channel of the entire signal. Thus, the extracted parameters were three features per channel and, as a whole, a feature vector for each parameter. 27 features (3 features for nine channels) were extracted and then averaged for all channels.

2.2.2.3 Nonlinear Features

Different nonlinear parameters have been shown significantly useful in the diagnosis of neurological disorders. Nonlinear parameters like approximate entropy (ApEn), Hurst exponent, and Correlation dimension have been used for automatic diagnosis of seizure onset and reported as a promising approach in differentiating normal, pre-ictal and epileptic seizure from EEG signals [119].

In the field of cortical neuronal dynamic study, the existence of long-range temporal correlation (LRTC) is considered a potential observed phenomenon as it is proven to be gradually reduced with the power-spectrum [120]. The LRTC property of an amplitude-time signal has vital importance as it is found to have a relationship with the distributed neural network [121]. Poil *et al.* reported the coexistence of LRTC property of amplitude time series with neuronal avalanche activity [122], and thus recommended a relationship between oscillatory activity detected in the EEG and the criticality hypothesis [122], [123]. Using these hypotheses, Shew *et al.* suggested a possible connection between optimal functioning and LRTC in the amplitude of oscillations [120]. Moreover, the significance of the LRTC property has also been proven in numerous clinical studies linking a number of neuronal diseases (including schizophrenia [124], Alzheimer's disease [125], major depressive disorder [126], and epilepsy [127] with altered LRTC properties. To quantify the degree of change in LRTC property in a signal, the Hurst exponent (H), (explained in a later paragraph) is measured [120]. Hurst exponent was used by Holler *et al.* for the disorder of consciousness studies [128] whereas Culic *et al.* reported this property to be important to differentiate epileptic patients [129].

Another nonlinear parameter that was calculated was ApEn. ApEn is a widely known mathematical algorithm, which computes the predictability of time series data by quantifying the regularity and complexity in the signal. ApEn quantifies the logarithmic likelihood of the patterns in the signal that remain closed on next incremental comparisons [130].

Values of the ApEn parameter have been reported significantly different between EEGs collected from epileptic seizure patients and normal EEG signals [131]. Guo *et al.* present a method based on approximate entropy for classifying the EEG regarding the existence and absence of seizures using the neural network with 99.85% accuracy [132].

Inspired by these publications, we tested the efficacy of these features to distinguish healthy and concussed athletes in this study. Approximate entropy (ApEn) and Hurst exponent were extracted as the nonlinear features to measure synchrony and complexity of the EEG signal as explained in the following sections.

Approximate Entropy

ApEn was calculated for each frequency (1 to 40 Hz) and for each of five frequency bands of EEG data for all three different conditions in order to find out if there was any relationship between the randomness of EEG data along with a concussion. A lower value of approximate entropy specifies that the EEG data is more deterministic whereas a higher value of ApEN determines the data is more random. This feature was calculated using the ApEn function provided by Kijoon Lee in the MATLAB central file exchange [133]. The tolerance chosen for ApEn calculation was two standard deviations.

Hurst Exponent

The Hurst exponent (H) calculates the extent information presented by a signal is related to the history of the signal. The value of H varies from 0 to 1; $0 < H < 0.5$ indicates the samples in the signals are far apart and independent and thus the signal is short-range dependent. However, if $0.5 < H < 1$, then the value is said to contain LRTC, with higher values of H representing a stronger LRTC property [134]. The Hurst exponent is thus known as the index of long-range dependence48.

The value of H was calculated for each channel over the entire EEG signal. A total of 9 components for 9 EEG channels were extracted for each signal.

2.3 Results

In this study, we calculated neurocognitive deficits combining EEG analysis with three standard post-concussive assessment tools. We utilized visual (K-D Test), postural (BESS) and neurological (ImPACT) tests, along with a novel EEG spectral analysis that computes the distinguishing features from each individual component of EEG, as well as from the set of conventional frequency bands. Data were collected for all testing modalities from 21 adolescent athletes (seven concussive and fourteen healthy) in three different trials. For EEG assessment, along with linear frequency-based features, we introduced a set of time-frequency (Hjorth Parameters) and nonlinear features (approximate entropy and Hurst exponent) for the first time to explore post-concussive deficits. In conjunction with traditional frequency band analysis, we also presented a new individual frequency based approach for EEG assessment that provides unique and complementary measures of post-concussion deficiencies. The results of all analyses are described in following sections.

2.3.1 Postural Deficits Result in terms of BESS Test

Postural deficits in terms of the BESS associated with concussion showed no significant difference between healthy and concussed group. Average sway per second was calculated using a modified Wii balance board during the BESS assessment for healthy group (group average sway=3.25±0.67 cm) and concussed group (group average sway=3.06±0.70 cm). The number of average BESS errors reported by the healthy group were twenty-eight compared to thirty-one reported by the concussed group. Though the average sway scores exhibited by both groups were quite similar, the concussed group reported more errors than their healthy matched controls. The t-test resulted in no significant differences (Average sway: p-value = 0.55, Number of errors: p-value = 0.37) between the groups regarding average sway and number of errors.

2.3.2 Visual Deficits Result in Terms of K-D Test

K-D test measures the deficiencies of attention and eye movements by capturing the speed of rapid number naming. The athletes who sustained concussions required slightly more time to complete the task than their peers in the healthy group (by approximately 0.3%), but the deficits did not reach a level of significance (Healthy group: 52.91±10.81, Concussed group: 53.10±11.21; p-value = 0.955).

2.3.3 Neurophysiological Deficits Result in Terms of ImPACT Test

The healthy and concussed groups were not significantly different with regard to age but were significantly different based on the number of prior concussions. A two-tailed t-test was performed to evaluate the differences in neuropsychological test performance regarding ImPACT battery between the concussed and control groups. Table 8 presents the detailed descriptive statistics for verbal and visual memory, processing speed, and reaction time composite scores.

Table 8. Group means and standard deviations for ImPACT composite scores of healthy and concussed groups

Composite Scores	Healthy Group Mean ± SD	Concussed Group Mean ± SD	F value	*p*-Value
Verbal Memory Index	89.86 ±7.84	87.57±9.25	0.58	0.59
Visual Memory Index	86.57±5.58	81.71±6.55	0.59	0.12
Motor Speed Index	40.38±5.82	37.23±5.17	0.81	0.23
Reaction Time Index	0.62±0.09	0.65±0.12	0.39	0.55
Impulse Control Index	6.14±3.30	5.71±3.30	0.93	0.78
Total Symptom Score Index	2.93±2.13	3.14±3.53	0.12	0.89

Though a number of studies reported the ability of the ImPACT to differentiate healthy and concussed groups, our analysis revealed no significant difference in any composite scores between the groups.

2.3.4 Neuronal Deficits in Terms of EEG Band-Power following Concussion

The EEG analysis was conducted to extract the neuronal deficits following a concussion. Athletes in the concussed group exhibited an increase in delta and theta bands, and a decrease in alpha, beta and gamma frequencies compared to their uninjured peers during all three testing conditions. As indicated in Table 9, the difference reached the significance level for the increase in delta band and decreased in alpha, beta and gamma frequency bands for all three conditions.

Table 9. Power deficit between healthy and concussed group

Condition	Subject	Delta(μV^2) Mean ± SD	Theta(μV^2) Mean ± SD	Alpha(μV^2) Mean ± SD	Beta(μV^2) Mean ± SD	Gamma(μV^2) Mean ± SD
VT Condition	Healthy	4.24±0.16	3.38±0.51	3.08±0.23	2.47±0.17	1.97±0.18
	Concussed	4.81±0.25*	3.59±0.17	2.63±0.26*	2.07±0.30*	1.51±0.24*
EO Condition	Healthy	4.34±0.26	3.47±0.34	3.12±0.36	2.49±0.31	1.95±0.13
	Concussed	4.84±0.32*	3.66±0.39	2.68±0.24*	2.13±0.19*	1.57±0.21*
EC Condition	Healthy	4.23±0.35	3.43±0.29	3.20±0.16	2.46±0.27	1.92±0.12
	Concussed	4.67±0.47*	3.61±0.32	2.84+0.35*	2.13±0.34*	1.50±0.35*

* denotes significant differences between healthy and concussed group at p-value = 0.05

2.3.5 Neuronal Deficits in Terms of EEG Individual Frequency Power following Concussion

This analysis considered individual EEG frequencies to find gaps between healthy and concussed groups. Figure 11 shows the results of both frequency band and individual frequency analysis for three experimental conditions (EO, EC, and VT). The dashed black line shows the confidence level of p=0.05. The solid red lines show the p-value for each frequency band (delta, theta, alpha, beta, and gamma bands). The bars in each frequency band show the p-value for individual frequencies.

The athletes who sustained a concussion had a range of frequencies with a significant difference from the healthy group during EO condition (1-3 Hz, 9-10 Hz, 20-24 Hz, 27-30Hz, and 34-38 Hz) as shown in Figure 2(a). A very similar, but not all range of significance was exhibited during EC condition (1-3 Hz, 6-7 Hz, 9-10 Hz, 15-17 Hz, 20-24 Hz, 28-30 Hz, and 35-38 Hz) as shown in Figure 11(b). The significant individual frequencies exhibiting the deficits between healthy and concussed groups during VT condition were (1-3 Hz, 6-7 Hz, 9-10 Hz, 19-30 Hz, 34-38 Hz) and were much consistent with EO condition as shown in Figure 2(c).

