Feasibility of Electroencephalography for Direct Assessment of Concussion

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William J. Ray, Elizabeth Teel, Michael Gay,
Semyon M. Slobounov, Robert Fornini, and Owen Griffith

Introduction

Recently, much research has focused on the role of concussion in athletics, particularly contact sports. An international conference on Concussion in Sport published a consensus statement that includes a summary of the most recently agreed-upon causes, diagnostic tools, symptoms, guidelines for return to sport and daily life, and prevention of sports-related concussion. The updated definition of sports-related concussion is:

> a traumatic brain injury induced by biomechanical forces, which may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head, typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously or evolve over a number of minutes to hours, and may result in neuropathological changes, but the acute clinical signs and symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies [1].

With the growing public concern regarding these injuries, the National Football League has supported studies of the long-term effects of concussion in professional athletes and many universities have established centers for the study of concussion on their athletes. Additionally, many individual states within the United States have established laws related to concussion assessment and management in

W. J. Ray · E. Teel · M. Gay · R. Fornini · O. Griffith
Center for Sports Concussion Research and Services, Department of Kinesiology, Pennsylvania State University, University Park, PA, USA

S. M. Slobounov (✉)
Center for Sports Concussion Research and Services, Department of Kinesiology and Neurosurgery, Pennsylvania State University, University Park, PA, USA
e-mail: sms18@psu.edu

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child-age athletics, as well as return to play and academic guidelines. In particular, high school athletes are at risk for repeat concussion since surveys suggest that this group believes that there is not a problem playing sports after injury. Furthermore, studies on high school athletes revealed common reasons for concussion not being reported including thinking the injury is serious enough to warrant medical attention, social and intrinsic motivation not to be withheld from competition, and lack of awareness of probable concussion [2–5]. The reasons for not self-reporting may also vary based on the stage, as motivation to stay in competition changes across age groups and level. In collegiate athletes for example, factors such as future professional career, scholarship, acceptance of peers, support from coaching staff, and personal identity as an athlete may all impact symptom reporting [6, 7]. Returning to play before the concussion has been fully resolved can increase the likelihood of long-term injures due to a higher risk of secondary injury during recovery. Athletes who suffer repeat concussion typically do so within the first 7–10 days after the initial injury [8]. Since adolescence is a time in which an individual's brain is still developing and goes through a series of cortical reorganizations, brain insults at this time can put the adolescent at greater risk for more serious injury or even death. For college and professional athletes, different internal, team, or societal pressures may cause players to ignore information concerning the effects of concussion. Overall, this can lead to a lack of candor when athletes describe their symptoms. Since, at this time, diagnosis is often based on the individual's self-reporting of their symptoms to a doctor, it is critical to utilize measures that can evaluate the effects of concussion beyond the traditional signs and symptoms, in a more objective way.

When the injury occurs, acceleration/deceleration forces are applied to the head and can often produce diffuse microstructural injury. Due to the diffuse nature of these injuries, standard structural imaging, such as MRI and CT, may not be able to identify all abnormalities [9]. Evidence collected from several animal studies implies that mTBI and SRC induce temporary variance in neuronal energy metabolism, excitatory neurotransmitter release, and cerebral blood flow [10, 11], establishing a functional injury, rather than solely a structural injury. With this evidence, numerous organizations have published position statements concluding that neuroimaging findings are generally normal in sports-related concussion individuals and imaging studies add little to the field of clinical concussion management [12–16]. Currently, authorities recommend that neuroimaging be used for patients in the acute phase of head injury, when there is suspicion of severe intracranial pathological conditions like subdural hematoma, epidural hematoma, or intraparenchymal hemorrhage (IPH), or in patients with extended disruption in consciousness, focal neurological deficits, or aggravated symptoms [12–18].

In summary, rather than the gross structural damage or lesions found in penetrating head injury or severe traumatic brain injuries, concussive episodes can be characterized by cognitive dysfunction, specifically in information processing and working memory [9].

Need for Physiologic Measurement in Clinical Concussion Diagnosis/Management

Athletic participation is unique in its requirement of the able-bodied participant. Physicians and allied health professionals making recommendations for athletes returning to sport from concussion must ultimately be comfortable with the concept of potential repeated injury. In other words, although unclear whether this is entirely possible, it is the clinician's goal to ensure that an athlete recovering from concussion and returning to full athletic participation be as resilient to head trauma as compared to an athlete with no previous head injury. Ultimately, clinicians must be assured that the athlete's risk of short-term or long-term effects from their concussive episode has been minimized as best as possible.

With these important clinical considerations in mind, management of sports-related concussion must evolve beyond the limitations in the currently accepted definition of concussion with *functional* recovery from concussion being representative of clinical healing. Considering the number of mTBI-linked short-term and long-term physical and mental health issues [19–22], clinicians and researchers alike must take important steps to ensure proper management of the recovering athlete. Intense scrutiny of residual physiological and functional deficits, as well as measuring and monitoring the athlete's rate of pathophysiological recovery from concussive injuries must become a primary focus. By increasing collective efforts, we can hope to reduce short- and long-term health issues. Yet, despite this need, clinical management of the mild head-injured athlete has evolved relatively slowly.

One of the reasons that clinical management of concussion has remained largely unchanged is due partly to a disproportionate focus on functional cognitive testing. Neuropsychological testing remains the mainstay in determining the clinical recovery for the concussed athlete. As neuropsychological testing is limited to cognitive functional performance, it has seemingly maximized its clinical utility at present. Therefore, clinical researchers need to push the constructs of other applicable and relevant diagnostic tools to provide athletes recovering from sports-related concussion with better assessment and management tools. These tools must be able to distinguish residual functional *and* structural (physiological) recovery from mTBI. As both diffuse functional and structural injury are present in mTBI [23, 24], clinicians and researchers must develop and research both functional and structural diagnostic tools when treating the athlete recovering from concussion.

Several organizations include the presence of pathophysiology in their definitions of concussion. Thus, it seems appropriate to utilize a physiological measure to denote the presence of concussion. Due to the diffuse nature of the injury and the consequential cognitive dysfunction, electroencephalograms or EEGs, which are able to systematically evaluate the underlying neural process that contributes to functional networks, are a sensitive and appropriate tool to evaluate the effects of concussive episodes.

