# An Evaluation of the NuroChek System for Concussion Assessment and Management

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# Abstract

Current methods of concussion assessment are subjective and vulnerable to error, and a missed concussion diagnosis could increase an athlete's risk of further injury. An objective method of concussion assessment could provide valuable physiological data about injury severity and duration. The NuroChek system uses a flashing light stimulus to evoke electrophysiological activity, which is measured from occipital electrode sites and used to calculate a signal-to-noise ratio (SNR) and determine the magnitude of activity at the target location. Reductions in this activity are proposed to be associated with dysfunction or damage after concussion; in a previous study, the SNR was shown to decrease after concussion, and then return to baseline strength upon recovery.

To examine the utility of the NuroChek system and SNR output in concussion assessment and management, 157 participants were assessed with the NuroChek system as rugby athletes (n = 121), combat athletes (n = 19), or non-athlete controls (n = 17). All athletes were assessed at multiple time points, while the non-athlete control group was only assessed at one time point. All participants completed two trials of the NuroChek headset and at least one cognitive measure.

The first study (Chapter 4) examines the acute effects of concussion on the SNR, as well as any SNR changes after injury. Rugby athletes who sustained concussions (n = 21) were tested at multiple time points after their injuries with the NuroChek system and either the King-Devick (K-D) or the Sport Concussion Assessment Tool (SCAT-5). The post-injury and baseline SNR were compared to identify any changes within 3 days of concussion, as well as changes during the follow-up time points that might correspond with concussion recovery (up to 20 days post-injury and mid-season or end-of-season if available). No statistically significant changes were seen after concussion, $W = 11.000$, $p = 0.612$, $d = -0.099$, $n = 8$. When compared to the non-concussed male rugby athletes, the concussed athletes had significantly lower SNRs than the athletes who sustained regular repetitive impacts by the end-of-season, $H(3) = 10.160$, $p = 0.017$, $d = 0.135$, $n = 76$.

The second study (Chapter 5) examines the different effects that concussion history, age, and sex have on the SNR and its trajectory over time in those experiencing repetitive impacts. While the SNR was not affected by concussion history or age, there was a main effect for sex: male athletes demonstrated significantly higher average SNRs

than female athletes at all three time points.[1] Additionally, the SNRs from female participants demonstrated a significantly greater proportion of a harmonic artefact (51.8%, compared to 15.1% of data from male participants) that decreased the quality of the female data. Sex and repetitive impacts were examined for any interaction, but the sample sizes were too small in some subgroups for statistical analysis. A main effect of repetitive impacts on the SNR was also seen in rugby[2] and combat athletes.[3] This could indicate that repetitive impacts lead to higher SNR in athletes over time.

Overall, the SNR in this study was not sensitive to changes after concussion or during recovery. No evidence was found to support NuroChek's use in the assessment or management of concussion in rugby athletes. Additionally, the potential effect of repetitive impacts on the SNR confounds the relationship between the SNR and concussion. Future development of electrophysiological assessment methods for concussion should consider the effects of repetitive impacts and sex.

[1] Baseline: U = 429.500, p < .001, d = -.519, z = -5.189, N = 100
Mid-season: U = 120.500, p < .001, d = -.507, z = -3.829, N = 57
End-of-season: U = 573.000, p = .007, d = -.287, z = -2.708, N = 89
[2] End-of-season: H(3) = 10.160, p = 0.017, d = 0.135, n = 76
[3] Repeated-measures 2×2 ANOVA: F(1, 18) = 5.021, p = .039, V = .228, N = 19

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# Terminology

## 0.1 Abbreviations

ACC: Accident Compensation Corporation

Bal: balance domain

BESS: balance error scoring system

BJJ: Brazilian Jiu Jitsu

BL: baseline

BNA: brain network activation

BOLD: blood-oxygen-level-dependent

Conc: concussion

CH or conc hist: concussion history

Concen: concentration domain

CSF: cerebrospinal fluid

CT: computed tomography

DMN: Default Mode Network

DS: digit span

DTI: diffuse tensor imaging

EB-COP: Evidence-Based Clinical Outcome assessment Platform

EEG: electroencephalogram

EOS: end-of-season

ERN: error-related negativity component

ERP: event-related potential

Exper: experience using the headset

FDG-PET: fluorodeoxyglucose positron emission tomography

fMRI: functional magnetic resonance imaging

g: gravity unit

GCS: Glasgow Coma Scale

GH: growth hormone

Hz: hertz

IGF-I: insulin-like growth factor-I

IQR: interquartile range

ImPACT: Immediate Post-concussion Assessment and Cognitive Testing

K-D: King-Devick

ML: machine learning

MMN: mismatch negativity component

MRI: magnetic resonance imaging

MS: mid-season

m-BESS: modified balance error scoring system

mTBI: mild traumatic brain injury

Neuro: neurological domain

NP: neuropsychological

NZ: New Zealand

Orient: orientation domain

PI: post-injury

Post: after the sparring session

Pre: before the sparring session

RHI: repetitive head injury

RTP: return to play

SCAT-5: Sport Concussion Assessment Tool, version 5

Sever: severity of symptoms

SNR: signal-to-noise ratio

SRC: sport-related concussion

SSVEP: steady-state visual evoked potential

Symx: symptoms

TBI: traumatic brain injury

TMTb: Trail-Making Test, version B

VEP: visual evoked potential

VR: virtual reality

## 0.2 Clarification of similar terminology

**Concussion** is most often used to describe a mild traumatic brain injury that results in loss of consciousness for less than 30 minutes (if at all) and a score of 13-15 on the Glasgow Coma Scale (GCS), which measures eye-opening, verbal, and motor responses. Studies on the general population often use the term "mild traumatic brain injury" (mTBI), which can include brain injuries more severe than concussion, often sustained by severe accidents or car crashes. While this literature overlaps, athlete populations can be tested at baseline, while survivors of accidents usually cannot.

**Repetitive impacts:** Commonly referred to in literature as repeated head injury (RHI) or subconcussion, the present study removes the specification of head impacts to

acknowledge that impacts to the body can still produce forces that can travel up to and cause movement in the brain.

**Sex** is used instead of gender because this study discusses physiological attributes, (not culturally assigned characteristics), and while the present study discusses sex in binary groups, it does not make assumptions about the gender identities of participants. Sex was instead inferred by the team with which the athletes trained.

**Electrophysiology** is a method of neurophysiology that specifically measures electrical behaviour in the brain. Other neurophysiological methods discussed include fMRI, DTI, and CT scans.

**Magnitude** is a measure of distance or quantity (like a ratio), while amplitude refers to a relative change from the central position. Therefore, magnitude is the proper term to describe the SNR, though amplitude is often discussed in relation to the field-adjacent ERP studies, which examine differences in the peaks and valleys of EEG patterns.

**Cognitive/neurocognitive** refers to tests that measure changes to domains affected by concussion, including attention, memory, information processing, and executive function, while neuropsychological refers to affective symptoms (i.e., depression, anxiety, or mood changes) in addition to these cognitive domains.

## 0.3 Note on data presentation

Because of the limited significance of many tests, much of the data is represented in tables, which are explained in the text. Note that changes or differences are only discussed as "significant" if they are statistically significant at $p < .05$.