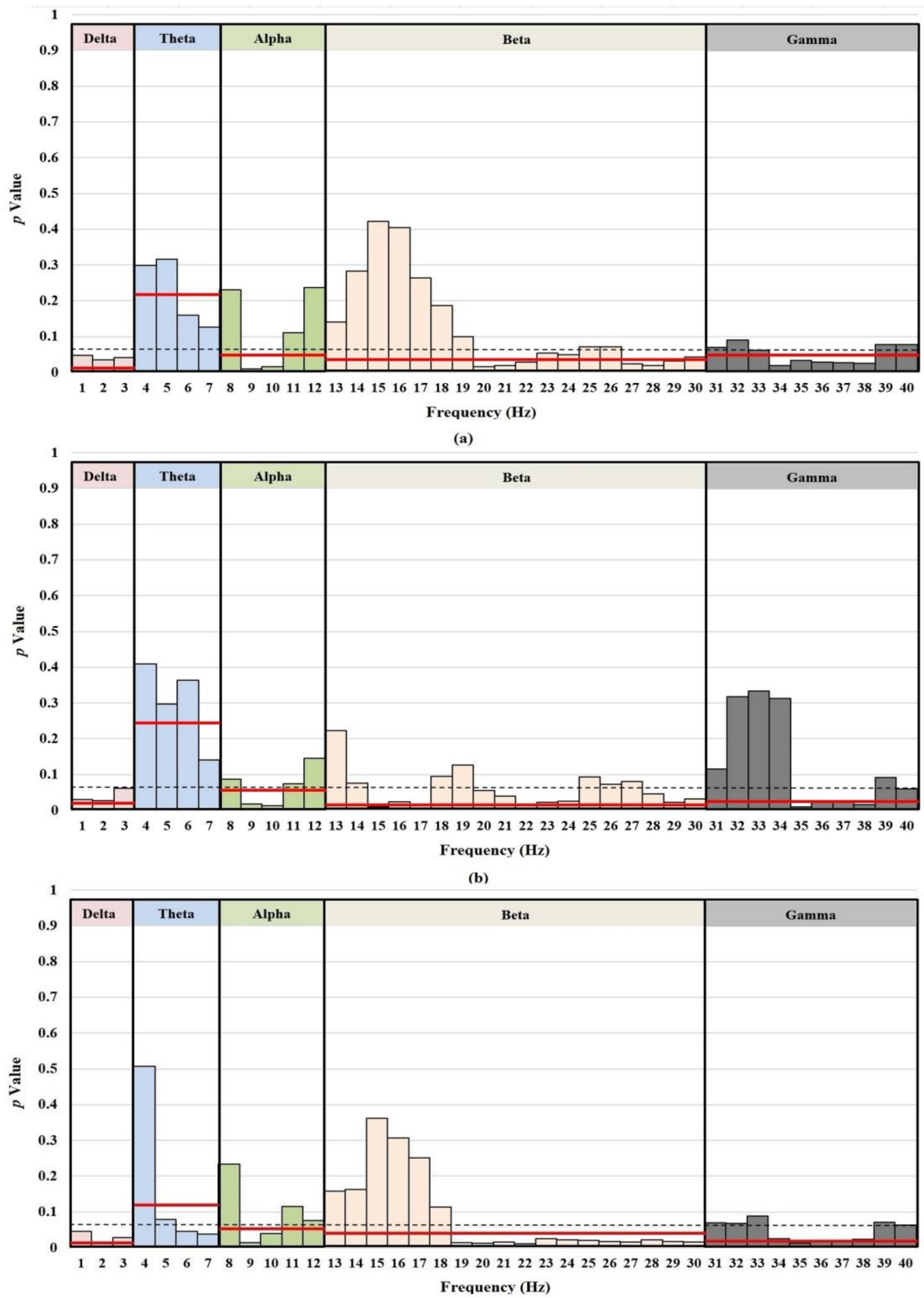

Figure 11. Level of significance for individual frequency bins. **A set of individual frequencies from EEG data exhibits power spectral density deficits between healthy and concussed athletes. The x-axis in the figure shows the individual frequencies and Y-axis shows the level of significance deficits. The color of bars is different based on each frequency band, and the level of significance for each**

EEG frequency band is shown by red lines. The *p*-value vs. frequency is shown during three conditions (a) eyes open (EO) (b) eyes closed (EC), and (c) vigilant task (VT).

2.3.6 Neuronal Deficits in terms of Nonlinear Features from EEG Individual Frequency following Concussion.

In the final analysis, nonlinear features were calculated in order to find out if new features extracted from the EEG data can tabulate the deficiencies due to a concussion. The extracted features were approximate entropy, activity, mobility, complexity and Hurst exponent features. While calculating these features for EEG frequency bands (delta, theta, alpha, beta, and gamma), no significant deficits were found between healthy and concussed athletes. But when the analysis was done for individual frequencies instead of frequency bands, interesting outcomes were exhibited. A set of individual frequencies was found for each nonlinear feature which can reveal significant deficits between healthy and concussed athletes as reported in Fig. 3. As shown in Fig.12(a) for EO condition, the frequencies indicating significant deficits between healthy and concussed groups in terms of 2 or more nonlinear features are 1-2 Hz, 19 Hz, 21 Hz, 23 Hz, 25 Hz, 31 Hz, 33 Hz and 37 Hz. For EC condition, Figure 12(b), the range of frequencies with deficits in two or more features was for 1-2 Hz, 13 Hz, 16 Hz, 34 Hz and 37 Hz, and for VT condition, from Figure 12(c), the range was 1-2 Hz, 8 Hz, 15-16 Hz, 26 Hz, 34-35 Hz and 37 Hz. The most efficient nonlinear features to reveal deficiency following concussion were approximate entropy, activity and Hurst exponent feature.

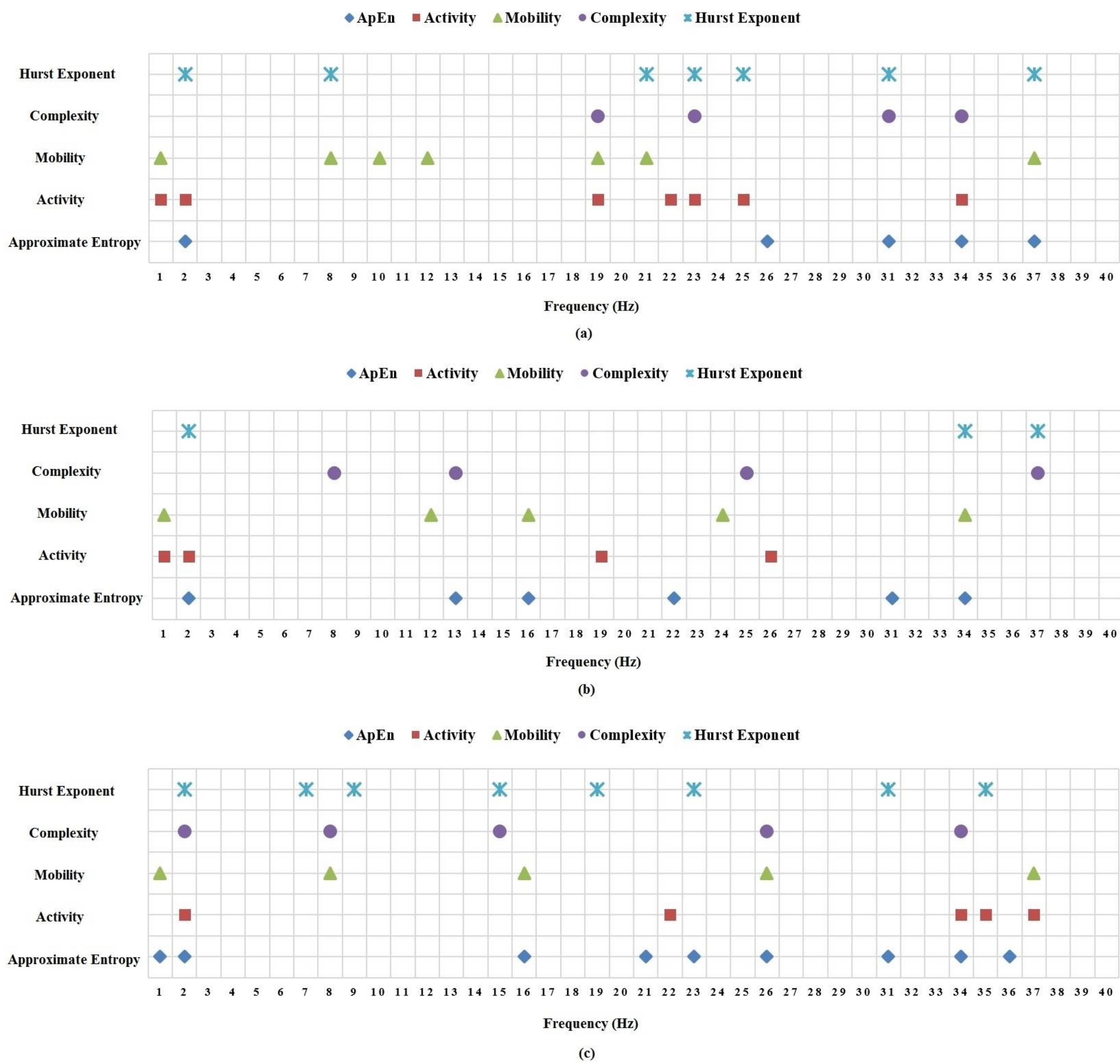

Figure 12. Frequencies with a significant difference in approximate entropy, activity, mobility, complexity and Hurst exponent between healthy and concussed athletes for three conditions: (a) eyes open (EO), (b) eyes closed (EC), and (c) vigilant task (VT).

2.4 Discussion

Residual damage to the brain due to concussion can often evade clinical detection. Enhancing ways in which concussion is assessed is pivotal, specifically in susceptible individuals such as adolescent athletes where functional deficits can be elusive and seriously underreported. Better assessment is also essential since early identification of the signs of a concussion can progress positive outcomes and thus suggests that there is a clear need for an effective evaluation approach to efficiently assess and quantify high-risk individuals such as athletes who may have already sustained a concussion. The current study aims to test the hypothesis that the concussion disrupts the normal brain activities of a person. To detect these deficits, we combined the BESS, K-D test, ImPACT, and EEG analysis to capture the postural, suboptimal, neurophysiological and neuronal deficits following a concussion.

Evidence from the previous studies [52], [90] shows that the balance impairment regarding the BESS is most pronounced during the time of injury and 24 hours post injury but appears to resolve by day five after a concussion incident. The balance deficit through the BESS in our research resulted in no significant difference between the healthy and concussed group and thus strengthened the already established hypothesis [52], [90] that the postural deficits resolve within a brief period post-injury and therefore may suggest that the BESS is not sensitive enough to interpret any residual deficits associated with long-term concussion history.

As expected, the K-D test, which is mainly a rapid screen tool and typically used immediately after concussion [30], was unable to detect any deficits in our study. This can be explained by the fact that the related visual deficits due to a concussion were resolved during the several months' time gap between the concussion incident and data collection.

The ImPACT was reported by multiple sports-related concussion studies as a potential tool to detect the impaired neurocognitive functioning due to concussion [63], [69], [108]. Also, some studies showed neuropsychological baseline assessment models like ImPACT could assist the diagnosis of subtle neurocognitive deviations in athletes after a concussion incident [63], [110].

Though several studies demonstrated that a history of concussion is associated with poorer performance in ImPACT [110], the role of concussion history remains a controversial issue, with various studies yielding no relationship between concussion history and ImPACT performance [69]. The results of this manuscript suggest that there is no significant effect of a history of concussion associated with performance measured by ImPACT, which is understandable, as ImPACT is an immediate post-concussion paradigm, and due to the long time gap between concussion incident and data collection, the sensitivity of the test deteriorates with time.