EEG was first demonstrated in humans by Hans Berger in 1924 and published 5 years later [25]. Since the neurons of the brain and their connections are constantly active, EEG can be measured in an individual both during conscious and

unconscious states as seen in sleep and brain trauma. As such, EEG was the first brain assessment tool that was able to establish an alteration in brain function in a traumatic brain injury population [26, 27] and has continued to be useful in the brain injury field.

Early EEG research including 300 patients clearly demonstrated the slowing of major frequency bands and focal abnormalities within 48 hours post injury [28]. A study by McClelland et al. has shown that EEG recordings performed during the immediate post-concussion period demonstrated a large amount of "diffusely distributed slow-wave potentials," which were markedly reduced when recordings were performed 6 weeks after injury [29]. Additionally, Tebano et al. showed a shift in the mean frequency in the alpha (8–10 Hz) band toward lower power and an overall decrease of beta (14–18 Hz) power in patients suffering from mTBI [30]. The reduction of theta power [31] accompanying a transient increase of alpha-theta ratios [32, 33] was identified as residual symptoms in concussion patients.

At the beginning of the twenty-first century, Gaetz and Bernstein [19] cited electrophysiological techniques as the most commonly used method to evaluate brain functioning, noting the relatively low cost, noninvasive nature of the test, and the long, well-documented history dating back to the 1930s. Leon-Carrion et al. [34] echo the benefits defined by Gaetz and Bernstein and also speak to the uncomplicated procedure, high test-retest reliability, and characteristic stability of EEGs as additional features that contribute to its appropriateness as a diagnostic testing tool.

The Nature of EEG

EEG reflects the electrical activity of the brain at the level of the synapse [35]. It is the product of changing excitatory and inhibitory currents. More specifically, graded postsynaptic potentials of the cell body and dendrites of vertically orientated pyramidal cells in cortical layers three to five give rise to the EEG recorded on the scalp. The ability to record the relatively small voltage at the scalp from these actions results from the fact that pyramidal cells tend to share a similar orientation and polarity and may be synchronously activated. Action potentials contribute very little to the EEG. However, since changes at the synapse do influence the production of action potentials, there is an association of EEG with spike trains [36]. The summation of these electrophysiological measures is precisely what makes EEGs better suited for the study of concussion compared to several other types of brain imaging techniques.

Historically, the system of locating electrodes in EEG is referred to as the International 10–20 system [37]. The name 10–20 refers to the fact that electrodes in this system are placed at sites 10% and 20% from four anatomical landmarks. One landmark is the front of the nasion (the bridge of the nose). In the rear of the head, the inion (the bump at the back of the head just above the neck) is used. The left and right landmarks are the preauricular points (depressions in front of the ears above the cheekbone). In this system, the letters refer to areas of the brain; 0 = occipital, P = parietal, C = central, F = frontal, and T = temporal. Numerical subscripts

indicate laterality (odd numbers left, even right) and degree of displacement from the midline (subscripted z). Thus, C3 describes an electrode over the central region of the brain on the left side whereas Cz would refer to an electrode placed at the top of the scalp above the central area. With the development of dense array systems, the historical 10–20 system has been greatly expanded (see Fig. 4.1 for an example cap).

To record the EEG, electrical signals of only a few microvolts must be detected on the scalp. A signal can be found by amplifying the differential between two electrodes, at least one of which is placed on the scalp. Since the signal must be amplified almost one million times, care must be taken that the resulting signal is indeed actual EEG and not artifact. Where the electrodes are placed and how many are used depend on the purpose of the recording. Almost all EEG procedures currently use a variety of EEG caps with up to 256 electrodes built into the cap, although it is always possible to record EEG from only two electrodes. Those recording caps that use 128 to 256 electrodes are generally referred to as dense array EEG recordings and are used in most research settings. However, research in clinical situations, such as the hospital emergency room, has shown that as few as 5 electrodes can be used for the screening of mild traumatic brain injuries [38]. That study demonstrated that EEG showed a 94.7% accuracy rate when compared with computed tomography for detecting mild traumatic brain injuries, highlighting the potential of using even simple EEG montages for detecting concussions in a sports setting.

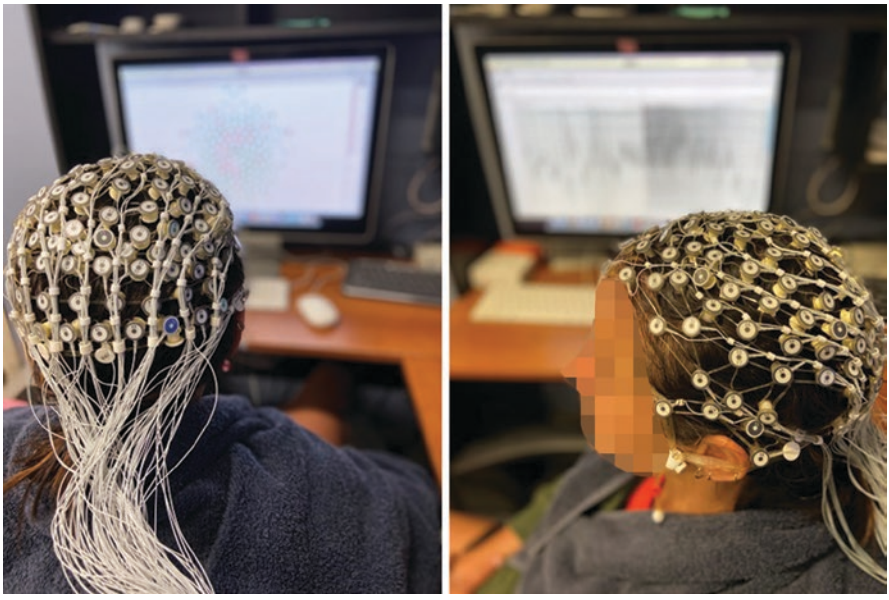

Fig. 4.1 128-electrode cap applied during routine EEG recording

EEG Frequency Bands

One important parameter of EEG is the determination of frequency. Although there are some minor discrepancies in the literature in terms of the beginning and ending of the specific frequency band, a general template is presented in Table 4.1. Frequency bands are generally determined through signal processing techniques such as Fourier analysis and wavelet analysis.