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# Chapter 1

# Introduction and Justification for Research

Accurate identification of concussion can prevent subsequent damage, allow for earlier access to treatment, and lead to better recovery outcomes (Barnhart et al., 2021; Eagle, Collins, et al., 2020; Forrest et al., 2018; Kontos et al., 2020). Concussion research has made great strides in the last 20 years, and studies have focused on improving and standardising methods of identification, treatment, and rehabilitation since 2010 (Eagle et al., 2021; McCrea et al., 2015). Yet despite the growing body of knowledge on the dangers of concussion, second impacts, and the importance of complete recovery, there remains no widely viable option for rapid and objective screenings of concussion in sport (Christoforou et al., 2020; McCrea et al., 2015; McCrory et al., 2017).

Concussion is a relatively common injury that can have serious and long-lasting consequences. A concussion is defined as an impact-induced alteration in brain function or consciousness that causes cognitive, behavioural, or physical changes (McCrory et al., 2017). Immediate symptoms include headache, confusion, dizziness, nausea, visual or memory disturbance, and neck pain; common sub-acute symptoms include light or noise sensitivity, problems sleeping, fatigue, emotional changes, and brain fog (Gardner, Iverson, Levi, et al., 2014; McCrory et al., 2017).

When an impact occurs (either directly to the head or indirectly), it causes a near-instant transfer of energy (Sicard et al., 2021), during which linear and rotational forces travel rapidly and collide through the brain (Beckwith et al., 2018). These forces damage the long, thin, and most vulnerable structure of the neuron called the axon (Dollé et al., 2018). Subsequent axonal breakdown triggers a "concussion cascade," during which the inflammatory response to the damage from the primary impact disrupts axonal transport and communication between regions (Giza & Hovda, 2001; Grady et al., 2012; Zetterberg et al., 2016). Such damage can take days to develop, which makes the symptom-related timeline unpredictable.

Once thought to be a transient injury that recovered within a week and with no long-term consequences (Aubry et al., 2002; Broglio, Guskiewicz, et al., 2017; Guskiewicz et al., 2003; McCrea et al., 2003; McCrea et al., 2002), concussion is now regarded as a serious neurological injury with the potential for lingering consequences over time. There is no single test or indicator of recovery, as different symptoms resolve at different times (Kamins et al., 2017; McCrory et al., 2017). Although someone may demonstrate

complete recovery according to the cognitive measures used, evidence from functional magnetic resonance imaging (fMRI) and diffuse tensor imaging (DTI) shows that concussion damage may regularly persist beyond one or two months, and potentially up to a year post-injury (Churchill et al., 2020a, 2020b; Dettwiler et al., 2014; R. King et al., 2019; Lancaster et al., 2018; Myer et al., 2019; Smits et al., 2011; Tan et al., 2023; Wong, 2021).

## 1.1 Incidence

New Zealand employs a national healthcare scheme called the Accident Compensation Corporation (ACC), which covers all accidental brain injuries (including concussion) and provides data from a centralised record on the prevalence and incidence of these injuries. The two main causes of mild traumatic brain injury (mTBI) in New Zealand are sport-related concussions (SRC) and accidents, including falls, work injuries, and car crashes (D. King et al., 2019; Starkey et al., 2022). ACC data from 2020–2021 (Accident Compensation Corporation, 2022) shows that 33,619 people sought treatment for concussion, and that 10,628 (31.6%) of these claims were for SRC. Over both years, this amounts to an average of 46 concussion claims each day, with 14.5 of these related to sport. Rugby accounts for the vast majority of SRCs in New Zealand, followed by soccer, snowboarding, cycling, and hockey. Of the SRCs, 3,891 were from rugby, for an average of 5.3 claims per day. Of the concussion claims from 2015–2021, only 0.4% required *"permanent high-level assistance"* (Accident Compensation Corporation, 2022).

These data represent the minimum possible annual number of concussions sustained because only a small percentage of athletes seek care beyond that provided by the team medical staff; thus, many are not reported to the ACC (Quarrie et al., 2020). At least 19% of SRCs may not be reported to anyone (Theadom et al., 2014) because these athletes may not realise how serious their injury is, they do not want to let the team down, or they may not want to miss playing time (LaRoche et al., 2016; McCrea et al., 2004; Meier et al., 2015; Treacy & Heflin, 2021). When asked, between 28–64% of athletes said they have not (or would not) reported a concussion and continued to play through symptoms (LaRoche et al., 2016; Leahy et al., 2020; Meehan et al., 2013); this highlights the lack of perceived severity of concussive injury in these athletes. An athlete may also continue to play if symptom onset is delayed (Barnhart et al., 2021); such undiagnosed concussions receive delayed or no treatment, which can result in more emotional symptoms (Forrest et al., 2018), a longer recovery timeline (Barnhart et al., 2021; Kontos et al., 2020), and increased sensitivity to lesser impacts (Caccese et al., 2018). If an athlete

continues to play through symptoms, they are also at risk of sustaining a second impact or concussion during a period of neural vulnerability, which can result in more complicated recovery, permanent brain damage, or even death (Bey & Ostick, 2009; Giza & DiFiori, 2011; Harmon et al., 2013; Wetjen et al., 2010).

While most people recover within a 3-month window, others struggle with persistent symptoms. At three months post-injury, Ponsford and colleagues (2000) found that 24% of adults in their study still experienced persistent mTBI symptoms. At six months post-injury, a review by Voormolen and colleagues (2018) found that 11–39% of patients still presented with symptoms, depending on when and how they were evaluated. Some studies of non-athletic populations found that only 20–40% of individuals with mTBIs consider themselves fully recovered at a year post-injury (Hours et al., 2013; Nhac-Vu et al., 2014; Theadom et al., 2016), while a systematic review puts this range between 47–88% (Brady et al., 2022). Brady and colleagues (2022) report that the average recovery time for sports-related concussion was between 7–14 days, but they note that these studies often did not include adequate follow-up time points. There is also some evidence of symptoms and cognitive deficits experienced up to five years post-mTBI (Möller et al., 2017; Theadom et al., 2018).

## 1.2 Risk factors

Two risk factors commonly explored in concussion research are a previous history of concussion or head impacts and an individual's sex. A past concussion is a risk factor for sustaining another concussion (Castellanos et al., 2021; Greco et al., 2019; Guskiewicz et al., 2003; Harmon et al., 2013; Nordström et al., 2014), as is a current concussion (Bey & Ostick, 2009; Giza & DiFiori, 2011; Kutcher & Eckner, 2010; Wetjen et al., 2010). Moreover, a higher number of previous concussions increases the risk of sustaining another concussion in the future (Guskiewicz et al., 2003), as well as increasing the risk of a longer or more complicated recovery (Ponsford et al., 2000).

Sustaining a high number of repetitive impacts in a short period is also a risk factor for sustaining a concussion (Beckwith et al., 2013; Stemper et al., 2019). Repetitive impact-induced injury occurs over time when contact athletes experience repetitive collisions that do not break the threshold for a diagnosable concussion, yet microscopic changes still occur. Since an athlete whose concussive injury is preceded by multiple impacts may have a delayed onset of symptoms when compared to a concussion sustained by one impact, these athletes are at unique risk to sustain further impacts and injury if their injuries are less observable and they are not removed from play (Beckwith et al.,

2013). Kutcher and Eckner (2010) describe athletes who sustained two impacts during a game, in which a first impact only produced mild symptoms, but a second smaller impact resulted in observable symptoms. Mummareddy and colleagues (2019) describe an extreme case in which a soccer player received two impacts and sustained an epidural haemorrhage. Thus, prevention of further impacts is essential to the concussion healing process.