To capture the signature neuronal deficits exhibited by concussed athletes that distinguish them from their healthy peers, we evaluated several approaches utilizing a set of linear, time-frequency based features along with nonlinear features extracted from EEG signals. In conjunction with band base analysis, this study undertook a systematic exploration to find out the deficits within specific frequency bins from 1 to 40 Hz. The system works by following four main steps: data acquisition, data preprocessing, feature extraction (power spectral, time domain and nonlinear) and statistical analysis (functional deficits detection).

For band base analysis, EEG was divided into traditional frequency bands (delta, theta, alpha, beta, and gamma). After normalization, power spectral density analysis revealed a significant difference between healthy and concussed athletes. There are several findings of interest. First, the PSD features collected from frequency sub-bands played an important role in distinguishing concussed individuals. Discriminative features were observed in delta, alpha, beta and gamma frequency bands. A difference was also noted at theta frequency band. It should be pointed out that similar frequency bands were targeted in some previous EEG studies of concussion [111], [135], [136]. An increase in delta and theta frequency and a decrease in beta frequency were also reported by McCrea et al.50 and Slobounov *et al.* [111]. The discrimination at reported by different frequency bands can indicate significant neuronal dysfunction. According to Demos *et al.* [136], an increase in delta frequency may indicate brain injuries, learning problems, or difficulties with cognition. The decrease in alpha band power exhibited through the analysis partially overlaps with the results reported by Thatcher *et al.* in a previously conducted mTBI based study [98]. The decrease in alpha power exhibited by concussed athletes compared to control peers may be interpreted as a reflection of reduced cortical excitability [137]. A substantial decrease in beta and gamma power was also revealed by the analysis. Certain levels of beta waves allow easy focus and involvement in conscious thought and logical thinking, whereas a decrease in beta waves may point to poor cognition, difficulty in concentration [136]. Moreover, a movement plan based study in terms of reaction time and endpoint error reported that a decrease in beta power is correlated with higher end point error [138]. A study conducted by Kwon *et al.* demonstrated a reduced gamma power by schizophrenia patients and concluded that the deficit might reveal a less effective local neuronal synchronization to external stimuli in the thalamic sensory oscillations or in the sensory cortex [139]. A decrease in gamma power was also reported to be correlated with lower consciousness in the anesthesia study conducted by Pritchett *et al.* [140]. Several studies also reported that a decrease in gamma power is frequently related to an increase in the low-frequency range (delta frequency band) power [141], [142] and interpreted to be related to lower neuronal activity of the brain region that operates to generate behavior [143]. All these specific power increases in the slower frequency band (delta), combined with the decrease of power in faster frequency bands (alpha, beta, gamma) exhibited by concussed athletes may imply that their neurological status is not as sound as their healthy matched peers in the control group are.

Though a lot of studies revealed significant differences in EEG sub-bands, there is no signature profile to indicate increase or decrease of band powers associated with concussion. That is why the pathophysiology of concussion is considered heterogeneous and not yet completely understood. To reinforce our EEG-based functional deficits hypothesis, in an innovative approach, the PSD based analysis for each of the EEG individual frequencies was conducted. After analyzing 189 cases, i.e., three different trials in three different conditions (EO, EC, VT) for 21 subjects as shown in Figure 11, it was concluded that four ranges of frequencies are more efficient in highlighting deficits following a concussion. These ranges are slow delta (1-2 Hz), slow alpha (9-10 Hz), fast beta (20-30 Hz) and fast gamma (34-39 Hz). A similar individual frequency-based analysis conducted by us on eyes closed EEG collected from a different dataset of 20 healthy and 20 immediate concussed athletes also resulted in a nearly similar range of frequencies (1-2 Hz of delta band, 8-10 Hz of the alpha band, 24-29 Hz of the beta band and 34-36 Hz range within the gamma band) [144]. To date, no individual frequency based study was conducted for concussion assessment and more collaborative research is needed to establish a direct relationship of these frequency bins with a concussion. The decrease in alpha band frequency bins exhibited through individual frequency analysis partially overlaps with the results reported by Thatcher *et al.* in a previously conducted mTBI based study [98]. An increase in theta band frequency bins during VT task may be associated with ADHD, depression, hyperactivity, impulsivity, and inattentiveness [52]. The individual frequency-based analysis also revealed significant differences in the upper level of beta bands compared to the lower level frequency bins. Oscillatory activity in the beta band was previously reported to reflect the presence of inhibition of the process of the ongoing motor task [145].

Elgendi *et al.* demonstrated an Alzheimer disease (AD) study and reported that new optimized frequency ranges (4–7Hz, 8–15Hz, 19–24Hz) resulted in better classification accuracy than the traditional frequency bands for the diagnosis of AD [146]. Similarly, if we consider the neurological deficits observed in individual frequency bins, as well as in the conventional frequency bands as a whole, the most reliable interpretation is that these deficits may be a consequence of their injury and can possibly be used as a concussion assessment index to identify the concussed athletes at the time of injury or during the post-concussion recovery period.

In the second phase of this study, a set of time-domain and nonlinear features were extracted. These features have been proven to be suitable to characterize neurological disorders like epilepsy, attention-deficit/hyperactivity disorder (ADHD) and Alzheimer disease in the literature [147]. It was hypothesized that the time domain and nonlinear feature based study could reveal new aspects and provide more information regarding the complex and chaotic nature of the EEG data. As reported by Mohammadi *et al*. [148], quantitative measures of chaos and non-linear features are convenient descriptive tools to characterize electrophysiological abnormalities in neuropsychiatric disorders that are not evident in linear analysis. To show the effectiveness of these features for a concussion, in a similar approach to power analysis, the features were calculated for both frequency bands and individual EEG frequencies. Though the concussed athletes exhibit different values for Hjorth time domain parameters and nonlinear parameters like approximate entropy and Hurst exponent, none of the parameters showed a significant difference compared to their healthy peers for traditional EEG frequency bands. However, when the analysis was done for each frequency, it was noted that significant differences were observed for certain frequencies as shown in Figure 12(a-c).

The observation of significantly different nonlinear features also revealed important notions about concussed athletes. The concussed athletes exhibited a decrease in Hjorth complexity and mobility. It has been reported by Pezard *et al*. [149] that depressive subjects tend to display lower complexity than controls. Moreover, Hamida *et al*. [150] reported the decreased complexity and mobility are associated with insomniac subjects. Approximate entropy quantifies the amount of regularity in data by calculating the upcoming amplitude values of the signal based on the knowledge of the preceding amplitude values [151]. Sohn *et al.* [152] reported a significantly lower approximate entropy for a group of ADHD subjects compared to matched controls and hypothesized that the patients might not have sufficient levels of cortical activation to reach the requirements of attention-demanding tasks. Following their hypothesis, a significant decrease in approximate entropy exhibited by concussed athletes may point out that their cortical information processing is altered compared to healthy athletes. Moreover, many pathological disorder studies like schizophrenia, posttraumatic stress disorder, panic disorder, and epilepsy reported lower complexity in pathological states compared to healthy subjects [153]. The notion claimed by the authors is that the lower EEG complexity is attributed to the abnormal neural integration in the above-mentioned mental disorders [124] and thus a lower value of ApEn demonstrated by concussed athletes in our study implies that they may still have some irregularity in their neural integration.

Another nonlinear feature with a significant difference was the Hurst exponent. Higher values of Hurst exponent indicate a stronger long-range temporal correlation of amplitude fluctuations of EEG35. In accordance with the result reported by Geng *et al.* [154] in their epileptic study, a decreased Hurst exponent exhibited by concussed athletes in our study implies that the degree of anti-correlation of concussed athletes is larger than that of healthy athletes.

The most efficient frequencies indicating the deficits were found to be 1-2 Hz, 21-23 Hz, 26 Hz and 34-37 Hz. Among the EEG task condition, EO and VT conditions were found to be more efficient in identifying hidden deficits due to a concussion. Though conventional band base analysis revealed no significant difference between healthy and concussed athletes regarding time domain and nonlinear features, individual frequency analysis was efficacious to exhibit these hidden discrepancies. These differences at specific frequencies would remain unnoticed if only conventional frequency bands were considered. Ultimately, this study exposed the fact that EEG analysis for each frequency is equally as important as conventional bands to evaluate the neurological dysfunction following a concussion.

CHAPTER 3

AUTOMATIC CLASSIFICATION OF POST-CONCUSSION DEFICITS

Concussion, also called mild traumatic brain injury (mTBI), is one of the most concerning and least understood neurological injuries. Although many studies have focused on the clinical aspects of concussion, not enough studies have been conducted to extract meaningful features from EEG signals, which could lead to the development of automatic classifications of concussed athletes. A number of studies have clearly demonstrated the feasibility of supervised and unsupervised pattern recognition algorithms to classify patients with various health-related issues such as utilizing neural networks to detect seizure activity [155] and support vector machine (SVM) for ADHD detection [156]. We hypothesized that a set of robust features would accurately differentiate concussed athletes from control athletes. Therefore, the objective of this analysis was to detect residual brain deficits through linear and nonlinear analysis of Electroencephalogram (EEG) signals and design an algorithm to classify concussed and control athletes.

3.1 Methodology

3.1.1 Concussion EEG Database Search

In order to develop a classification algorithm for detecting athletes with post-concussion deficits, we were looking for a larger database since we just have a database with 21 participants.

The separate database also verified the efficacy of the EEG analysis algorithm developed by us in the previous chapter to detect the post-concussion residual deficits. It was a challenge to collect a database since there is no publicly available database for concussion assessment. To assemble this new database, we developed a list of the available dataset from the published concussion assessment literature. Table 10 listed our search for the dataset.