Alpha activity can be seen in about three-fourths of all individuals when they are awake and relaxed. Asking these individuals to further relax and close their eyes will result in recurring periods of several seconds in which the EEG consists of relatively large, rhythmic waves of about 8–12 Hz. This is the *alpha rhythm*, the presence of which has been related to relaxation and the lack of active cognitive processes. If someone who displays alpha activity is asked to perform cognitive activity such as solving an arithmetic problem in their head, alpha activity will no longer be present in the EEG. This is referred to as alpha blocking. Typically, cognitive activity causes the alpha rhythm to be replaced by high frequency, low amplitude EEG activity referred to as beta activity. Since the discovery of the alpha rhythm, a variety of studies have focused on its relationship to psychological processes and broad developments of the cognitive and affective neurosciences amplified this interest [see [39, 40] for reviews].

High-frequency activity occurs when one is alert. Traditionally, lower voltage variations ranging from about 18 to 30 Hz have been referred to as beta and higher frequency, lower voltage variations ranging from about 30 to 70 Hz or higher are referred to as gamma. Initial work suggests that gamma activity is related to the brain's ability to integrate a variety of stimuli into a coherent whole. For example, Tallon-Baudry and colleagues [41] showed individual pictures of a hidden Dalmatian dog that was difficult to see because of the black and white background. After training individuals to see the dog, differences in the gamma band suggested meaningful and non-meaningful stimuli produced differential responses.

Additional patterns of spontaneous EEG activity include delta activity (0.5–4 Hz), theta activity (4–8 Hz), and lambda and Kcomplex waves and sleep spindles, which are not defined solely in terms of frequency. Theta activity refers to EEG activity in the 4–8 Hz range. Grey Walter [42], who introduced the term theta rhythm, suggested that theta was seen at the cessation of a pleasurable activity. More recent

Table 4.1 Frequency ranges for each given bandwidth

Bandwidth name	Frequency	Brain function correlation
Delta	0.5–4 Hz	Deep sleep, memory consolidation, infant resting state
Theta	4–8 Hz	Beginning phases of sleep, working memory, information uptake and processing
Alpha	8–13 Hz	Relaxation/meditation, mind-body integration
Beta1	13–24 Hz	Active thinking, problem solving, decision making
Beta2	24–32 Hz	
Gamma	32–60 Hz	Heightened perception and processing

research associated theta with such processes as hypnagogic imagery, REM (rapid eye movement) sleep, problem solving, attention, and hypnosis, and source analysis of midline theta suggests that the anterior cingulate is involved in its generation [42]. In an early review of theta activity, Schacter [43] suggested that there are actually two different types of theta activity: (1) theta activity associated with low levels of alertness as would be seen as one falls asleep and (2) theta activity associated with attention and active and efficient processing of cognitive and perceptual tasks. This is consistent with the suggestion of Vogel et al. [44] that there two types of behavioral inhibition, one associated with a gross inactivation of an entire excitatory process resulting in less active behavioral states and one associated with selective inactivity as seen in over-learned processes.

Delta activity is low frequency (0.5–4 Hz) and has been traditionally associated with sleep in healthy humans as well as pathological conditions including cerebral infarct, contusion, local infection, tumor, epileptic foci, and subdural hematoma. The idea is that these types of disorders influence the neural tissue that in turn creates abnormal neural activity in the delta range by cutting off these tissues from major input sources. Although these observations were first seen with intracranial electrodes, more recent work has found similar results using MEG and EEG techniques. Additionally, EEG delta activity is the predominant frequency of human infants during the first 2 years of life.

EEG and Concussion

While conventional EEGs are not part of the current clinical "gold-standard" assessment battery, a number of studies show EEG differences in those individuals suffering from concussion compared to healthy controls [see [45] for an overview]. Of the differences observed on conventional EEGs, the most common abnormalities seen are generalized or focal slowing as well as weakened posterior alpha in mTBI patients [28, 46, 47]. These deficits were found in the immediate post-injury period (within a few hours of a concussive episode); however, similar findings have been reported even when there is a longer period between injury occurrence and evaluation.

These common abnormalities seen on conventional EEG recordings usually resolve within the first few months post injury [48], similar to the resolution of functional and symptomatic deficits in concussive recovery. However, up to 10% of individuals diagnosed with mTBI still show atypical electrophysiological readings in the late post-injury period [48, 49]. This small but significant portion of individuals who show electrophysiological abnormalities in the late post-injury period parallels those individuals who have atypical resolution of concussive symptoms and functioning.

Traditionally, in clinical settings, conventional EEGs were interpreted by the visual inspection of raw EEG signals. However, studies show that visual inspection of EEG lacks the sensitivity to detect changes following concussion. With the advancement of computerized signal processing techniques, there is a growing body

of literature that suggests more complex EEG paradigms may be used to assess changes in functional status after concussive injuries [9]. Compared to visually inspected EEGs, computerized EEG analyses are advantageous because they can detect subtle differences in signal patterns and shifts not visible to the naked eye [23]. Due to these benefits, Cannon et al. [50] indicated the usefulness of EEG as an assessment tool for brain injury is due to its "direct signature of neural activity" and "ideal temporal resolution."

Several different types of variables can be isolated using quantitative EEG methods. Spectral analysis, relative amplitude, and power in particular frequency bandwidth, coherence, and phase are the most common types of analyses performed in EEGs. In terms of mTBI, frequency and coherence analyses of particular cortical areas can offer important information [9, 23, 51]. By examining the pattern of activity between the cortical areas, it is also possible to delineate brain networks, see how they are involved in different types of tasks, and determine how they differ under certain conditions such as the presence of a concussion.