Sex can be a risk factor for sustaining a concussion, symptoms experienced, and duration of recovery. Men are more vulnerable to concussions/TBIs and experience more severe complications overall (Bazarian et al., 2003; Bruns Jr & Hauser, 2003; Elkbuli et al., 2020; Lariviere et al., 2019; Späni et al., 2018); however, there is evidence that in sports that both sexes play, concussion affects female athletes more severely (Broshek et al., 2005; Covassin et al., 2012; Covassin et al., 2018; Harmon et al., 2013) and in greater proportion (Cheng et al., 2019; Harmon et al., 2013; Kutcher & Eckner, 2010; Merritt et al., 2019). This difference may be explained by sampling factors, since research that reports that male athletes sustained more concussions overall than female athletes (Gardner, Iverson, Williams, et al., 2014; Pieter & Zemper, 1998; Ponsford et al., 2000; Theadom et al., 2020) may come from specific sport populations.

Sex may also interact with other factors to complicate the relationship with concussion and recovery (Clair et al., 2020; Covassin et al., 2012; Starkey et al., 2022); for instance, a female athlete experiencing her first concussion may have a more severe outcome than a male athlete during his first concussion, but multi-concussed male athletes may have a worse outcome than multi-concussed female athletes (Covassin et al., 2018). These differences could also be due to gender differences in sport culture (Henne, 2020; Hunt et al., 2019), hormonal changes (La Fountaine et al., 2019), neck anatomy (Tierney et al., 2005), or timely access to care (Kontos et al., 2020; Mikolic et al., 2020). Women are also more likely to report more symptoms (D. A. Brown et al., 2015; Kieffer et al., 2021). Additionally, women show a higher risk of a prolonged recovery in a non-athlete population (Booker et al., 2019a; N. S. King, 2014; Lariviere et al., 2019; Mikolic et al., 2020), though the duration of this risk is unclear (Clair et al., 2020). It is difficult to draw general conclusions, as 90% of athletes in New Zealand are male (Quarrie et al., 2020), and most TBI studies focus on male populations, even in animal research (Späni et al., 2018).

Beyond concussion history and sex, several other characteristics can put an individual at increased risk for concussion. Many age groups are vulnerable to concussion/mTBI in different ways; mTBI risk from falls or accidents is high in children

and older adults (Booker et al., 2019a; Bruns Jr & Hauser, 2003; Kutcher & Eckner, 2010), while sport-specific concussion risk is high in youth athletes and young adults (Caccese et al., 2021; Harmon et al., 2013). Other risk factors include genetics (Antrobus et al., 2021; Finnoff et al., 2011), mood or learning disorders (Booker et al., 2019a; Lariviere et al., 2019; Ponsford et al., 2000), and history of other neurological conditions, including migraines (Kutcher & Eckner, 2010). A psychiatric history and alcohol intoxication or assault at the time of injury were also associated with worse outcomes at one year post-mTBI (Booker et al., 2019b).

## 1.3 Assessment methods

Concussion is a type of mTBI, and while these terms are often used interchangeably, they describe slightly different injuries. Concussion typically refers to a transient and uncomplicated injury with momentary or no loss of consciousness (Harmon et al., 2013; McCrory et al., 2017), while mTBI refers to a slightly more severe injury, often with less than 30 minutes of loss of consciousness or up to 24 hours of post-traumatic amnesia, and may include an injury visible on standard imaging (Wortzel & Arciniegas, 2014). While loss of consciousness and post-traumatic amnesia can be severe consequences of concussion, they are not necessary for a diagnosis. The Glasgow Coma Scale (GCS) is a commonly used measure of alertness (from 3–15); a score between 13–15 on the GCS indicates a likely concussion or mTBI (Wortzel & Arciniegas, 2014). Since concussion is not associated with hematomas, lesions, or other macroscopic structural damage to brain tissue or blood vessels, any abnormalities seen on standard imaging can be used to rule out a diagnosis of concussion, but not of mTBI (Bigler, 2018; G. Davis et al., 2009; Grady et al., 2012; Ledwidge, 2018; McCrory et al., 2017; Wortzel & Arciniegas, 2014).

### 1.3.1 Sideline and acute diagnosis

The gold standard of concussion diagnosis in sport is a decision by the team physiotherapist or other medical staff, based on a post-injury assessment with the athlete after an observed impact or a reported injury. Primarily, injuries are evaluated by self-reported symptoms and observed behavioural impairments in consciousness, balance/gait, or eye movements (Broglio, Guskiewicz, et al., 2017; Daly et al., 2022; R. Smith et al., 2019). Common acute symptoms of concussion are headache (including pressure or migraine), neck pain, fatigue, feelings of disorientation, anxiety or depression, and visual disturbance (Anderson et al., 2022; Daly et al., 2022; Merritt et al., 2015; Zeldovich et al., 2020). The health professional may also perform one or several brief cognitive tests to determine whether the athlete can return to play or must undergo further concussion

evaluation protocols. An athlete with a suspected concussion should not be allowed to return the same day at any level of play, according to International Rugby Board (Gardner, Iverson, Williams, et al., 2014). Baseline testing and the "sports as a laboratory assessment model" have become the standard paradigms for concussion research (Barth et al., 1989; Broglio, Guskiewicz, et al., 2017; Guty & Arnett, 2018; McCrea et al., 2015), so most athletes are given cognitive tests before the season begins, and these are compared with post-injury scores to determine the degree of impairment and estimate recovery from a return-to-baseline.

According to the most recent consensus statement on concussion in sport (McCrory et al., 2017), neuropsychological (or neurocognitive) assessment is the "cornerstone" of SRC management, since changes to cognitive, behavioural, and emotional symptoms can be measured over time. Concussions may cause impairment in the domains of attention, verbal learning and memory, working memory, visual learning, processing speed, and executive function (Collins et al., 1999; Guskiewicz et al., 2005; Karr et al., 2014; Ledwidge, 2018; Leininger et al., 1990; Macciocchi et al., 1996; McAllister & McCrea, 2017; McCrea et al., 2003; McCrory et al., 2017; Shah-Basak et al., 2018; Sinclair et al., 2013). In addition to cognition, other frequently-used measures assess the oculomotor, auditory, vestibular, sensory, and fine motor function domains (Eagle, Kontos, et al., 2020; Leddy et al., 2021; McGeown et al., 2021; Pearce et al., 2015; R. Smith et al., 2019; Thompson et al., 2021).

Several measures can be used on the sideline or during the acute post-injury phase. The Sport Concussion Assessment Tool (SCAT-5) includes elements of many common sideline measures and is the fifth version developed through international consensus (McCrory et al., 2017). The SCAT-5 uses several subtests for acute concussion assessment and diagnosis including orientation, verbal learning and memory, balance, executive function, and also includes a symptom inventory (McCrory et al., 2017). To allow the effects of exertion to pass, the post-injury assessment may be performed up to 15 minutes after the injury occurs (Molloy et al., 2017). Another commonly used measure of concussion assessment is the King-Devick (K-D) number reading test, which measures visual processing, attention, eye movements, and language (Galetta, Barrett, et al., 2011; Galetta, Brandes, et al., 2011; D. King et al., 2015; Legarreta et al., 2019; Molloy et al., 2017; Moody et al., 2019; Rizzo et al., 2016). For additional confirmation, some coaches or trainers may refer to video footage of the impact, which can show the any immediate change in the athlete's behaviour (such as confusion or staggering) after the impact (Daly et al., 2022; McCrory et al., 2017; R. Smith et al., 2019).