Table 10. List of datasets

Serial No.	Paper title	Author Name	Contact information	EEG Datatype	Subject	Subject information	Details
1	Residual brain dysfunction observed one-year post-mild traumatic brain injury: Combined EEG and balance study	Semyon Slobounov,	sms18@psu.edu, slobounovsm@ninds.nih	19 Channel	49 concussed subjects	Pennsylvania State University athletes	EEG data at baseline, on day 7, 15, 30 days, 6 months and 12 months post-injury
2	Acute Effects and Recovery After Sport-Related Concussion:A Neurocognitive and Quantitative Brain Electrical Activity Study	Michael McCrea,	michael.mccrea@phci.org	10 minutes of eyes closed resting EEG recording on the BrainScope	396 baseline test_28 concussed_28 matched control	396 football players from 8 high schools and 2 colleges in the midwestern United States	EEG data at baseline, on day 1, 3, 5, 8 and 45 days post-injury
3	Residual alterations of brain electrical activity in clinically asymptomatic concussed individuals: An EEG study	Semyon Slobounov	sms18@psu.edu, slobounovsm@ninds.nih	2 min. 128 channel, eyes open sitting, eyes closed sitting, eyes open standing, and eyes closed standing.	12 control, 7 concussed	Pennsylvania State University athletes	
4	Source-domain Spectral EEG Analysis of Sports-Related Concussion via Measure Projection Analysis	1. Ozgur Balkan 2. Scott Makeig	1. obalkan@ucsd.edu 2. smakeigucsd.edu	64 channel, eyes closed for 5 minutes	21 concussed, 33 healthy,	Uni of British Columbia Athletes	3 months after a concussion
5	Changes in Functional Brain Networks following Sports-Related Concussion in Adolescents	Naznin Virji-Babul	naznin.virji-babul@ubc.ca	64 channel, resting state EEG	9 concussed, 33 control	Uni of British Columbia Athletes	2 months after a concussion
6	Preliminary evidence of reduced brain network activation in patients with a post-traumatic migraine following concussion	Anthony P. Kontos1	akontos@pitt.edu	128 channel EEG for go/no-go task	37(15 concussed with PTM+22 concussed without PTM) concussed, 20 healthy	School and college-aged athletes and students recruited from concussion clinic	1,2, 3, and 4-week postinjury
7	Measuring brain electrical activity to track recovery from sport-related concussion	William B. Barr	William.barr@nyumc.org	five frontal electrode sites	59 injured athletes and 31 controls	NYU Langone Medical Center Emergency Department (ED)	at the time of injury and at 8 and 45 days afterward

8	Time Course of Clinical and Electrophysiological Recovery After Sport-Related Concussion	Leslie Prichep	Leslie.Prichep@nyumc.org	EEG was collected from forehead locations	65 male athletes with concussion	Male athletes	24 hours after a concussion, with follow-up at 8 and 45 days post injury
9	Long-term electrophysiological changes in athletes with a history of multiple concussions	Louis De Beaumonta	louis.de.beaumont@umontreal.ca	ERP data	47 concussed	Male athletes	31 months for athletes in the multi-concussion group and 59 months for the single-concussion group.
10	An EEG Severity Index of Traumatic Brain Injury	Robert W. Thatcher,	rwthatcher2@yahoo.com	19 channel _ 2 to 5 min eyes closed resting EEG	108 concussed	Defense and Veterans Head Injury Program (DVHIP),	Average Interval was 224 days (range 15–1,436 days).

After contacting all the corresponding authors listed in the Table, we were able to collect a dataset with 20 health and 20 concussed subjects EEG data from Dr. Naznin Virji Babul of the University of British Columbia. All the analysis done on this collected database is described in this chapter.

3.1.2 Participants of Collected Dataset

The data were collected by Dr. Naznin Virji-Babul and her team from University of British Columbia (Vancouver, Canada) and were shared with us. A total of 40 male adolescent athletes were recruited for participation in this study. Twenty participants (age: 16.0±0.9 years) were clinically diagnosed with a subacute sport-related concussion, less than three months prior to data collection and were recruited as the concussed group for this study. Twenty participants (age: 15.8±1.3 years) were recruited as the control group, with no self-reported history of previous concussion. The participants were recruited from the Whitecaps FC Residency soccer program in Burnaby, British Columbia, Canada, along with some participants from minor league ice hockey teams in Vancouver. Athletes with any neurological disorders like ADHD, learning disability, mental disorders, psychiatric treatment or use of psychotropic medication and substance abuse were excluded from the study. Adolescent athletes were selected as participants since it is a well-known hypothesis that adolescents are more sensitive to concussion than adults, with prolonged symptoms and a lengthier RTP timeline [72], [157]. Written and informed consent for participation was collected from the athletes and from their parents or guardians. Each participant participated voluntarily in the study and completed a demographic information form with previous concussion history before data collection. All experimental protocols of this study were approved by the University of British Columbia Institutional Review Board (IRB). All the experiments were performed as per the guidelines and regulations set by the research ethics board of the University of British Columbia. The participants had an option to terminate the data collection any point.

3.1.3 EEG Data Collection Protocol

EEG data were recorded for five minutes from each participant using a 64-channel Hydrogel Geodesic Sensor Net (EGI, Eugene, OR) under eyes-closed resting conditions. Since our ultimate goal is to develop an EEG based sideline concussion-assessment tool, the EEG data collection task was designed as simple as possible with five-minute eyes closed resting condition only, so that the procedure would be easier after a concussion incident. The sampling rate for data collection was 250 Hz to minimize the computing time and the scalp-electrode impedance was less than 50 KΩ. Figure 13 shows the locations of electrode placement on the scalp for an EEG recording using 64-channel Hydrogel Geodesic Sensor Net (Electrode map used from Electrical Geodesics, Inc, Eugene, OR). Each electrode captures electrical activity reflecting information pertaining to brain function.

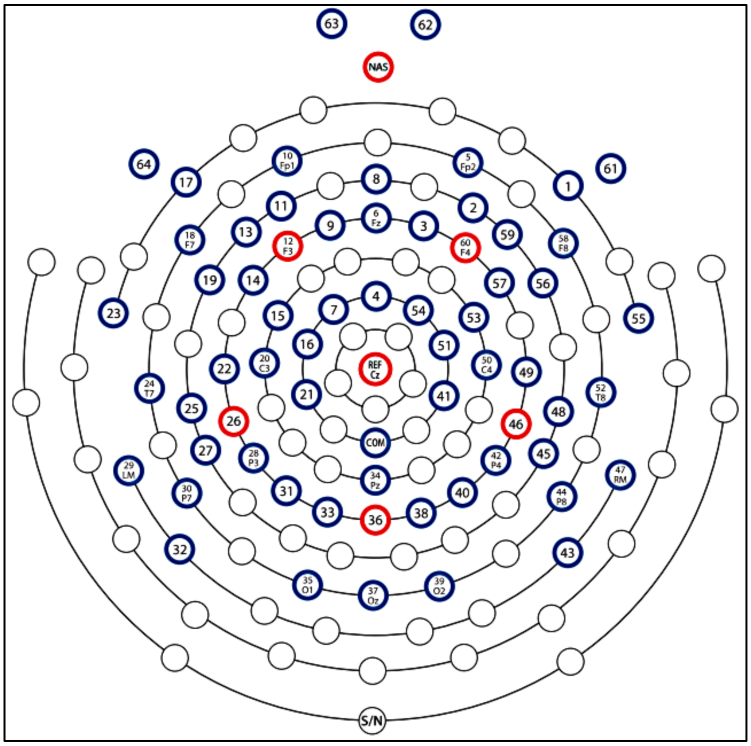

Figure 13. Locations of electrode placement for EEG recording using 64-channels [158]

3.2 EEG Data Analysis

EEG data were collected from twenty concussed and twenty age-matched controls. A set of power-spectral, wavelet, statistical and nonlinear features were extracted to identify the post-concussion abnormalities. Various techniques were applied to classify control and concussed athletes. The performance of the classifiers was compared to ensure the best accuracy. A list of EEG biomarkers was found to be significantly different between control and concussed group even though the concussed subjects were declared clinically asymptomatic.

3.2.1 EEG Data Preprocessing

To remove the high-frequency noises, EEG signals were band-pass filtered from 1 Hz to 50 Hz using a digital Butterworth IIR band-pass filter. Channels that are not consistently correlated with the time series of other channels were removed as noise. Large amplitude artifacts with power more than or equal to three standard deviations with respect to clean EEG were cleaned. Any artifact that was not detected by the software's artifact rejection toolbox were eliminated visually. Epochs that contained movement artifacts such as eye blinks, heartbeats or eye movements were eliminated from further analyses. A minimum of four minutes of artifact-free EEG with a 5-second epoch was used for further analysis. Using EEGLAB [114], zero phase-shift was applied to each of the artifact-free records. To compute the power spectra of the signal, Fast Fourier Transform (FFT) based power calculation was implemented for each epoch and the then averaged across them for the following frequency bands: delta (1-4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–40 Hz). Instead of absolute power, we computed the relative power for each frequency to ensure the homogeneous data processing. The power for each of the frequency from 1 Hz to 40 Hz was also computed.

3.2.2 Analysis using discrete wavelet transform

The EEG signal is inherently non-stationary in nature, and the application of Fourier transform is contingent on stationary (constant mean and variance with respect to time) signal behavior. Thus, it is not ideal to apply Fourier transforms directly to such signals. In a situation like this non-stationary EEG data, a time-frequency based method such as wavelet transform is preferable. Wavelet analysis uses a variety of different probing functions. EEG applications may require bilateral transformations, so it would be preferred to use a transform that can accurately recover the original signal by producing the minimum number of required coefficients. The discrete wavelet transform (DWT) accomplishes this by limiting the variations in translation and scale.

The selection of suitable wavelet and the number of levels of decomposition is critical during the analysis of signals using DWT. The number of decomposition levels was chosen based on the dominant frequency components of the signal. The selection of levels is performed such that the portion of the signal that correlated more with the frequencies essential for signal classification is restored in the wavelet coefficients. Since the EEG signals do not have any frequency components of interest above 30 Hz [159], the number of levels was chosen to be 6. Thus, the signal was decomposed into details D1–D6 and approximations A1-A6. These approximation and detail records were reconstructed from the Daubechies 8 (DB8) wavelet filter. Daubechies wavelet was chosen since it is the most common orthogonal wavelet that follows the admissibility conditions and thus allows the reconstruction of the original signal from its wavelets coefficients [160] and found to effective in EEG analysis for neurological disorders like ADHD and epilepsy [161], [162]. Different orders (2, 4, 6, 8, 12… 20) were examined for the analysis of post-concussion deficits. Daubechies wavelet with order 8 (db8) was found to be most suitable through our analysis to detect post concussive deficits as the lower order wavelets of this wavelet-family were found to be too coarse to represent EEG spikes properly whereas very high orders were too oscillatory [163]. Figure 14 (a) shows the approximate and detailed coefficients of EEG signal taken from a control subject whereas Figure 14 (b) shows those for a concussed subject. All data analysis using DWT was performed using MATLAB [164].