Coherence analysis describes how the EEG signal at each of two electrodes is related to one another. In other words, coherence reflects the manner in which two signals "co-vary" at a particular frequency and represents the correlation of signal phase stability between two different electrodes. Coherence measurements within the same frequency band offer an estimate of the temporal relationships between adjacent neural systems. Like correlation, coherence is a measure between 0 and 1, where 1 represents a perfect phase correlation between two groups and 0 represents no correlation. Thus, in performing the coherence analysis, one can also obtain a measure of phase or synchrony (see Fig. 4.2 for an example of various EEG outputs).

The particular interest in EEG coherence is due to the biological nature of concussive injury. The brain structures involved in neural connectivity, such as the reticular system activation and thalamocortical tracts, are the structures most likely to be affected by concussion. Considering the probability that these areas are altered following concussion, frequency and coherence analyses are likely to be the most sensitive electrophysiological measures to indicate deficits due to concussive injury.

According to Arciniegas [23], frequency measures can vary with the number of neurons (smaller number, smaller amplitude/power), the integrity of the thalamocortical circuits in which the neurons contribute (injury to the circuit causes slower frequencies), and the influence of activation from the reticular system (increases in reticular system activity cause higher frequencies, while decreases in reticular system activity cause lower frequencies). Coherence, which by definition correlates the frequency measures between two different electrodes, may indicate the level of communication between different areas of the brain and signify neural network connectivity and dynamics [23]. Reduced coherence values can be attributed to damage in myelinated fibers and/or gray matter. If lowered coherence values are seen in concussion patients, it is still unknown which of these factors, or if a combination of all of them, produces these results.

Each concussive episode is individualized and may produce different changes in the brain. In turn, one might expect that the respective EEG measures would be different in each concussion patient. While the electrophysiological deficits found for

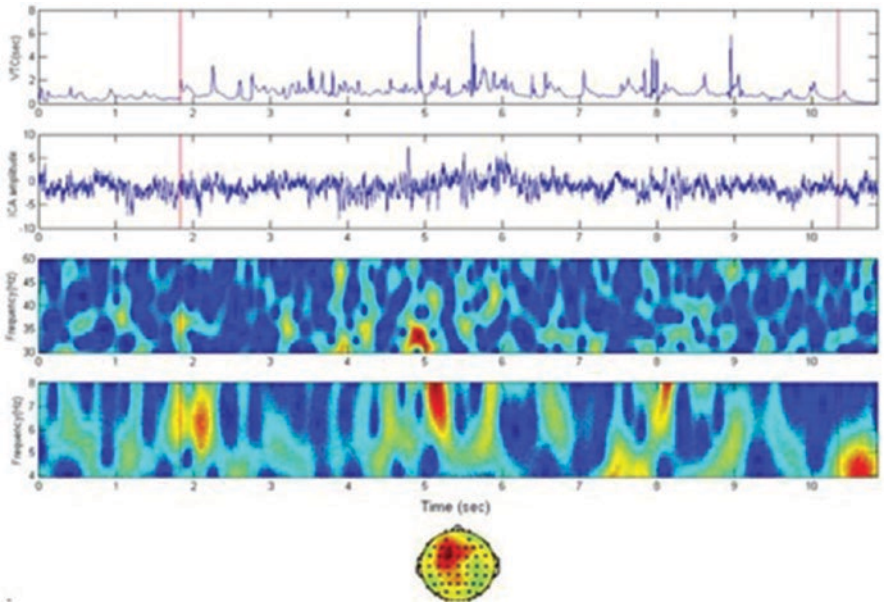

Fig. 4.2 An example of various EEG outputs: (top panel) wave frequency; (middle panel) example of ICA analysis; (bottom two panels) frequency domain color map where warm colors, that is, red, indicate higher activity. (Used with permission from Slobounov et al. [108])

each concussive episode remain unique, several consistent EEG patterns have been identified. According to a review by Arciniegas [23], the most common EEG findings in concussion include: (1) a decrease in mean alpha frequency [30, 33, 52–55], increase in theta activity [29, 31, 56, 57], or increased alpha-theta ratio [32, 33, 52, 55, 58], lessened alpha and beta power between anterior and posterior regions, weakened alpha power (posterior region), and increased coherence between frontal and temporal regions [59–61].

Along with these findings, a review by Nuwer et al. [47] listed other common EEG findings after concussive episodes. These findings concluded that changes in EEG measures resolved along the same timeline as symptoms, with gradual changes mainly occurring over weeks to months. They also found that left temporal slowing may correspond to lingering cognitive symptoms. Importantly, in all the studies evaluated by Nuwer, coherence was not correlated to outcome or diffuse axonal injury. Due to how quickly EEG patterns can change in an mTBI population [23], it is critically important that research involving individuals being tested after a concussive injury are evaluated at as similar time points as possible.

Evidence provided by Thornton [62] and Thatcher [63] indicates that the EEG patterns seen in a concussed athlete do not change over time and, therefore, should be present at the initial time of injury. While this is useful in describing EEG as a possible tool in diagnosing and evaluating concussed individuals, it also indicates that concussive episodes, even "mild" or "typical" episodes, cause long-lasting

alterations in brain electrophysiology. Work by Barr et al. [64] showed that despite improvement or normal levels of cognitive functioning, brain patterns remain altered in mTBI patients. This further suggests that the brain may not completely heal from concussive episodes; instead, the individual learns to compensate for the deficit in order to achieve normal performance. The idea of compensation instead of recovery has been examined in a study by Thornton [65] and discussed in a book chapter [51].

A study by Theriault and colleagues revealed the cumulative effects of concussions in athletes by EEG abnormalities on visual working memory. They found that athletes with a history of three or more concussions exhibited significantly reduced sustained posterior contralateral negativity (SPCN) amplitude, relative to both athletes without concussion and those with only one or two prior concussions [66]. Sustained posterior contralateral activity has been shown to indicate the processing of visual stimulus, specifically in relation to a changing visual environment [67]. Additionally, SPCN amplitude was found to significantly correlate with the number of previous concussions, indicating visual working memory storage is further depleted with successive concussions [66].