An athlete who sustains a concussion is re-assessed at multiple points after the injury for deficits or changes from the baseline. During the first 72 hours post-injury, common tests that incorporate cognitive assessments are the SCAT-5, ImPACT, and CogState (Moody et al., 2019). ImPACT and CogState are computerised assessments that measure domains of verbal and visual memory, visual motor speed, reaction time, impulse control, cognitive efficiency, and symptoms reported against normative data or a baseline if available (Marinides et al., 2014). Additionally, ImPACT can detect some degree of intentional poor performance by an athlete on a baseline test (Moody et al., 2019), but it is unclear how well this feature actually works.

### 1.3.2 Recovery

To identify post-injury deficits that sideline tests may not detect, neuropsychological assessment is most sensitive in athletes who were tested at baseline. Performance on a single post-injury assessment can indicate gross damage, but multiple assessments can guide the recovery process more meaningfully because subtle damage is better measured by the differences between post-injury and baseline assessments, or normative data if a baseline is not available (Lovell & Solomon, 2011). Additionally, some symptoms may demonstrate a delayed onset, and may not be detectable until up to 48 hours after injury. Athletes must return to their baseline performance across all cognitive and symptom domains before they return to play.

As their symptoms decrease, athletes begin to complete a graduated return-to-play (RTP) protocol after their concussion. According to the current international recommendations, an athlete with concussion should rest or perform light exercise for the first 48 hours post-injury (Leddy et al., 2023), then begin a seven-day (minimum) progressive RTP process when able. Each step of the protocol (from low-threshold exercise up to contact practice) requires the player to return to their baseline level of symptoms for 24 hours before moving onto the next (McCrory et al., 2017); if an athlete becomes symptomatic, they should return to the previous level and remain symptom-free for 24 hours before continuing through the protocol. Recovery is ultimately determined by the team physiotherapist or doctor, whose RTP decision is based on reported or observed symptoms and a return-to-baseline performance on any cognitive measures.

### 1.3.3 Repetitive impact-induced injuries

The majority of impacts an athlete experiences will not result in concussion, but can still cause short-term or cumulative neurological damage. Though the symptoms are not always as apparent as with concussion, these low-magnitude repetitive impacts can

render an athlete more vulnerable to a concussion or further injury. The threshold of impact tolerance before concussion varies for each person and can depend on many factors, like a recent history of similar impacts,[4] though this weakened threshold may recover once the exposure to repetitive impacts stops (Bari et al., 2019). Repetitive impacts may contribute to long-term cognitive deficits, depression, and later, even neurodegenerative disease if enough impacts are sustained (Bailes et al., 2013; Lepage et al., 2019; McAllister & McCrea, 2017; McCrea et al., 2015; McKee et al., 2016).

Some effects of repetitive impacts can be seen acutely. When tested before and after impact exposure (e.g., a boxing match or heading a soccer ball), athletes can show impairments to memory, attention, planning (Matser et al., 2000), and number-reading ability (Galetta, Barrett, et al., 2011; Nowak et al., 2020). Oculomotor, cognitive, and vestibular symptoms are common in athletes up to four weeks after their last impact exposure (Stephen et al., 2022). Some researchers have found neurocognitive deficits in undiagnosed and asymptomatic athletes after a single season of contact, such as acute processing speed and divided attention (Espinoza et al., 2021), working memory (E. L. Breedlove et al., 2012), visual working memory (Talavage et al., 2014), and verbal memory (McAllister et al., 2012; McAllister et al., 2014). Athletes can also experience concussion-associated symptoms (e.g., fatigue, drowsiness, headache, feeling in a fog) during one season of exposure to repetitive impacts (Kieffer et al., 2021). However, many other studies have failed to find significant neurocognitive deficits after a single season (Bailes et al., 2013; Belanger et al., 2016; McAllister & McCrea, 2017; Miller et al., 2007). As such, subconcussive injury is not well-measured by neurocognitive tests, but it can be detected by imaging methods (Bailes et al., 2013; Belanger et al., 2016).

White matter can be damaged without a concussion diagnosis or any accompanying visible or behavioural symptoms, blurring the line between a concussion and damage from repetitive impacts (Voss et al., 2015). The effects of repetitive impacts might appear on fMRI as changes or alterations in blood flow, network activation, and impaired connectivity (Abbas et al., 2015; E. L. Breedlove et al., 2012; Champagne et al.,

[4] Increased exposure to repetitive impacts may lower the threshold of force required for a subsequent impact to cause a concussion, and these forces are measured by accelerometers in the athlete's helmet or mouthguard (Stephen et al., 2022). Concussive force is typically estimated at around 100 *g* (where one *g* represents the force of gravity at sea level), but those with higher amounts of repetitive impacts in the days leading up to the concussion sustained concussions at forces as low as 30–40 *g* (Beckwith et al., 2013; Stemper et al., 2019). Soccer players who regularly "head" the ball are also at risk; headers may be only 10–35 *g*, but can still lead to increased neurological injury over an athlete's career (Di Virgilio et al., 2016; Moore, Lepine, & Ellemberg, 2017; Nowak et al., 2020).

2021; Hirad et al., 2019; Manning et al., 2020; Talavage et al., 2014), on DTI as diffuse white matter damage (Asselin et al., 2020; Bazarian et al., 2014; Hirad et al., 2019; McAllister et al., 2014; Myer et al., 2019), on structural MRI as changes to the sizes of brain regions or organelles such as the limbic structures and midbrain (Hirad et al., 2019; Lepage et al., 2019; Singh et al., 2014; Stanwell et al., 2022), or as changes to biomarkers such as S100β, which is associated with blood-brain barrier integrity (Bazarian et al., 2014; Hunter et al., 2019; Soriano et al., 2021). These methods can provide clues to the underlying metabolic mechanisms and sequelae of repetitive impacts.

Changes from one season of repetitive impacts can be seen by these imaging methods. Using fMRI to examine regional activation, Talavage and colleagues (2014) found evidence of functional impairment and decreased activation in 50% of high school football athletes without a clinically diagnosed concussion at one to three months after the season ended. The group who exhibited functional impairment sustained more collisions than either the non-concussed or clinically concussed athletes (Talavage et al., 2014). In another study, persistent white matter changes were seen after six months of rest in athletes who were not diagnosed with concussion during the playing season (Bazarian et al., 2014). Other changes reported in athletes after one season include structural changes to the midbrain (Bari et al., 2019; Hirad et al., 2019), white matter diffusivity changes to the corpus callosum, cerebellum, and limbic regions (McAllister et al., 2014), or alterations to cerebrovascular oxygen delivery (Owens et al., 2021). Taken together, repetitive impacts can observably affect midbrain and subcortical structures after one season.

Researchers have increased their attention to subconcussive and repetitive impacts since 2000 and as athletes continue to get bigger and stronger (Bailes et al., 2013), but many questions remain, including the very definition of terms like “subconcussion” (Belanger et al., 2016). While some research has focused on female athletes (Kieffer et al., 2021; D. King et al., 2018; Manning et al., 2020; Myer et al., 2019), sex differences in the symptoms and damage of repetitive impacts are still not well understood. A review by Stephen and colleagues (2022) found that 46% of the articles they referenced included only male athletes, and many of the remaining studies did not include female athletes at equal rates. Thus, more research that includes female participants is needed to understand the nuanced effects of repetitive impacts on contact athletes.