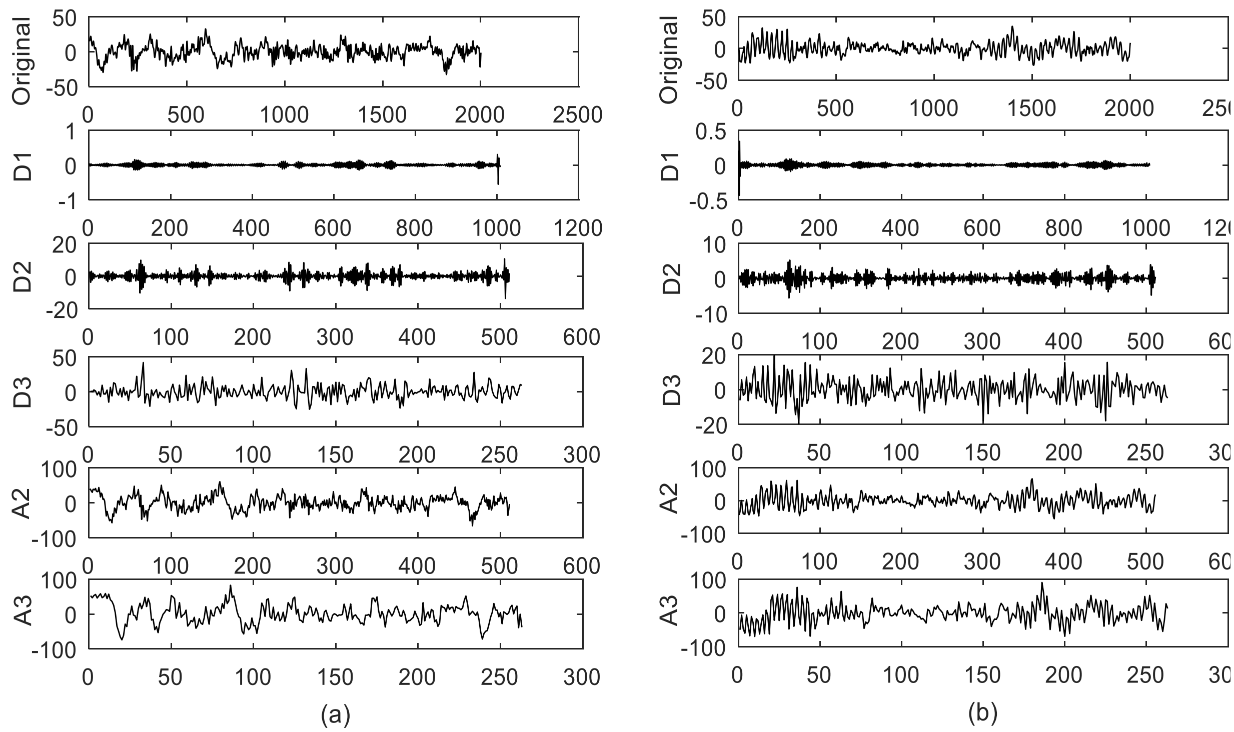

Figure 14. Approximate and detailed coefficients of EEG signal taken from: (a) control subject (b) concussed subject.

3.2.3 Linear and Nonlinear Analysis for EEG Feature Extraction

To identify the post-concussion deficits, below listed linear (power spectral, wavelet, statistical), and nonlinear features were extracted from the EEG signals.

3.2.3.1 Power Spectral Features

Five power spectral density features over the EEG frequency bands – alpha, beta, gamma, delta, and theta – were extracted.

3.2.3.2 Wavelet Features

Wavelet features were extracted using Debouches 8 wavelet transform. The extracted wavelet features provide a compact representation showing the energy distribution of the EEG signal with respect to time. The various detail and approximate wavelet coefficients entered into the feature matrix are as follows:

i. The mean of absolute values of the detail (D1-D6) and approximate (A1-A6) coefficients [12 features].

ii. The average power of the wavelet detail (D1-D6) and approximate (A1-A6) coefficients in each signal [12 features].

iii. The standard deviation of the wavelet coefficients in each signal [12 features].

3.2.3.3 Statistical Features

The skewness and kurtosis of EEG signals were extracted as statistical features. These features were successfully employed for classification in prior studies [165], [166].

3.2.3.4 Nonlinear Features

Nonlinear features were extracted to measure synchrony, complexity, and frequency of the signal. The details of the extracted features in this study are as follows:

Hjorth Parameters: Hjorth parameters [118] include activity, mobility, and complexity. Activity characterizes the signal power by computing the change in time signal, mobility calculates the average frequency of the spectral power and complexity specifies the alteration in frequency of the signal. Each of these features was evaluated separately for each channel to the whole signal. Thus, the extracted parameter was a feature per channel and, as a whole, a feature vector for each parameter. A total of 3 features (mean value of the three features for all channels) were extracted.

Partial Directed Coherence (PDC) Feature and Directed Transfer Function (DTF): The PDC and DTF [167] were calculated with functions provided by Omidvarnia [168], including functions from the BioSig toolbox [169] and the arfit toolbox [170]. PDC and DTF are the full multivariate spectral measures that compute the directed influences between a given pair of signals of a multivariate dataset [167], [171]. These features are based on the concept of Granger causality and they compute the direction of information flow among the time series [172], [173]). Two features were extracted from each signal.

Entropy: The time phase based entropy measure Approximate Entropy (ApEn) [174], and frequency spectrum based entropy measure Shanon Wavelet Entropy (SWE) [175] were calculated from each signal. ApEn computes the randomness or unpredictability of a signal by measuring the predictability of succeeding amplitude values. The computation includes embedding the full-time series into the phase space and approximating the rate of increment of phase space pattern number within a predefined measure [176]. The tolerance chosen for approximate entropy calculation was two standard deviations. The details of the algorithm can be found at Bruhn *et al.* [151]. Shanon Entropy computes a measure of the information by analyzing and comparing the probability distribution of a signal and SWE is the Shanon entropy in the wavelet domain which measures the variation of the signal in each frequency scale [175]. The details of the algorithm used for SWE calculation can be seen in Särkelä *et al.* [177].

Hurst Exponent: The Hurst exponent [134], also known as the index of long-range dependence, was calculated for each channel over the whole signal. The parameter evaluates the correlation properties and self-similarities of a time series by computing the existence and degree of long-range dependence in a time series [178]. The value H is defined as:

$$H = {}^{\log(R/S)}\Big/_{\log(T)} \quad 4$$

where T is the duration of the data sample and R/S is the corresponding value of the rescaled range. The mean value of Hurst exponent for all channels was extracted as a feature from each EEG signal.

Brain-rate: The BioSig implementation [169] of the brain-rate [179] was used to extract brain-rate from the EEG signal. Brain-rate, also defined as EEG-spectrum weighted frequency, is the mean frequency of the brain rhythm and is correlated with the brain's electric, mental, and metabolic activity [179]. The brain-rate was computed in stationary mode for each channel over the whole signal and the average value of all channels was extracted as a feature.

Total features extracted through the EEG analysis for both concussed and control athletes are listed in Table 11.

Table 11. List of features extracted from EEG signal

Method of Analysis	Features Extracted	Number of Extracted Features
Power Spectral	Power at delta, theta, alpha, beta, gamma frequency bands	5
Wavelet	Mean; standard deviation; and average power value of the detail (D1-D6) and approximate (A1-A6) coefficients	36
Statistical	Average skewness; Average kurtosis	2
Nonlinear	Hjorth activity, mobility, and complexity; Partial Directed Coherence (PDC); Directed Transfer Function (DTF); Approximate Entropy; Shannon Entropy; Hurst Exponent; Brain-rate.	9

3.2.4 Statistical Analysis

All the statistical analysis was carried out using the statistical toolbox in MATLAB [164]. The comparison between the control and concussed group was conducted with either independent sample two tail t-test or the Wilcoxon rank sum test, based on the normality distribution of the continuous variable. The normality of data was verified using the Shapiro-Wilk test. The critical value for tests of significance was set at $p<0.05$. All the feature values resulted from the statistical analysis within the groups were presented as mean ± standard deviation format.

3.2.5 EEG Classification

The aim of classification was to distinguish concussed athletes from the healthy control group based on the features extracted from their EEG signals. To ensure the best classification accuracy, we tested a set of classification techniques including support vector machines (SVM), k-nearest neighbor (kNN), random forest, and decision trees. The state-of-the-art SVM-based classifier was applied first. To classify the concussed athletes from healthy ones, we required a binary classification approach. To map the data into higher dimensional space, SVM employs linear and nonlinear kernels [180]. Linear SVM was initially applied to the extracted features, and then nonlinear kernels, such as Gaussian, quadratic, and cubic kernels were tested to improve the results.

The instance-based classification technique kNN was applied next. kNN classifies the data set based on the principle that instances having similar properties are in close proximity [181]. Different trials with kNN classifiers were conducted by changing the value of k and the best result was achieved with k=10. The distance was calculated using Euclidean distance matrix with equal distance weight.

The model's performance was verified next by using the decision tree classifier [182]. Different values of splits for the decision tree were tested and based on the performance of the classifier, the maximum number of splits was set at twenty. Gini’s diversity index method [183] was used as split criteria.

Random forest [184] technique was the last classification technique evaluated for the system. This technique improves the performance of the decision tree classifier by avoiding the overfitting problem. The best performance was given by the AdaBoost ensemble method with a maximum number of splits set at twenty and number of learners set at thirty with a learning rate of 0.1. The parameter values were set through trial and error method.

After testing these classifiers, the best classifier was selected to differentiate the control and concussed athletes. The accuracy of a classification technique was determined based on its prediction correctness. Since we had a small dataset, to ensure the best evaluation, we applied the leave-one-out technique to predict from the classes. The current research problem involves binary classification, so in addition to accuracy, we also calculated sensitivity (a measure of true positive, TP), specificity (a measure of true negative ratio, TN), and area under the curve (AUC) as other performance measures.

3.3 Results

The objective was to detect residual brain deficits through linear and nonlinear analysis of Electroencephalogram (EEG) signals and design an algorithm to classify concussed and control athletes. EEG data were collected from twenty concussed and twenty age-matched controls. A set of power-spectral, wavelet, statistical and nonlinear features were extracted to identify the post-concussion abnormalities. In addition to the analysis based on the conventional frequency band, additional analysis for each individual frequency from 1 to 40 Hz was also conducted. Various techniques were applied to classify control and concussed athletes. The performance of the classifiers was compared to ensure the best accuracy.

3.3.1 Neuronal Deficits in Terms of EEG Band-Power following Concussion

Figure 1 lists the neurological deficits in terms of power spectral density (PSD) between 20 control and 20 concussed subjects for traditional EEG frequency bands. As shown in the figure, the power spectral density analysis resulted in a significant increase in delta and theta power along with a significant decrease in alpha and beta band power.