Two prominent studies have examined the reproducibility of EEG absolute measures. First, a study by Corsi-Cabera et al. [68] tested nine subjects 11 times over a 1-month period. When looking at absolute amplitude, the median correlation coefficient over the 11 sessions was 0.94 while alpha and beta bands showed greater variability than any of the other bands. Pollock et al. [69] evaluated test-retest reliability in each bandwidth over a 20-week period on 46 normal controls. Absolute amplitude in theta, alpha, and beta1 had correlation coefficients that exceeded 0.60 while beta2 and delta correlation coefficients were found to be lower, with delta showing the poorest correlation. The authors also found that absolute amplitude has higher correlation coefficients than relative power and is, therefore, recommended for use in future studies. The high levels of correlation found in these studies, combined with the varying intervals between testing sessions (a common feature in concussion testing), imply that absolute amplitude is an appropriate measure for research purposes.

Although related to amplitude, several studies have separately analyzed the reproducibility of power (see Figs. 4.3 and 4.4 for an example of a power map). Salinksy et al. [70] tested absolute and relative power and found correlation coefficients of 0.84. Tests were run between 12 and 16 weeks apart on 25 normal controls. Cannon et al. [50] examined test-retest EEG power reliability by examining 19 normative controls over a 30-day testing period. Each participant was recorded for a 4-minute interval under an eyes open and eyes closed condition. Intraclass correlation coefficients for absolute power were 0.90 for eyes closed data and 0.77 for eyes open data. The results of these studies closely mimic those found when evaluating amplitude, with power having sufficiently high levels of reliability over both short (days) and long (months) testing periods.

Mathematically distinct from amplitude and power, researchers have spent time considering the reproducibility of coherence values. Studies by Harmony et al. [71] and Nikulin and Brismar [72] evaluated the reproducibility of coherence during rest

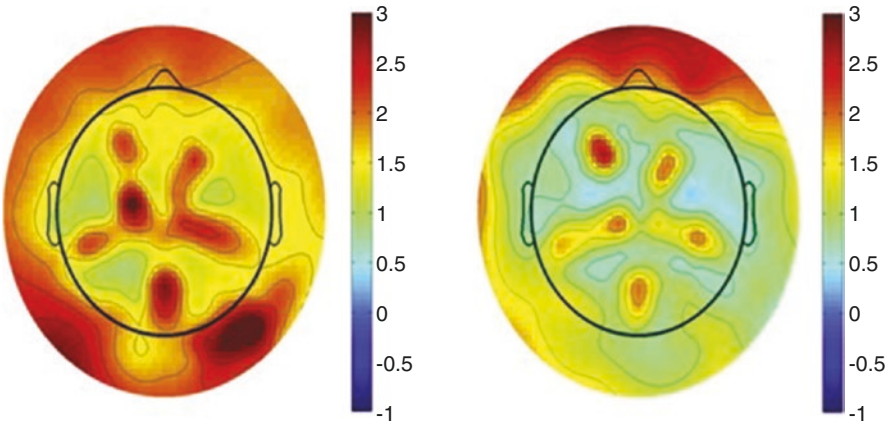

Fig. 4.3 Power images for the beta frequency band during the eyes closed seated baseline EEG condition for the control (left) and concussed (right) groups. (Used with permission from Teel et al. [109])

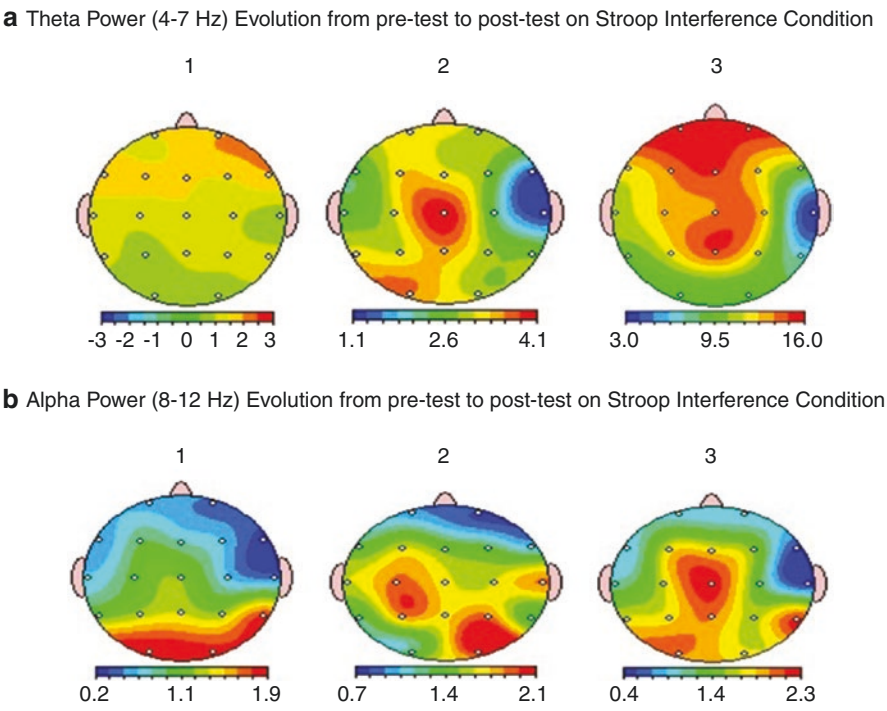

Fig. 4.4 An example EEG power map. (**a**) shows theta power map and (**b**) shows alpha power map. (Used with permission from Barwick et al. [110])

and cognitive tasks in individuals. Both studies found good correlations within a given task or under resting-state conditions, but Harmony et al. reported much lower correlation values between sessions, even within the same subject during the same condition.

While these early tests show low levels of reproducibility, even within testing sessions, more recent research has provided vastly different results. The Cannon et al. [50] study mentioned earlier also examined coherence over a 30-day testing period. For eyes closed coherence measures, intraclass correlation coefficients (ICCs) for delta, theta, alpha, and beta bandwidths were all greater than 0.90. For the eyes open condition, coherence in all bandwidths had ICCs above 0.85. This indicates "good" to "very good" reproducibility for all EEG variables examined and deems coherence as a reliable enough measure to use in both a research and clinical setting.

In all of the studies presented, roughly half of the variance seen in all EEG variables was reproducible within the given subject. These measures have all been determined to have a sufficient level of reproducibility to use in future research. However, it should be noted that these results do not necessarily indicate that EEG can currently be considered a reliable diagnostic tool and differentiate between concussed and healthy individuals.