## 1.4 Limitations of current methods

Current methods of concussion assessment are inadequate. Standard diagnosis is vulnerable to a doctor's error or oversight, differences in concussion-specific training, and an athlete's desire to continue playing (Clacy et al., 2017). A doctor or physiotherapist diagnoses concussion based on the self-reported symptoms from the patient or athlete, and the decision may or may not be supported by specific questions or appropriate measures of concussion-specific domains (Broglio, Guskiewicz, et al., 2017; Leddy et al., 2021; Moody et al., 2019). Repeated administration of such tests can also induce a practice effect that may obscure concussive damage (K. M. Breedlove et al., 2019; Dupuis et al., 2000; Galetta, Brandes, et al., 2011; Gunasekaran et al., 2020; Heick et al., 2016; Nandrajog et al., 2017; Teel et al., 2014; Thompson et al., 2021). Finally, symptom severity and cognitive deficits are not precise measures of recovery from physiological damage (McCrea et al., 2015), and a return to baseline does not necessarily mean a full recovery.

Neuropsychological assessments can be helpful in determining a symptom profile and course of treatment, but no single test is adequately sensitive to all affected domains (Moody et al., 2019). The effects of concussion can be complex, affecting separate or multiple aspects of cognitive functioning; this individualised damage is *"difficult to disentangle based on gross performance on standard neuropsychological tests"* (Brush et al., 2018; p. 125). No measure or test (including the SCAT-5 or ImPACT) can independently determine a concussion with full accuracy, though sensitivity increases when two or three tests are used (Broglio et al., 2007; Daly et al., 2022; Resch et al., 2016). However, performing a complete neuropsychological assessment to assess all affected domains would be expensive and overly burdensome on an athlete's time.

Neuropsychological assessment measures used in sport begin to lose their sensitivity quickly; this is one reason that athletes can demonstrate a return to baseline performance while they are still symptomatic (Teel et al., 2014). Acute neuropsychological measures like the SCAT-5 may lose their sensitivity three to seven days after injury (G. Davis et al., 2009; Ledwidge & Molfese, 2016; McCrea et al., 2003; McCrory et al., 2017; Slobounov et al., 2009), since they were designed to detect sudden and substantial neurocognitive deficits, not subtle or persistent deficits (Broglio et al., 2011; Pontifex et al., 2009). Notably, measures like the SCAT-5 can be vulnerable to the practice effect; a concussed individual's score may improve if tests are administered multiple times during a season (even with alternate forms), obscuring persistent damage (Dupuis et al., 2000; Nandrajog et al., 2017). In other words, an athlete's performances

on baseline and post-injury may be equivalent because for the baseline they were unfamiliar with the protocol, and at post-injury the effect of familiarity was cancelled out by cognitive deficits from the concussion. The ImPACT computerised assessment method is similarly vulnerable to the practice effect and insensitive to deficits after symptom resolution (Teel et al., 2014; Thompson et al., 2021).

Moreover, current neuropsychological tests may not be fully valid for concussion assessment. They may not weight an individual's linguistic or cultural background heavily enough (Bilder & Reise, 2019; Houck et al., 2018), and the original reasons these tests were developed does not always make them appropriate for the domains they are currently used to measure (Bilder & Reise, 2019). Athletes may under-report their symptoms to RTP faster (Meier et al., 2015), or under-report their previous concussions at baseline, which affects perception of risk (Cunningham et al., 2020) and the accuracy of the measures. Further, the common symptoms and cognitive impairments seen after concussion are also common in many other conditions and across the general population (Dikmen et al., 2004; Gunstad & Suhr, 2002; Stafford et al., 2020; Voormolen et al., 2019). Finally, affective domains are not widely assessed as part of post-injury protocols, yet up to 30% of athletes with concussion may experience at least one affective symptom (Thomas et al., 2022). Appropriately specific measures of concussion should be sensitive to all possible domains of injury.

As indicators of concussion, neuropsychological testing and symptomology are fundamentally limited because they look for the consequences of damage, rather than looking for the damage itself (Reches et al., 2017; Teel et al., 2014). After head injury, acute concussion-induced alterations such as cerebral blood flow changes and diffuse axonal (white matter) damage can sometimes be seen on structural or functional imaging such as MRI or CT scans, fMRI, DTI, or FDG-PET, as well as magnetic resonance or near-infrared spectroscopy (Bigler, 2018; Churchill et al., 2019; G. Davis et al., 2009; Dimou & Lagopoulos, 2014; Ellemberg et al., 2009; Gosselin et al., 2010; Henry et al., 2010; Hirad et al., 2019; Kirov et al., 2013; Len & Neary, 2011; Mummareddy et al., 2019; Wang et al., 2019), but these imaging methods can only be performed at hospitals with the necessary equipment. This type of damage cannot be seen acutely or consistently enough to justify the cost of performing these methods diagnostically, although they are used more frequently to monitor recovery. Other physiological measures (e.g., post-concussive alterations in heart-rate variability) have been considered for acute assessment, but the changes seen are too variable between individuals and not yet reliable or sensitive enough to act as diagnostic aids (G. Davis et al., 2009; Haider et al., 2020; Harrison et al.,

2021; Hutchison et al., 2017; Solbakk et al., 2005). We have yet to identify the hallmark damage of concussive injury.

Another acute or sub-acute assessment method still being explored is fluid biomarkers. Changes to levels of proteins or hormones in biofluids are commonly called "biomarkers," and these can indicate axonal or neuroglial injury, inflammation, and hormonal disturbances (Senaratne et al., 2022). These can be measured in blood (G. Davis et al., 2009; Di Battista et al., 2018; Edwards et al., 2020; Giza et al., 2021; Mondello et al., 2020; G. C. O'Connell et al., 2020; Sun et al., 2021), saliva (Di Pietro et al., 2021; Hicks et al., 2020), and cerebrospinal fluid, or CSF (Alosco et al., 2018; Alosco et al., 2019; Finnoff et al., 2011). Acute concussion is associated with changes to several neurochemicals, including total tau, neurofilament-light levels, glial fibrillary acidic protein, and ubiquitin C-terminal hydrolase L1 (Tabor et al., 2023; Zetterberg et al., 2013). Sub-acute changes after concussion are associated with neuron-specific enolase and S100β, among others (Di Battista et al., 2018; Zetterberg et al., 2016). Biomarkers can reflect changes in neurometabolism or damage to the grey or white matter, but not predictably enough to be diagnostically useful.

While there is some evidence for fluid biomarkers, these tests are invasive, still relatively new and unvalidated, and do not give a complete picture of the complexity of a player's symptoms. Alterations to levels of tau, S100β, neuron-specific enolase, and ApoA1 have been reported in athletes who did not sustain a concussion (Bazarian et al., 2014; Di Battista et al., 2018). Adrenocorticotropic and thyroid-stimulating hormones can be more accurately analysed during the subacute phase of recovery, but these neuroendocrine changes may be more common in moderate or severe TBIs than mild TBIs (Tanriverdi & Kelestimur, 2015). Tau also shows strong association with severe concussions (Senaratne et al., 2022), and while it appears in blood serum, the quality is lesser than that of CSF tau, possibly because it degrades in the bloodstream (Zetterberg et al., 2016). It is also present in saliva, but its role in central nervous system damage is not clear (Zetterberg et al., 2016). Additionally, the biofluids with higher concentrations are obtained by more invasive methods: CSF has the highest concentration levels but is more painful to obtain as blood, which has more widespread circulation and lower concentrations of the relevant proteins that degrade or are modified more quickly (Zetterberg et al., 2016; Zetterberg et al., 2013). Saliva biomarkers are another possibility, but its concentrations are often too weak to be meaningful (Zetterberg et al., 2016). Cultural factors may also complicate or prohibit the use of bodily fluid biomarkers to assess concussion. Finally, biomarker testing is expensive to collect and perform, and the

results are not immediately available, which makes it a poor candidate for sideline or frequent testing.