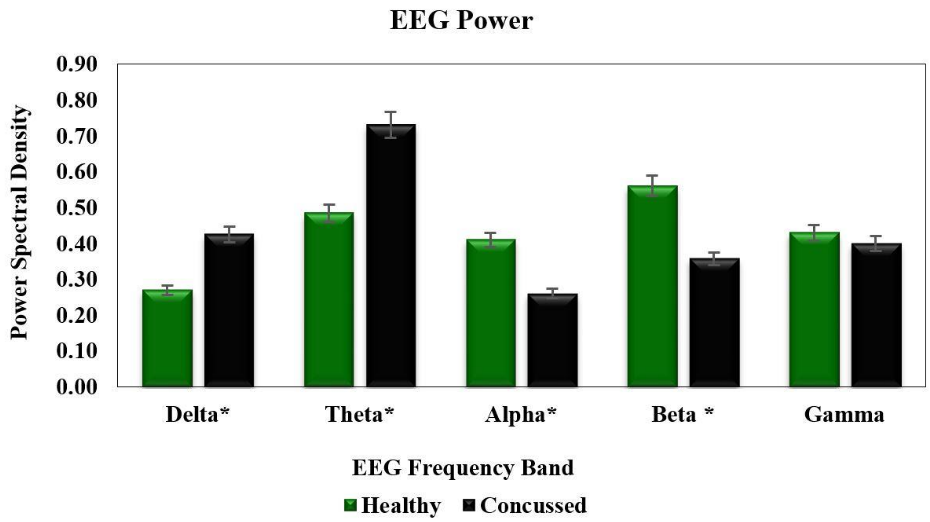

Figure 15. Power spectral density of different EEG frequency bands when normalized.

* indicates statistically significant difference ($p<0.05$) between control and concussed athletes ensuring robustness of selected feature.

If the channel spectra are mapped using EEGLAB for each frequency band, the channel-wise discrepancies can be observed. Fig. 15 shows a comparison of channel spectra of a control subject and a healthy subject for delta, theta, alpha, beta and gamma frequency bands for all channel. As seen in Fig. 16, the deficits were mainly in the frontal region of the brain.

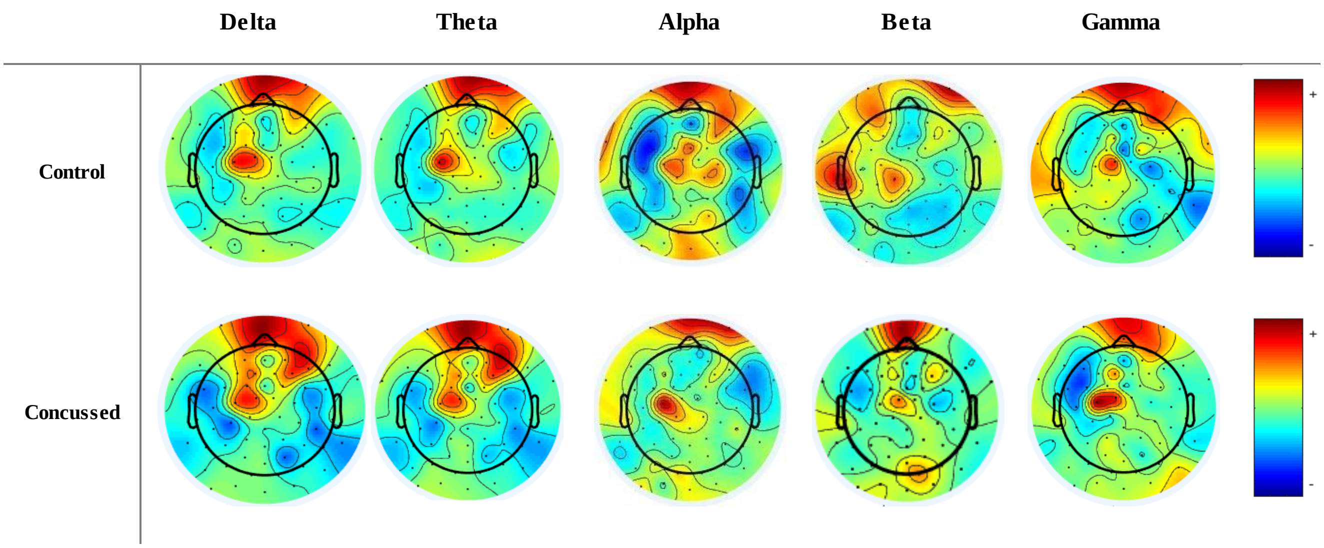

Figure 16. Delta, Theta, Alpha, Beta and Gamma spectra comparison between control and concussed subjects.

The first row of Figure 16 shows the channel spectra mapped for a control subject. The second row shows the channel spectra mapped for a concussed athlete.

3.3.2 Neuronal Deficits in Terms of EEG Single Frequency following Concussion

The spectra based analysis for all frequencies from 1 to 40 Hz was done in the second step to reveal the specific frequencies are exhibiting the significant power deficits. Fig. 17 shows the comparison of significance level for traditional frequency bands by the solid red lines and all the other frequencies from 1 to 40 Hz using the bar graph. Bars representing frequencies within each of five frequency bands (Delta, Theta, Alpha, Beta, and Gamma) are colored differently. The black dashed line indicates the significance level for p-value at p=0.05.

From Fig. 15, we can see that not all the frequencies within a particular frequency band (e.g., Gamma band) exhibit deficits in control and concussed athletes. However, from Fig.17 it is evident that the frequencies with significant deficits within Delta band are 1 Hz and 2 Hz, for Theta are 6

Hz and 7 Hz, for Alpha are 8 Hz, 9 Hz, and 10 Hz, for Beta is 16 Hz, 17 Hz, 18 Hz and all the frequencies from 24 Hz to 29 Hz. In addition, for Gamma frequency band, though the deficit between concussed and control subject was not significant, interestingly within the band, significant deficiencies were found at 34 Hz, 35 Hz, and 36 Hz (Fig. 17).

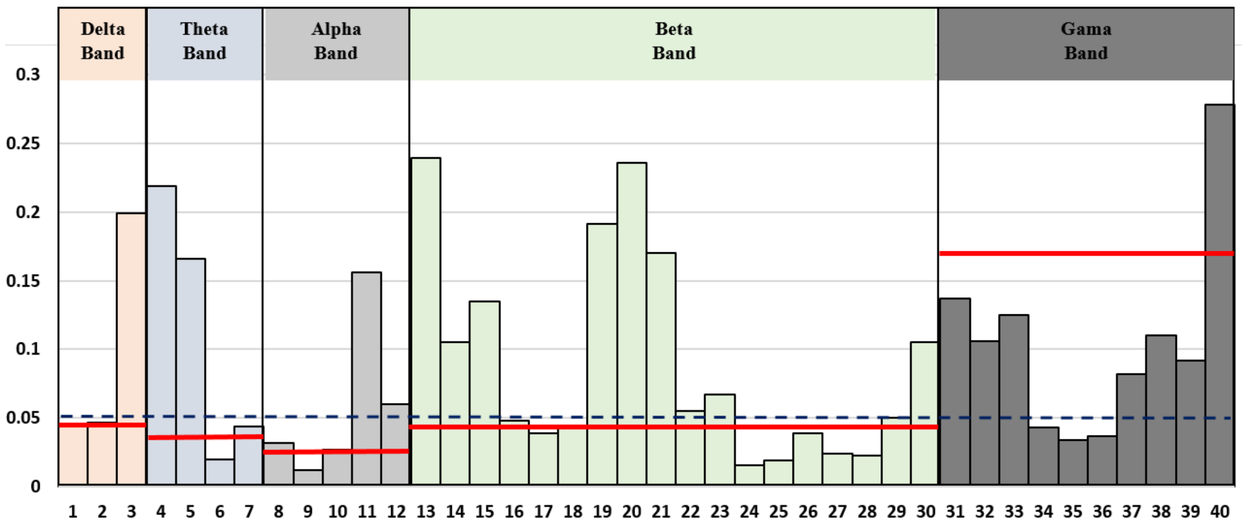

Figure 17. Functional deficit significance level for 1 Hz to 40 Hz between control and concussed group.

The black dashed line in Figure 17 indicates the significance level for p-value at p=0.05. The bar graphs indicate the p-value for 1 Hz to 40 Hz frequencies. The solid red lines plot the p-value for five conventional frequency bands; delta, theta, alpha, beta and gamma bands.

3.3.3 Neuronal Deficits in Terms of EEG Wavelet and Nonlinear Features

Table 12 lists the mean, standard deviation, and range of significant wavelet coefficients and nonlinear features. Features with a significant difference ($p<0.05$) between the groups are marked. Out of all wavelet detail and approximate coefficients, D3 and D6 revealed a significant difference ($p<0.05$) between healthy control and concussed athletes. Statistical features were unable to highlight the deficits between the groups. For the nonlinear analysis, Hjorth mobility, Hjorth complexity, approximate entropy, Hurst component, and brain-rate were significantly different ($p<0.05$) between control and concussed athletes.

Table 12. Mean, standard deviation and range of wavelet features that are significantly different between control and concussed athletes and all non-linear features

	Control Subjects		Concussed Subjects		
Features	Mean ± SD	Range	Mean ± SD	Range	*p*-Value
D3 Coefficients	0.047 ± 0.090	-0.0178 - 0.3423	0.007 ± 0.035	-0.0378 - 0.1365	0.002*
D6 Coefficients	-0.151 ± 0.184	-0.6044 - 0.0733	-0.046 ± 0.140	-0.5061 - 0.1500	0.050*
Hjroth Activity	91.097 ± 71.841	37.259 - 332.832	85.198 ± 59.018	21.199-271.309	0.785
Hjroth Mobility	0.230 ± 0.025	0.1920 - 0.2934	0.1913 ± 0.023	0.1503 - 0.2281	0.001*
Hjroth Complexity	0.480 ± 0.041	0.3811 - 0.5456	0.443 ± 0.057	0.3089 - 0.5281	0.030*
Brain-rate	6.879 ± 0.341	6.2528 - 7.4704	6.540 ± 0.361	5.8971 - 7.1639	0.026*
Partial Directed Coherence (PDC)	0.097 ± 0.011	0.0668 - 0.1075	0.097 ± 0.012	0.0621-0.1089	0.875
Directed Transfer Function (DTF)	0.119 ± 0.008	0.0959 - 0.1245	0.122 ± 0.003	0.1132-0.1243	0.215
Approximate Entropy	0.708 ± 0.060	0.6374 - 0.8950	0.663 ± 0.060	0.5694-0.7604	0.033*
Shannon Entropy	-0.032 ± 0.103	(-0.419) - 0.055	-0.005 ± 0.063	(-0.18)-0.129	0.322
Hurst Component	0.564 ± 0.035	0.5249 - 0.6584	0.524 ± 0.036	0.4606 - 0.5741	0.006*

3.3.4 EEG Classification Results

To perform the classification operation, the parameters extracted through power spectral, wavelet, statistical and nonlinear analysis of EEG signal were congregated to create a feature matrix, which was used as an input to the classifier. A visualization of two such features (average power at delta and theta frequency sub-bands) is presented in Figure 18 for both control and concussed athletes.