Although there are many benefits to using EEGs in concussion research and a wealth of knowledge has been gained, the use of EEGs in this type of research is not without its criticisms and limitations. Nuwer et al. [47] questioned the use of EEG in concussion research, citing the lack of clear EEG features that are specifically unique to mTBI patients, especially late after injury. While there is merit to a lack of unique abnormalities, several studies [73, 74] have found deficits in concussed participants up to 3 years post injury. Additionally, another study found that relative to former athletes with no history of sports concussion, former athletes who sustained their last sports concussion more than 30 years ago reveal cognitive and motor system alterations that closely resemble those found in previous electrophysiological studies on asymptomatic concussed athletes tested at 3 years post concussion [75]. This implies that there may be lifetime effects of sports-related concussion that are measurable using EEG.

Most EEG and concussion research focuses on lower frequency bands, but several studies by Thornton [51, 62, 65, 74] demonstrated that extending the frequency to include gamma bands provides important additional information, particularly between correlating EEG variables and the participant's cognitive deficits. Additionally, most research and consequently normative databases provide information solely about eyes closed conditions. This severely limits the type of cognitive testing that can be simultaneously completed, restricting neuropsychological testing to auditory-based tests. While auditory-based cognitive research has provided valuable EEG patterns, such as those outlined in Thorton and Carmody [51], several cognitive domains cannot be adequately assessed via auditory tasks. As mentioned above, the link between EEG patterns and cognitive domains, such as visual memory and attention, remains weakly established, with further research ongoing.

Additionally, further consideration when validating EEG as a tool for "on field" concussion assessment should be given to the standardization of EEG baseline testing protocol, particularly with respect to the effects of exercise on baseline levels. Portable EEG devices can in theory be used "on field" as an objective measure of change in cortical activity directly after a head injury [76], but exercise, in addition to changes in cognitive function measures, also increase cortical activity measured by EEG. Although a limited amount of evidence shows that EEG spectrum differs before and after acute bouts of exercise, it has been identified in connection with changes in alpha and beta range [77–79].

In summary, reviews by Arciniegas [23] and Nuwer et al. [47] have cited numerous studies that have proven EEG is a useful tool for identifying and managing concussive injuries. While EEGs are one of the least expensive and easiest to use neuroimaging tools, the expertise needed to administer and evaluate EEG results, as well as the lack of research between EEG and concussion, has kept EEG evaluations from becoming part of the current clinical gold standard. The most comprehensive EEG study using a database of 608 mTBI subjects that were followed up to 8 years post injury revealed a number of findings. These include the following: (a) increased coherence in frontal-temporal regions; (b) decreased power differences between anterior and posterior cortical regions; and (c) reduced alpha power in the posterior cortical region, which was attributed to mechanical head injury [61]. A study by Thornton [71] has shown a similar data trend in addition to demonstrating the attenuation of EEG within the high-frequency gamma cluster (32–64 Hz) in mTBI patients. Overall, resting EEG has demonstrated alterations in power dynamics across electrical spectra [23], increased short-distance coherences [80], and decreases in connectivity across long-distance connections [80]. These consistent findings in resting EEG and mTBI research point to the sensitivity and validity of using EEG in the assessment and management of concussion. Resting-state electroencephalography (rs-EEG) may also be the most affordable, accessible, and sensitive method of assessing severity of brain injury and rate of recovery after a concussion [81]. However, it should be noted that one controversial report concluded that no clear EEG features are unique to mTBI, especially late after injury [47].

Current Work from Our Lab

In our previous work, a significant reduction of the cortical potentials amplitude and concomitant alteration of gamma activity (40 Hz) was observed in MTBI subjects performing force production tasks 3 years post injury [73]. More recently, we showed a significant reduction of EEG power within theta and delta frequency bands during standing postures in subjects with single and multiple concussions up to 3 years post injury [74] and reduced amplitude of cortical potentials (MRCP) up to 30 days post injury [82].

We applied advanced *EEG-wavelet entropy* measures to detect brain functional deficits in concussion subjects. These EEG measures were significantly reduced

after the first and more significantly after the second concussion far beyond 7 days post injury. Most importantly, the rate of recovery of EEG entropy measures was significantly slower after second concussion compared to the first concussion [26]. Recently, we reported the alteration of EEG signals in concussion subjects detected by a novel measure of nonstationarity, named Shannon entropy of the peak frequency shifting [83]. These findings are complementary to our previously published concussion report indicating the presence of residual deficits in concussion subjects detected by multi-channel EEG signals classifier using support vector machine [84]. We also conducted an EEG resting-state study and reported the alteration of cortical functional connectivity in concussion subjects revealed by graph theory, ICA, and LORETA analyses. Overall, a clear departure from a *small world-like network* was observed in concussion subjects [80].

The presence of a residual disturbance of the neuronal network is involved in the execution of postural movement in concussion subjects incorporating EEG and VR-induced measures [85]. As shown in Fig. 4.5, there was a significant increase of *theta* power during the progression of a balance task. Specifically, this *theta* increase was obvious initially at central areas with further diffusion to frontal electrode sites bilaterally. Interestingly, no significant *theta* power was present in concussed subjects at either phase of postural task progression. Most recently, we reported that 85% of concussion subjects who showed significant alteration of alpha power in acute phase of injury did not return to pre-injury status up to 12 months [26].

Another recent EEG-related study in our lab examined the practical use of the supplement Enzogenol, an extract of the *Pinus radiata* tree with antioxidant, anti-inflammatory, and possible neuro-protective properties, as a combatant of the chronic effects of sports concussion (6 months–3 years). Post-concussion symptom scale, virtual reality, and neurocognitive testing were administered to subjects with history of concussion both prior to and after being provided either Enzogenol or a placebo daily for 3 months. EEG recording was administered during testing, examining differences in brain activity within groups.