### 1.4.1 Justification for research

Better and more objective diagnostic methods of concussion are essential to improve brain health in sport. Assessment methods should focus on physiological damage instead of only on the functional correlates, especially because of the variability in symptom or deficit presentation. There is an overall lack of clarity and consistency in concussion assessment and management, resulting from the differences in available medical personnel by play level[5] and different levels of concussion training between physiotherapists, doctors, and other medical personnel (Clacy et al., 2017). Further, since much of concussion assessment research focuses on male athletes (Daly et al., 2022), the standard assessments used may not be sensitive enough to concussive symptoms in female athletes, and researchers should be aware of sex-related differences or gender bias (Henne, 2020; Moody et al., 2019; Robinson, 2019). For instance analyses by Robinson (2019) indicate that 10 of the 22 symptoms of the SCAT-5 are differentially biased by sex, and that the SCAT-5 could be improved by creating sex-specific versions. If female athletes do experience worse concussions (Broshek et al., 2005; Covassin et al., 2018), and their outcome depends on shortening the interval between injury and receiving care (Barnhart et al., 2021; Kontos et al., 2020), then extra efforts should be made to assess concussions accurately in female athletes (Moody et al., 2019).

[5] Physiotherapists may be available at community-level practices and matches instead of doctors.

# Chapter 2
# Literature Review: Electrophysiology and Concussion Assessment

Neuroelectrophysiology is a method of functional analysis that examines electrical activity in neurons or networks of neurons. Concussion damages the brain by widespread stretching, shearing, and tearing of axonal fibres; these distortions result in focal and/or diffuse damage to small groups or networks of neurons in many areas of the brain (D. H. Smith et al., 2003) since communication must be rerouted. Thus, the electrical activity in affected regions can become diminished, latent, or otherwise altered, leaving concussed brains with less available cognitive resources and requiring them to compensate for the damage by recruiting other networks to help perform the same tasks equivalently (De Beaumont et al., 2007; Duncan et al., 2003; Fratantoni et al., 2017; Hudac et al., 2018; Kozak, 2018; Ledwidge & Molfese, 2016; Molfese, 2015; Olson et al., 2018; Teel et al., 2014). These inefficiencies cause deficits in neuropsychological domains (such as attention, information processing, and working memory) that can be read by non-invasive electroencephalogram (EEG) at the scalp, and these may even be detected when no cognitive deficits are observed.

EEG signals are an aggregate measure of the surface (cortical) brain activity in real time; these can be detected during passive sensory stimulation, active sensory stimulation, or cognitive tasks (Gosselin et al., 2010; Pravitha et al., 2005). Quantifiable changes in these readings can provide physiological evidence of acute and sub-acute injury, as well as evidence of prolonged injury for individuals accused of malingering, involved in litigation (Gaetz & Weinberg, 2000), or those seeking aid and accommodations for an otherwise invisible illness (Nandrajog et al., 2017). Many EEG testing techniques are also used in concussion/mTBI assessment (Brooks et al., 2018; Lai et al., 2020; Major et al., 2015; Slobounov et al., 2009; Slobounov et al., 2012), since EEG changes have been recognized as a biomarker for concussion since 1940 (J. C. Brown et al., 2023; Jasper et al., 1940; Mayer et al., 2018).

## 2.1 Event-related potentials

Event-related potentials (ERPs) represent specific and predictable electrical brain activity that follows a stimulus. The “event” can be a behaviour or a change in time-locked sensory or cognitive stimuli (Brush et al., 2018; Donchin, 1981). The word

"potential" describes the amount of electricity (potentially) required to travel from one area of the brain to another, as explained by Folmer and colleagues (2011).[6]

The specific evoked activity (a component of the full EEG signal) is named for its polarity (positive or negative) and the approximate number of milliseconds after stimulus that it appears. For example, P300 (also referred to as P3) represents the positive amplitude wave that occurs at or around 300 milliseconds after stimulus presentation (Clayton et al., 2020; Dupuis et al., 2000; Ledwidge & Molfese, 2016), though this is somewhat misleading; the components proceed in sequence, and there is an estimated window of time for each component to appear, depending on the behaviour or latency of the component before it. The earliest components (P50 up to N200 and P300) are studied for their involvement in stimulus filtering, inhibition, and attentional allocation processes, while the later components (N400 and P600, for example) are associated with semantic interpretation and response processing (Broglio et al., 2009; Fickling et al., 2019; Gosselin et al., 2006; Hudac et al., 2018; Kozak, 2018; Ledwidge, 2018). Most ERPs cannot be identified by their localisation because they are generated by widespread attention and memory networks (Broglio et al., 2011; Mazzini, 2004; Polich, 2007); localisation is instead measured as the electrical impulses travel across the necessary regions and structures; as explained by Gaetz and Weinberg (2000, p. 817):

> Generators of N2–P3 waveforms have been attributed to medial temporal structures, hippocampus, thalamus, parietal lobe, temporal-parietal junction, frontal lobe representing multiple generators. Therefore, it is likely that the N2-P3 is not generated in a single area of the brain but rather involves different areas as required by the task.

To observe these subtle changes in electrical potential, the target brain activity can be evoked in several ways. Visual evoked potentials (VEPs) are generated by images, while auditory evoked potentials use tones. The most frequently used method is the visual or auditory "oddball" paradigm, in which the participant sees or hears a set of stimuli (composed of the standard items and the less-frequent target item), and they are asked to

[6] From page 4: "Potential refers to the electrical potential difference (or voltage) between two points, defined as the electrical force that would drive an electric current between those points. In the case of ERPs and EEG, the 'two points' are electrodes attached to the patient's head that record voltages generated by neural activity from populations of neurons within a sensory pathway. These voltage changes result from movement of ions (e.g., K+, Ca++, Na+, and Cl−) and other charged particles within and between neurons in the brain."

identify the "odd" one (Boshra et al., 2019; Cavanagh et al., 2019; Clayton et al., 2020; Dockree & Robertson, 2011; Dupuis et al., 2000; Gaetz & Weinberg, 2000; Kozak, 2018; Krokhine et al., 2020; Moore et al., 2017). The stimuli can be symbols (shapes, numbers, letters, or words) or tones of different pitches (Gaetz & Weinberg, 2000). Beyond oddball paradigms, ERPs are also often measured while participants perform other tasks that use cognitive processes such as working memory or inhibition as the stimulus (Brush et al., 2018).

When studying ERPs in concussion, designs that use multiple types of ERP stimuli are recommended because concussion can damage more than one aspect of functioning (Lew, Garvert, et al., 2009; Lew, Gray, et al., 2009; Moore, Hillman, et al., 2014). The electrophysiological changes of interest are best revealed while an individual performs relevant neurocognitive tasks, even when no corresponding neurocognitive deficits are seen. While this may seem to undermine the connection between the two, the validity of representation of the neurocognitive domain is supported by the different strategies of network recruitment seen in functional imaging during the same tasks (De Beaumont et al., 2007; Ledwidge & Molfese, 2016). Moreover, ERP methods may be more sensitive to concussive damage than traditional cognitive tests because cognitive tests reflect only performance, regardless of compensatory strategies, while the ERP tests reflect measurable functional deficits (Broglio et al., 2011; Gosselin et al., 2006; Moore et al., 2017).