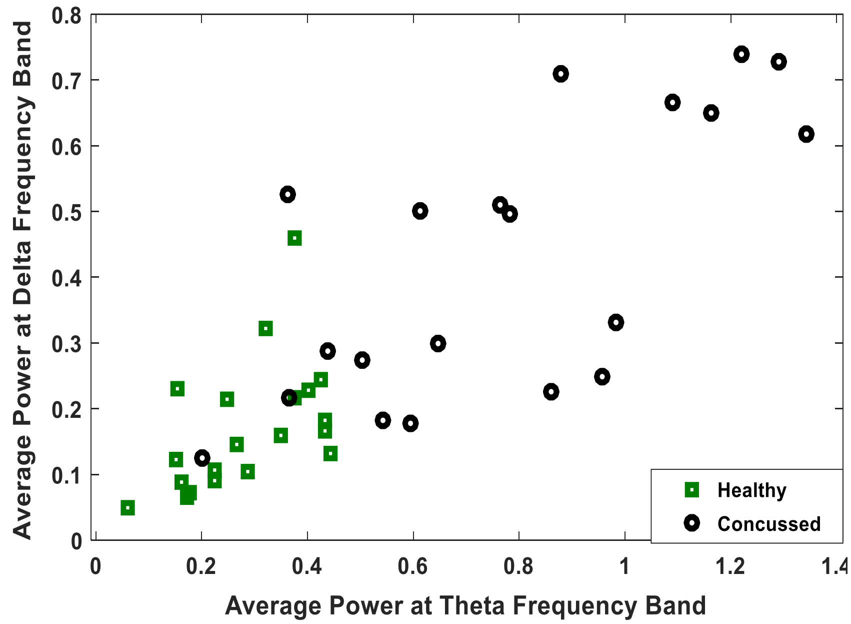

Figure 18. EEG power at delta and theta frequency bands for control and concussed athletes.

Y-axis in Figure 18 represents the power for delta frequency band, while X-axis represents the power at theta frequency band.

A set of meaningful features is critical for achieving higher classification accuracy. Therefore, the potential and significance of features to differentiate concussed and control athletes were validated by determining significant deficits between the groups during the statistical test of significance (Figure 15 and Table 12).

Table 13 displays the classification accuracy resulted by the four different classifiers experimented in the study. It shows that the classification accuracy with SVM was highest, exhibiting 5% greater performance than the second-best classifier (kNN).

Table 12. Comparison of different classifiers

Classifier	Accuracy	Sensitivity	Specificity	AUC
SVM (Linear)	85.0%	87.0%	83.0%	0.89
kNN	80.0%	85.0%	75.0%	0.80
Decision tree	77.5%	75.0%	80.0%	0.84
Random Forest	80.5%	75.0%	88.0%	0.82

Since SVM exhibited the highest accuracy, within SVM, the system performance for various kernel function was also analyzed to find out the best performing kernel. The results of this analysis are shown in Table 14. From Table 14, it can be concluded that the cubic kernel outperformed the linear, quadratic, and Gaussian SVM kernels.

Table 13. Comparison of different kernels of SVM classifiers

Kernel	Accuracy	Sensitivity	Specificity	AUC
Linear	85.0%	87.0%	83.0%	0.89
Gaussian	90.5%	95.0%	86.0%	0.92
Quadratic	87.5%	95.0%	80.0%	0.86
Cubic	95.0%	98.0%	92.0%	0.98

Table 15 shows a comparison of SVM (cubic kernel) classification accuracy calculated separately for features extracted through power spectral, wavelet, statistical, and nonlinear analysis of EEG signal while used separately for the same classification (classifier used for comparison was SVM with the cubic kernel).

Table 14. Comparison of accuracy of various features

Features	Accuracy	Sensitivity	Specificity	AUC
Power Spectral	82.5%	95.0%	70.0%	0.84
Wavelet + Statistical	67.5%	70.0%	65.0%	0.67
Nonlinear	85.0%	85.0%	85.0%	0.89
Power Spectral + Wavelet + Statistical	87.0%	88.0%	86.0%	0.91
Power Spectral + Wavelet + Statistical+ Nonlinear	95.0%	98.0%	92.0%	0.98

3.4 Discussion

Typical recovery time following a sport-related concussion is believed to be rapid, with the acute physiological symptoms resolving within hours and the person to be symptom-free within 10 days post-injury [111]. However, growing evidence shows that the physical, emotional, or neurocognitive deficits can persist months or even years and inaccurate diagnosis of the injury severity leads to a premature return to play. Therefore, detecting the differential dynamics of the neuronal dysfunction in well-controlled experimental settings is important in the area of concussion research and that is why the current study was aimed at detecting EEG biomarkers that can evaluate the post-concussion deficits even when the athletes were declared clinically asymptomatic. Additionally, this study undertook a systematic approach to verify the efficacy of the biomarkers to classify the concussed athletes from their healthy matched peers along with a comparison of the classification performance of several well-known classifiers.

There are several major findings of interest. First, the power spectral density analysis revealed a significant difference in the delta, theta, alpha, and beta frequency sub-bands power between control and concussed athletes (Figure 3). It should be noted that similar frequency bands were targeted in a number of previous EEG studies of concussion [41], [82], [185]. An increase in delta and theta frequency and a decrease in beta frequency was also reported in the literature [90], [111]. These discriminations raise concern about the concussed subjects' neuronal resolution since converging evidence shows that the deficits in these frequency bands may have a linear relationship with some pathological conditions. According to Demos et al., an increase in delta frequency may indicate brain injuries, learning problems, or difficulties with cognition and an increase in theta power are associated with ADHD, depression, hyperactivity, impulsivity, and inattentiveness [136]. Concussed athletes exhibited a decrease in alpha power and prior studies showed that the oscillation of alpha power is negatively correlated with task performance and cortical excitability [186]. An inverse association between alpha power and task difficulty has also been reported and inferred as alpha sensitivity to cortical idling, task difficulty, and disengagement [187]. In accordance with these views, decreased alpha power indicates an increased attention demand and/or cerebral effort [188] (Gevins *et al.,* 1997) and may imply that the concussed athletes required more effort to remain stable during eyes closed condition. A substantial decrease in beta power was also revealed by the analysis while certain levels of beta waves allow easy focus and involvement in conscious thought and logical thinking, and a decrease in beta waves may point to poor cognition [136].

EEG analysis was conducted for every single frequency ranging from 1 Hz to 40 Hz and interesting outcomes were observed displaying considerable variability between the testing paradigms. A set of noble frequency was found that could be used to identify the functional deficits between control and concussed athletes. In this study, slow Delta (1-2 Hz), fast Theta (6-7 Hz), slow Alpha (8-10 Hz), and 16-18 Hz and 24-29 Hz within Beta reveal significant functional deficits. This discrepancy at the specific frequencies would remain unnoticed if only conventional frequency bands were considered. Similarly, Gamma frequency band fails to exhibit any significant deficit. However, once the Gamma band is analyzed and explored for every single frequency, the differences between the control and the concussed groups was unveiled at a range of frequency (34-36 Hz). Eventually, this study exposed the fact that EEG analysis for each frequency is equally as important as conventional bands to evaluate the neurological dysfunction following a concussion.

Wavelet-based feature extraction through DWT revealed that the detail coefficients at level 3 and level 6 provided the biggest difference between the groups as the mean value of these coefficients was significantly different between control and concussed athletes (Table 2). Unlike power spectral and wavelet analysis, the statistical features like skewness and kurtosis were not able to highlight any significant deficits due to concussion, most likely due to the fact that these features describe the asymmetry and amplitude distribution of the data around the mean, and any correlation between the shape of the distribution of EEG and concussion is yet to be found.

The proposed nonlinear analysis of EEG measures appeared to be an effective tool for detecting residual cerebral dysfunction due to the concussion. We found five nonlinear features that showed a significant difference between control and concussed athletes (Table 2). A decrease in complexity, mobility, approximate entropy, Hurst exponent and brain rate was exhibited by the concussed group. Converging evidence shows that a decrease in mobility and complexity is related to insomniac patients [150]. Moreover, a decrease in mobility was reported to be related to cerebral physical or physiological alteration [121] as well as Alzheimer's disease [189]. A decrease in approximate entropy, which mainly highlights a decrease in complexity of the concussed group brain signal, was reported to indicate the incomplete information processing of the brain due to inactivation of the previously active neuronal networks of the brain [190]. The decrease in ApEn was also exhibited by subjects associated with various pathological conditions like depression [149], ADHD [191], epilepsy, post-traumatic stress disorder, schizophrenia and panic disorder [153]. The decrease in Hurst exponent highlighted the larger degree of anti-correlation in the brain signal and was also exhibited during epilepsy [154] and mental disorders [178]. An anesthesia study conducted by Liang *et al*. reported that the Hurst exponent decreased when the anesthesia was deepened [176]. The brain-rate measures the attention and cognition [179] and a decreased brain-rate reported in concussed athletes in the study may suggest under arousal condition of their brain compared to control athletes. Therefore, from the deficits exhibited by the nonlinear features, we can converge that the concussed group brain signal was less complex (due to lower mobility, complexity, and approximate entropy) and less awakened (due to lower Hurst exponent, brain rate). Among many others, three reasons are reported in the literature which can be responsible for the decrease of complexity in EEG signal: neuronal death, neurotransmitter shortage and loss of connectivity of the neural networks [190], [192]. The decrease in these parameters also suggests that the randomness of brain activity is reduced as fewer parallel functional processes are active in the concussed athlete's brain [193], [194].