EEG results showed mental fatigue during testing in subjects through alpha, beta, and theta frequencies, which reflect arousal levels of the brain. Increases in mental fatigue, a noted symptom of the acute and chronic phase of concussion, was further induced by the strenuousness of the virtual reality and neuropsychological

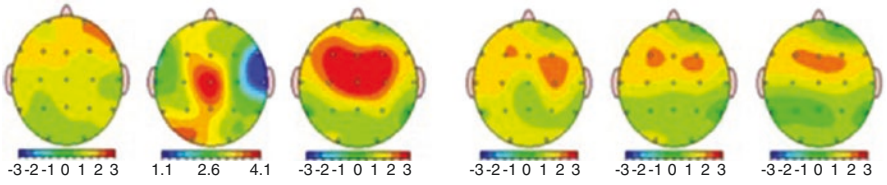

Fig. 4.5 Example 2D plots grand-average of theta power as the postural task progressed at 10, 15, and 27 seconds in before and after mTBI time points. EEG data included during the VR "roll" condition. Note a significant enhancement of theta power over frontal-central electrode sites as trial progressed during baseline, but not in concussed subjects. (Used with permission from: Slobounov et al. [111])

testing. Most notably, the EEG results during testing showed modulation and attenuation of FMT power, and parietal theta. The increase in FMT, more evident in the Enzogenol group, implied increases in brain resource allocation during focus and task completion, and with reference to previous findings could indicate that untreated subjects are less able to allocate brain resources during prolonged neuropsychological testing. With regard to the shift of theta bands to posterior regions; this has been connected to mental fatigue [86] and decreased efficiency of cognitive tasks [87]. The Enzogenol group did show less posterior theta which is certainly a promising indication of potential supplemental benefits on neurocognitive function in the chronic phase of concussion, but the most glaring conclusion of this study with regard to EEG, is its usefulness and sensitivity in measuring small changes in brain activity in concussion subjects [88].

Compensatory Approach During Concussion Assessment Batteries

Several studies have found electrophysiological deficits in asymptomatic concussed participants [26, 89, 90]. In these studies, concussed participants displayed normal levels of cognitive functioning, yet continue to show physiological dysfunction on EEG measures. The authors cite an unknown compensatory mechanism as an explanation for the findings. As part of our research, we sought to investigate this compensatory mechanism in more detail. In order to assess this, we chose to record EEG signals while participants were completing clinical concussion assessment measures. Subjects took the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) neuropsychological assessment as well as completed VR balance and spatial navigation modules. They also participated in EEG resting-state evaluations in order to highlight the differences between clinical cognitive and balance performance and neuroelectric measures.

In a sample of 13 normal volunteers and 7 concussed participants, no differences were found between groups on ImPACT and VR composite outcome scores. When looking at outcomes, the only group difference was worse stationary balance in the concussed group. However, several significant group differences were found when looking at the EEG variables. For EEG resting-state and ImPACT conditions, the concussed group had significantly lower power in the theta and beta bandwidths. Additionally, the concussed group had significantly lower alpha power during the ImPACT conditions and significantly lower delta power in the VR conditions. Conversely, the concussed group displayed significantly higher levels of coherence during EEG resting-state and ImPACT evaluations, but lower levels of coherence during VR balance and spatial navigation testing.

Overall, for EEG resting state and ImPACT, results indicated that concussed participants could not establish enough local effort (seen via lower power), so they recruited additional long-distance network connections (seen via the increased coherence). By recruiting additional networks, the concussed participants were able to successfully compensate for their neuroelectric deficits and produce normal

clinical results. This research indicates a disconnect between cognitive and neuroelectric resolution. Future research projects aim at determining whether cognitive functions resolve before physiological function or if current clinical concussion assessments are not sensitive enough to detect the residual effects of concussion.

"Return to Play" and EEG Concussion Research

One specific aspect of concussion injury that is still lacking in research is the area of return to work or play. In 2004, the World Health Organization (WHO) task force found no studies that demonstrate acceptable evidence to suggest when a person or athlete may safely return to work or the athletic field. A decade later, the International Collaboration on Mild Traumatic Brain Injury Prognosis (ICoMP) formed to update the original WHO Task Force publications, stating that although return to play guidelines are widely used, there are no studies of acceptable standard that assess their impact on fitness to play or prevention of additional injury [91]. They also stated that there is some evidence suggesting that the majority of athletes were assessed for return to play within the same game or within a few days post injury [91]. Despite the growing concern over return to play after sport concussion, research quality continues to be poor, establishing little to no methodological advances since the WHO Task Force review in 2004.

Additionally, return to play decision-making tools, like the Zurich Consensus guidelines, are based on expert opinion and clinical judgment, rather than scientific evidence [16]. As it has demonstrated its ability to identify physiological differences in the recovery from TBI, EEG should be considered as a feasible diagnostic tool for recommendations given to athletes returning to activity and sport.

EEG has been used to study concussion or mTBI throughout many phases of recovery from acute, sub-acute to chronic or long term. One clinical-stage EEG has not been used is within the "Return to Play" stepwise progression back into athletic participation. The "Return to Play" protocol is the internationally accepted method for the safe return to activity of an athlete recovering from concussion [16]. This formalized "Return to Play" protocol has been in place since the original 2001 Concussion in Sport Group (CISG) Consensus Statement and with continued updates is widely accepted as the "Gold Standard" for returning athletes to competition but without evidence to support either the progression sequence or the time spent in each stage [18].

Under this procedure, "Return to Play" after a concussion follows a stepwise progression of increasing efforts and risk as outlined in Table 4.2. An initial period of 24–48 hours of both relative physical rest and cognitive rest is recommended before beginning the RTS progression [1]. Once asymptomatic and cleared by a supervising physician, the athlete may progress to a light aerobic exercise such as walking or stationary cycling. This light aerobic challenge is limited by restricting an athlete to <70% of their calculated maximum heart rate.

With this activity progression, each stage of increasing efforts should be separated by 24 hours with health professionals monitoring the athlete and their

Table 4.2 Graduated "return to play" protocol

Stage/aim	Activity	Objective
1. Symptom-limited activity	Daily activities that do not provoke symptoms	Gradual reintroduction of work/school activities
2. Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training	Increase heart rate
3. Sports-specific exercise	Running or skating drills. No head impact activities	Add movement
4. Non-contact training drills	Harder training drills, for example, passing drills. May start progressive resistance training	Exercise, coordination, and increased thinking
5. Full contact practice	Following medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

symptom status. If any of the athlete's post-concussion symptoms should manifest before, during, or after a stage within the protocol, the athlete is instructed to drop back to the previous asymptomatic stage and try to progress again after a further 24-hour period of rest.