### 2.1.1 ERPs in concussion

Scalp-derived ERPs provide *"a direct link between brain function and cognitive states"* to reflect the cognitive processes taking place, and they are *"uniquely sensitive […and] well-suited for discovery of aberrant neural mechanisms that underlie complicated disease states"* (Cavanagh et al., 2019, p. 2). The use of ERPs in the neurocognitive assessment of sport-related concussion was first published by two Canadian labs in 2000 (Broglio et al., 2011; Dupuis et al., 2000; Gaetz et al., 2000; Gaetz & Weinberg, 2000). ERPs can act as functional correlates of the otherwise invisible yet persistent concussive damage, identifying deficits during tasks of psychomotor function, attention thresholds, and executive function in concussed individuals who do not have symptoms or demonstrate cognitive impairment (Broglio et al., 2009; Clayton et al., 2020; Fratantoni et al., 2017; Gosselin et al., 2012; Hudac et al., 2018; Kozak, 2018; Ledwidge & Molfese, 2016; Olson et al., 2018; Ozen et al., 2013; Thériault et al., 2011). These objective deficits that persist after cognitive or behavioural symptoms have disappeared

support the growing finding that physiological recovery from concussion takes longer than the typical timelines of RTP or estimated cognitive recovery (J. C. Brown et al., 2023).

Electrophysiological deficits are seen as measurable changes to signal strength (amplitude) or timing (latency). An increase in amplitude may seem like evidence of healthier brain activity, but it could also represent a less regulated response due to increased sensitivity, a disproportionate amount of mental resources occupied by a disruptive stimulus, or disrupted excitatory/inhibitory networks (Clayton et al., 2020; Fickling et al., 2019). Amplitude is measured in microvolts, and relative increases in amplitude are interpreted as additional resources being used to perform the task (Fickling et al., 2019; Hudac et al., 2018), while relative decreases in amplitude are correlated with symptom severity (Dupuis et al., 2000; Lavoie et al., 2004), allocation or availability of fewer resources (Hudac et al., 2018), history of concussion (Moore, Broglio, et al., 2014), or long-term deficits (Brush et al., 2018). ERP amplitude may be associated with sites of brain damage (Dupuis et al., 2000), but because most ERPs are generated by multiple areas, abnormalities cannot be easily correlated with specific localisations, and it is more appropriate to interpret deficits as estimations of damage to communication pathways (Folmer et al., 2011).

The P100 component is sensitive to visual aspects of concussive damage and has been primarily studied in the occipital region using a flashing light stimulus (X.-P. Chen et al., 2006; Moore, Broglio, et al., 2014; Papathanasopoulos et al., 1994). P100 is associated with visual processing, and is associated with activity near the thalamus, striate cortex, and peri-striate cortex (Gaetz & Weinberg, 2000). Studies that use VEPs to examine brain activity after concussion have found mixed outcomes. Chen and colleagues (2006) found that the P100 amplitude was significantly lower in patients with concussion than controls at 48 hours post-injury, but equivalent when assessed at a three-month follow-up. Similarly, Papathanasopoulos and colleagues (1994) found that those in hospital with head injuries demonstrated increases in P100 amplitude from day one to day 30 post-injury, but they did not find any differences in P100 behaviour between the head injury and the control groups. In contrast, young adults with a remote history of concussion (average of 6.7 years prior) demonstrated reduced P100 amplitude when compared to controls of the same age group with no previous concussions (Moore, Broglio, et al., 2014). Using an alternating checkerboard stimulus, Yadav and Ciuffreda (2015) used P100 to study visual attention deficits in participants with a remote history of concussion; the concussed group with the attentional deficits demonstrated reduced

activation when compared to the concussed group with no attentional deficits. Taken together, P100 shows increases during the recovery phase (without pre-injury baselines), and may also indicate long-term changes after concussion.

Components N200 and P300 are of particular interest when studying concussion (Gosselin et al., 2010). They are often studied together or in combination as the N200-P300 complex because they occur sequentially and potentially within the same average windows of time (Boshra et al., 2019; Ledwidge & Molfese, 2016). Both are associated with attention allocation and stimulus discrimination, and N200 is also studied for its involvement in inhibition. In general, concussion is associated with lower N200 and P300 amplitudes, though some studies have found evidence of increased amplitude for each (Hudac et al., 2018; Ledwidge & Molfese, 2016; Moore, Hillman, et al., 2014; Moore et al., 2015; Ozen et al., 2013).

After concussion, the P300 component decreases the most consistently when compared to baseline. Clayton and colleagues (2020) assessed athletes using an auditory oddball paradigm within 48 hours of concussion and saw amplitude decreases of the P300 component beyond 1.5 standard deviations from baseline in 88% of these athletes, compared to in 16% of non-concussed athletes. Fickling and colleagues (2019) also saw acute decreases in P300 of hockey players within 24 hours after concussion, as well as decreases in the N100 and N400. Moreover, the P300 amplitude of the concussed participants was significantly lower than that of non-injured control participants within a week of concussion in another study (Nandrajog et al., 2017). These studies also reported evidence of long-term deficits: incomplete recovery of P300 amplitude by RTP in concussed athletes (Clayton et al., 2020; Fickling et al., 2019) and persistent cognitive deficits at three months post-injury in non-athletes (Nandrajog et al., 2017). In turn, the sequential P3a and P3b subcomponents have shown predictive value of who will suffer long-term impairment (Cavanagh et al., 2019). Since the present study does not deal with cognitive stimuli or the components most widely used, better information about these methods can be found elsewhere.[7]

[7] Several excellent reviews explore the uses of ERPs in TBI (Dockree et al., 2011; Folmer et al., 2011), while the use of ERPs in athletes specifically is described by a review by Brush and colleagues (2018), and extensively in the work of Broglio (2009; 2011; 2017), de Beaumont (2007; 2009), Gosselin (2006; 2010; 2012), Moore (2014; 2015; 2017), and Thériault (2009; 2011), among others. This chapter also does not specifically address auditory ERPs, transient VEPs, or standard EEG testing.

### 2.1.2 ERPs in repetitive impacts

Repetitive impacts can cause similar deficits as a history of concussion, and changes to P300 and its subcomponents have been seen across a season of repetitive impacts from American football. In one study (Richards, 2017), a group of American football players were tested before and after a season and their P300 and SCAT-3 results were compared; P3a amplitude increased over time, while P3b amplitude decreased. Additionally, the linemen (who sustain impacts every play, similar to the front row in rugby) were the only group to show an inverse correlation between ERP amplitude and symptoms reported, as well as a concentration deficit, indicating that they may experience more impairment than athletes playing positions with less repetitive impact exposure. Wilson and colleagues (2015) also tested American football players before and after a season; while they found no changes in the first- and second-year players, they did find a weaker P3b amplitude in the third- and fourth-year players at the end of the season, suggesting that subconcussive injury can accumulate over years of play. When Clayton and colleagues (2020) studied athletes over two seasons, they found that roughly half of the athletes whose P300 amplitude had not normalised by RTP had not actually sustained a concussion, but instead experienced *"a series of subacute events such as those experienced by the offensive line in football"* (p. 88) and had been removed from play. Though football players and rugby athletes experience different degrees of repetitive impacts, a season of rugby impact exposure may also cause electrophysiological alterations.