As the power spectral, wavelet and nonlinear analysis of EEG signal showed remarkable deficits between the groups, it seemed of interest to us to interpret the possible use of these parameters to differentiate concussed subjects from healthy peers. Therefore, in the second part of the study, we have experimented with this possibility by using the above-mentioned parameters extracted from the EEG signal as input for a classifier to differentiate the concussed athletes. A set of classifiers including SVM, kNN, decision tree and random forest were tested using the leave-one-out method on the data set to find out the best accuracy. As shown in Tables 3 and 4, the informative and descriptive features extracted from the EEG, combined with SVM classifier using cubic kernel resulted in an accuracy of 95% in the classification of concussed and control athletes. The classifier has a sensitivity of 98% (cubic kernel SVM) with an acceptable specificity of 92%. The area under the curve was reported as 0.98. Among all the classifiers, the best classification performance was exhibited by SVM, which can be justified by the fact that, unlike other classifiers which separate the classes using flat plane hyperplane, SVM broadens the concept of hyperplane by using kernel functions to build linear boundaries in a high dimensional space through nonlinear mappings of the predictors and thus extract better discriminatory information from the feature space which makes the classification more accurate [159]. Moreover, the use of cubic kernel allowed a more flexible decision boundary in the data space to improve the accuracy [159].

Though the spectral analysis of EEG has been extensively studied in a concussion, its usefulness as a concussion detection tool (in isolation) is low [195]. Therefore, the proposed study may be used as a concussion detection approach. A very limited work has been done to automatically classify concussed athletes from control athletes. With a dataset of 31 control and 30 concussed athletes, Cao *et al*. reported an accuracy of 77.1% with a sensitivity of 96.7% and selectivity of 69.1% to classify healthy and concussed athletes applying SVM classifier on a set of frequency-based features [196]. Garg *et al.* also implemented an SVM-based classification approach using power spectral and wavelet features and reported an accuracy of 88.3% with a sensitivity of 85.19% and specificity of 90.91% in distinguishing concussed subjects from matched healthy controls [83]. Though our dataset is different from the above-mentioned studies, our approach provided better results in our database on each of the evaluation metrics. As reported in Table 5, the use of nonlinear feature combined with other features, improved the classification accuracy by 7%. The increase in accuracy by adding nonlinear features may be justified by following the already established hypothesis that due to the complex and chaotic nature of the EEG signal, quantitative analysis through nonlinear features is convenient to highlight the neurophysiological irregularities in pathological conditions that are not apparent through linear analysis [197].

The high classification accuracy of our analysis verified that the features and discriminant functions are robust and gives insight into the combination of power spectral, wavelet, statistical, and nonlinear features used for defining the EEG signals. The study provides further light to the ongoing debate on literature regarding the cumulative post-concussion effects and suggests that these features could be used as biomarkers to reflect the neuronal deficits following a concussion. Both in the conventional frequency band based study and the individual frequency based study, the concussed athletes recruited more power than the control athletes did. As per suggestion from [9] and [10], we can hypothesize that the concussed athletes may not be able to engage appropriate resources to complete the task at hand, so they achieve normative functioning by recruiting additional brain resources. More importantly, these neurological deficits detected through EEG analysis raise considerations about reliability and neurophysiologic validity of conventional concussion assessment tools as all the athletes in the concussed group were declared clinically asymptomatic. Hence, it is pertinent to emphasize developing an alternative EEG based assessment device which can also provide additional information about the deficits in the functional brain network [90], [111].

CHAPTER 4

CONCLUSION, CONTRIBUTION AND FUTURE WORK

4.1 Conclusion

Accumulated evidence from our study suggested that there may be a residual detrimental cognitive and electrophysiological effect of past concussion history. In addition, the findings cross-validate the efficacy of some widely used neurocognitive and electrophysiological concussion assessment tools. Thus, the current study highlights towards a potential application in concussion management by providing evidence to identify the athletes who are at risk for sustaining physiological deficits and thus can play a significant role in RTP decision.

The combined neurocognitive and EEG study suggests that EEG analysis is more sensitive compared to cognitive testing to decipher persistent sequelae of sport-related concussion. For the first time, a set of time domain and nonlinear EEG features was utilized in addition to the standard frequency band features to highlight neuronal deficits following a concussion. In addition, the approach of analysis using individual frequencies of EEG was conducted for the first time to study concussion. This innovative approach combined with novel features opens a new door to interpret subtle post-concussion deficits. While no previous work was done to find the post-concussive deficits in individual frequency level, the result demonstrated a new range of frequency, which is more successful to reveal the discrepancies. In sum, accumulated evidence from this study suggests that the proposed approach of EEG analysis was successful to identify that the athletes with a history of concussive injury still exhibited neurological alterations, despite reporting to be symptom-free by standard postural, visual or neurophysiological tests.

For designing the automatic classification approach, we found that a set of meaningful features extracted from the EEG could differentiate concussed athletes from control athletes. The application of nonlinear features combined with well-established power spectral, wavelet and statistical features provided new information about electrophysiological abnormalities caused by concussion, and, thus, were helpful in differentiating a concussed group from healthy controls. The classification results indicated that SVM with cubic kernel had superior performance in EEG signal classification compared to kNN, decision tree, and random forest classifiers. Therefore, the proposed SVM-based diagnostic system can be used in clinical studies as a concussion assessment tool along with other modern approaches (e.g., analysis of biomechanical impact, brain-imaging studies, duration of symptoms resolution, etc.) and for more accurate return-to-sport participation criteria, clinicians can use such a system after concussive episodes.

4.2 Future work

The future work will aim at the extensive testing of the proposed algorithm with a larger data set consisting of recordings of a large number of subjects so that, more rigorous quantitative and qualitative analysis can be performed. Future work would also include EEG data collection from participants while doing more rigorous physical or mental task so that the deficits during task performance can be highlighted. We would like to give emphasis on improving the classification accuracy of two classes, namely healthy and concussed, to detect and predict the concussion from EEG signals. In addition, we hope the current outcomes will lead to producing more inclusive evaluations in future towards developing an EEG-based sideline device to proactively assess the post-concussion clinical disorders. Thus, our findings will engender more comprehensive evaluations towards clinical applicability of concussion assessment for proper diagnosis and prevention through accurate RTP decision, as well as managing the treatment and rehabilitation efficacy post-concussion.

4.3 My Contribution

My contribution to this research was to develop an algorithm to detect post-concussion residual deficits from the athletes with a history of concussion. I have also developed an algorithm to calculate a set of linear, time-frequency and nonlinear EEG markers that were found to be significantly different in the concussed group compared to their matched peers in the healthy group. As the result of research conducted in this thesis, the following journal and conference papers were published:

1. **Tamanna T. K. Munia**, Ali Haider, Charles Schneider, Mark Romanick, Collin Combs, & Reza Fazel-Rezai, "A Novel EEG Based Spectral Analysis of Persistent Brain Function Alteration in Athletes with Concussion History", manuscript in review at Nature Scientific report.

2. **Tamanna T. K. Munia**, Shaun Porter , Naznin Virji-Babul, Mark Romanick, and Reza Fazel-Rezai, "Detection of Residual Brain Deficits in Athletes with Concussion based on Linear and Nonlinear EEG Analysis", manuscript submitted to Clinical Neurophysiology.

3. **Tamanna T. K. Munia**, Gendreau, J.L., Verma, A.K., Johnson, B.D., Romanick, M., Tavakolian, K. and Fazel-Rezai, R., 2016, August. Preliminary results of residual deficits observed in athletes with concussion history: Combined EEG and cognitive study. In Engineering in

Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the (pp. 41-44). IEEE.

4. Tamanna T. K. Munia, Gendreau, J.L., Johnson, B.D., Romanick, M., Tavakolian, K. and Fazel-Rezai, R., 2016, May. "Neurocognitive deficits observed on high school football players with history of concussion: A preliminary study". In Electro Information Technology (EIT), 2016 IEEE International Conference on (pp. 0734-0738). IEEE.

5. Tamanna T. K. Munia, Haider, A. & Fazel-Rezai, R. Evidences of Brain Functional Deficits Following Sport-Related Mild Traumatic Brain Injury. in IEEE Engineering in Medicine and Biology Society 3212–3215. (IEEE, 2017).

6. Charles M. Schneider, Ajay K. Verma, **Tamanna T. K. Munia**, Mark Romanick, Kouhyar Tavakolian, Reza Fazel-Rezai, "Analysis of Postural Stability Post Concussion using Empirical Mode Decomposition" 2017 Design of Medical Devices Conference, Publisher: ASME.

4.4 Other Publications

1. **Tamanna T. K. Munia**, Intisar Rizwan i Haque, Abby Aymond, Nicholas MacKinnon, Daniel L. Farkas, Minhal Al-Hashim, Fartash Vasefi, Reza Fazel-Rezai, "Automatic Clustering-Based Segmentation and Plaque Localization in Psoriasis Digital Images", Accepted NIH-IEEE Special Topics Conference on Healthcare Innovations and Point of Care Technologies (Hi-POCT 2017).
2. **Tamanna T. K. Munia**, Tavakolian, K., Verma, A.K., Zakeri, V., Khosrow-Khavar, F., Fazel-Rezai, R. and Akhbardeh, A., 2016, September. "Heart sound classification from

wavelet decomposed signal using morphological and statistical features". In Computing in Cardiology Conference (CinC), 2016 (pp. 597-600). IEEE.

3. **Tamanna T. K. Munia,** Alam, M.N., Neubert, J. and Fazel-Rezai, R., 2017, July. Automatic diagnosis of melanoma using linear and nonlinear features from digital image. In Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual International Conference of the IEEE (pp. 4281-4284). IEEE**.**
4. Md N Alam, **Tamanna T. K. Munia**, Kouhyar Tavakolian, Fartash Vasefi, Nick MacKinnon, and Reza Fazel-Rezai. "Automatic detection and severity measurement of eczema using image processing." In Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the, pp. 1365-1368. IEEE, 2016.
5. Alam, M.N., **Tamanna T. K. Munia** and Fazel-Rezai, R., 2017, July. Gait speed estimation using Kalman Filtering on inertial measurement unit data. In Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual International Conference of the IEEE (pp. 2406-2409). IEEE.
6. Md N Alam, Amanmeet Garg, **Tamanna T. K. Munia**, Reza Fazel-Rezai, and Kouhyar Tavakolian. "Vertical ground reaction force marker for Parkinson's disease." PloS one 12, no. 5 (2017): e0175951.
7. Md N Alam, **Tamanna T. K. Munia**, Ajay K. Verma, Jau-Shin Lou, Collin Combs, Kouhyar Tavakolian, Reza Fazel-Rezai, "A Quantitative Assessment of Bradykinesia Using Initial Measurement Unit" 2017 Design of Medical Devices Conference, Publisher: ASME.

8. Vasefi, F., MacKinnon, N.B., Horita, T., Shi, K.,**Tamanna T. K. Munia,** Tavakolian, K., Alhashim, M. and Fazel-Rezai, R., 2017, April. “A smartphone application for psoriasis segmentation and classification” (Conference Presentation). In SPIE BiOS (pp. 1006819-1006819). International Society for Optics and Photonics.

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