In our lab, we investigated the use of EEG as a supplementary tool in the clinical assessment of concussion during the "Return to Play" phase of recovery. Specifically, we looked at the differential effect of exercise (modified YMCA Bike protocol) on the quantitative EEG measures of spectral absolute power and coherence in normal volunteers vs. concussion subjects. There were several major findings from this study. Of particular clinical significance was that all concussed subjects had met the clinical criteria for asymptomatic at rest [92] for a period of at least 24 hours prior to exercise testing. These athletes had also been cleared by a sports medicine physician for the initiation of the "Return to Play" protocol as outlined above.

When completing the modified YMCA bike protocol, there were no group differences in dynamic measures of heart rate at any time and both groups demonstrated no differences in symptom presentation after completion. However, some differences were evident when reviewing the physiological data from the EEG evaluation. Both groups demonstrated no regional power differences at rest and at 24-hour follow-up. In addition, both groups demonstrated no significant differences in mean or regional coherence values at rest or at 24-hour follow-up. Historically within the literature, abnormal attenuation of alpha power and an increase in focal slow wave distribution is short lasting and typically returns to normal within the sub-acute phase of experimental concussion [93–95]. Further, in a recent quantitative EEG examination by McCrea et al. no resting-state differences in athletes recovering from concussion at days 8 and 45 post injury were found when compared to age-matched controls [96]. Within the neural imaging research, resting-state fMRI findings of concussion cohorts at rest do not vary significantly from normal volunteers [97]. This is an important finding as researchers look to develop the clinical significance of EEG as a diagnostic tool for concussion. Resting-state EEG measurement remains largely normal as reported throughout the literature.

There were group differences however with the modified YMCA Bike protocol causing an increase in Alpha, Beta, Theta, and Delta absolute power amplitudes across all regions (frontal, central, and posterior). Specifically, exercise significantly increased the power of Theta and Delta frequency ranges. Theta power increases stem from injury and pathophysiologic changes in the cerebral cortex [31]. As is known, concussion results in altered cerebral blood flow [98, 99], decreased energy metabolism [100], release of excitatory amino acids (EAA), and decreased post-synaptic function among other effects already mentioned. In the work by Nagata, they demonstrated that cortical blood flow (CBF) and oxygen (O_2) metabolism correlated negatively with Delta and Theta power [101]. The lack of specificity of this effect linked with a range of pathological conditions suggests that increases of slow waves (Delta/Theta frequencies) represent a typical response to any brain injury, pathology, and disruption of neural homeostasis.

The inclusion of EEG as a physiologic tool proves to have some worth in examining the recovering athlete and may provide clinicians with valuable data when making "Return to Activity" decisions. Furthermore, as demonstrated by this investigation, exercise may be an effective mechanism for uncovering residual abnormalities in recovering athletes.

Brain Lateralization Analysis, Psychological Symptoms, and the Evaluation of Both Using EEG

Brain lateralization has been a popular topic of research for many years and has been used to investigate neural processes in many different species. Specifically, brain lateralization describes the presence of asymmetrical signaling between the left and right hemispheres of the brain. The difference is seen in the power of the specific EEG waves mentioned in the *EEG Frequency Bands* section of this chapter. These differences in power can appear at various anatomical locations within the brain resulting in various outcomes, including differences in behavior, personality, and mood within a species as well as differences in developmental processes between different species [102]. To analyze the symmetrical components of the brain, one of the most commonly used tools is EEG. EEG has the ability to capture the difference in signaling between the two hemispheres in a practical, efficient manner, making it a leading tool in this field of study. Moreover, brain lateralization and EEG methods have been applied to research on many disorders, especially psychological disorders. These studies have shown promising results that have helped provide insight on the neurophysiological basis behind psychological disorders.

Depression is one of the most prevalent mental health disorders, with studies showing it affecting nearly 17.5 million people annually across the United States [103]. With the complex nature of the disease, the diagnostic and treatment processes have varying success depending on the individual. Since the late twentieth century, brain lateralization analysis through EEG has been a popular method for observing the differences between depressed and non-depressed brains. Pioneers of the topic had shown that individuals with depression present with alpha wave

asymmetries in the frontal cortex of the brain [104, 105]. Specifically, studies have shown increased approach behavior in subjects with a relative increase in left frontal activation whereas an individual with a relative increase in right frontal activation demonstrated stronger inhibitory behavior [104]. Furthermore, EEG has even shown asymmetries in subjects who do not suffer from depression but have a family history of the disorder. A study by Bruder et al. investigated EEG differences between children with a family history of depression and children with no family history. Results supported noticeable EEG asymmetry present in the parietal brain region of the children who have at least one grandparent and one parent suffering from depression. More specifically, these individuals showed enhanced signaling in the right hemisphere relative to the left, resulting in asymmetrical readings [106]. There is still developing research for using brain lateralization on EEG as a diagnostic tool for depression; however, the progress made using this method to investigate psychological disorders is undeniable.

Depression is not only one of the most common psychological disorders throughout the world; it is also the most common psychological symptoms following a concussion or mTBI. The onset of depression following the injury has been shown to affect recovery time, performance, and overall self-efficacy, making it a popular topic of interest [107]. The greatest challenge when assessing an athlete for psychological symptoms following a concussion is the fact that these symptoms are invisible and often misconstrued by the athlete. However, EEG has potential to be a vital tool in assessing these symptoms objectively, by searching for brain asymmetries. Currently, our lab is conducting a study to explore the relationship between depression and concussion. Specifically, the study aims to investigate the physiological and functional differences between college-aged athletes who have depression, have a history of concussed, or have a combination of both. The physiological differences between groups will be measured using EEG while functional and cognitive performance will be assessed. The study hopes to increase knowledge about the complications following a concussion, especially in the realm of psychological symptoms, as well as show how EEG can be used in future practice as part of the complete assessment following a concussive injury.

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