Such changes can even be seen acutely after a single period of subconcussive exposure. A deficit of the electrophysiological orienting response (N2b) was seen in the ERPs of boxers when compared to their baselines; using a two-hour auditory oddball paradigm protocol that began 1.5 hours after the fight, researchers found decreases of the N2b amplitude when the stimulus was delivered to the right ear (Pincemaille et al., 1989), and that the effect was stronger in boxers who were hit in the left side of the head (Breton et al., 1990). The other components studied (N100, P200, and N2a/the mismatch negativity, or MMN) did not change after the fight (Breton et al., 1990; Pincemaille et al., 1989). In a study comparing different repetitive impact exposure groups before and after heading a soccer ball, Moore and colleagues (2017) found that both the contact athletes with no concussion history (who were assumed to be subconcussed) and the contact athletes with previous concussions (an average of over two years since the most recent) demonstrated reduced amplitudes of the P3a and P3b subcomponents. Further, the relationship between impact exposure and impairment is not clear. Moore and colleagues

(2017) found no correlation between neurocognitive or ERP impairment and estimated number of impacts in the subconcussed group. While Fickling and colleagues (2021) found a correlation between number of impacts and ERP impairment, the average age of the group with greater impact exposure was also higher than that of the group with lower impact exposure. Olson and colleagues (2018) found no correlation between error-related negativity (ERN, a component of ERP) amplitude and number of years playing a contact sport, but they acknowledged that the ERN and years of sport are not the most sensitive measures of subconcussive effects. Long-term effects of repetitive impacts can also be seen in combat athletes: when fencers and boxers completed a go/no-go task, Di Russo and Spinelli (2010) found that the fencers (no-impact combat athletes) demonstrated higher N100 and N200 amplitudes than the boxers or non-athlete controls, which they interpreted as enhanced cognitive skills in the fencers. The ERP effects of repetitive impacts are subtler and more difficult to interpret, but they may become more apparent with continued impact exposure over time.

To study subconcussion in male youth athletes, researchers (Fickling et al., 2019; Fickling, Smith, et al., 2021; Ghosh Hajra et al., 2016) have proposed a model of the brain's "vital signs," in which N100 represents auditory sensation, P300 represents basic attention, and N400 represents cognitive processing. The amplitude and latency of these frontal, parietal, and central ERPs (respectively) were assessed using oddball tones and spoken word pairs (that were congruent or not). Findings revealed significant reductions in the cognitive processing "vital sign" after one season of ice hockey in the group with no diagnosed concussion; specifically, increased latency of the N400 component represented a cognitive/semantic processing deficit (Fickling et al., 2019). Another study that focused on subconcussion over a season of hockey (Fickling, Smith, et al., 2021) reported decreased N100 amplitude, as well as non-significant trends of decreased N400 amplitude and increased N100 latency. The latency of N400 correlated with the number of impacts (as measured by an accelerometer), which may indicate its utility as a marker of subconcussion severity (Fickling, Smith, et al., 2021). Another study examining youth football players across one season (Fickling, Poel, et al., 2021) again saw amplitude and latency changes in N400 and N100, which were attributed to higher impact exposure. The effects of subconcussive injury on ERPs have only been studied since 2010 (Fickling, Smith, et al., 2021), which likely explains the lack of clarity surrounding the unique effects of subconcussion acutely and over time.

Though ERPs appear to be sensitive to a previously unidentified aspect of concussive damage, this method has several drawbacks. Because it collects data in real-

time, the protocols can be long, in some cases up to 18 minutes (Clayton et al., 2020). Real-time readings can also be specifically vulnerable to increased noise or confounding factors. Additionally, these studies do not represent a standard approach for using ERPs in concussion; different studies may use slightly different time windows for the same component, depending on the other signals being measured and the purpose of the study. These ERP studies are also highly different from each other in terms of types of stimuli used, sample sizes, follow-up time points, and populations of interest; this complicates how meaningful these changes may be in other populations.

## 2.2 Steady-state visual evoked potentials

The steady-state visual evoked potential (SSVEP) is an electrophysiological method that is less vulnerable to noise and movement artifacts than the real-time VEPs and ERPs. The SSVEP uses a time-locked flickering visual stimulus at a target frequency to evoke the same frequency of activity as the visual flicker within the brain (Adrian & Matthews, 1934; Fong et al., 2020; Norcia et al., 2015; Skosnik et al., 2006). Neuroelectric activity synchronises to the frequency of the stimulus, which can be a flashing light (da Silva et al., 1999; Krishnan et al., 2005; Pastor et al., 2003; Takahashi & Tsukahara, 1998; Wada et al., 1995) or screen (Fong et al., 2020; Skosnik et al., 2006), or a pattern reversal (like a checkerboard) in black and white (R. G. O'Connell et al., 2009; Tobimatsu, 2002) or red and green (Tobimatsu, 2002). The amplitude of the target activity is either measured in real time (Norcia et al., 2015; R. G. O'Connell et al., 2009) or calculated as a signal-to-noise ratio (SNR) over a period of stimulus exposure; the latter method of aggregating the signals eliminates much of the EEG activity at frequencies other than the target ("noise"), and leads to a cleaner EEG reading that is measured in magnitude (Fong et al., 2021; Ghosh Hajra et al., 2021).

The use of SSVEP in occipital EEG activity was first described in depth by Adrian and Matthews (1934), who referred to EEG as the "Berger rhythm" because they did not yet know how widespread this activity was throughout the cortex (though they acknowledge that Berger himself called it an "electrencephalagram" [sic]). To determine the source and characteristics of the EEG signal, they amplified a 10 Hz passive signal from square copper electrodes placed occipitally on the scalp,[8] then recorded the waveforms by an oscillograph; a condenser was used to cancel out distortions from slow

[8] Their innovation and forward thinking also helped to standardise the use of scalp electrodes: "In a few preliminary experiments we followed Berger's technique, using steel needles thrust through the scalp, but we were relieved to find that pad electrodes gave equally good results." (p. 357)

potentials for a cleaner reading. They elicited SSVEPs up to the 25 Hz frequency in their participants by using a lightbulb set in a "sector wheel:" a device with light and dark sections that rotated by a gramophone to create the flicker frequencies. To isolate the stimulus, the participant and apparatus were covered by a curtain. According to Adrian and Matthews (1934, p. 378):

> At a signal the eyes are opened and the shutter lifted to turn on the flickering light. The result is a series of potential waves having the same frequency as that of the flicker. … The rhythms induced by flicker represent a positive activity, but one which cannot often occur normally.

SSVEP is associated with several types of research, including in vision studies (Norcia et al., 2015) to examine perceptual quality (Acqualagna et al., 2015), texture (Bosse et al., 2017), directionality (Ales & Norcia, 2009), and saccades (J. Chen et al., 2019). Many SSVEP studies have centred on schizophrenia because of the visual dysfunction and abnormal SSVEP responses found in this population, including lower occipital amplitude (Krishnan et al., 2005; Riel et al., 2019; Sumich et al., 2014; Wada et al., 1995). Several other researchers have used SSVEP to study attention (Davidson et al., 2020), particularly as it relates to fatigue (Zheng et al., 2020), sustained attention (R. G. O'Connell et al., 2009), internally vs externally directed attention (Kritzman et al., 2022), and anxiety (E. R. Davis, 2022). SSVEP has also been investigated for its use in sensory processing during sleep (Norton et al., 2017; Sharon & Nir, 2017), and its potential in brain-computer interfacing (Dreyer & Herrmann, 2015).

SSVEP has been used in combination with positron emission tomography (PET), an imaging method that utilises a tracer to examine different patterns of activation in the brain. da Silva and colleagues (1999) used flickering lights to study resting cerebral blood flow (by PET) and EEG activity in patients with and without epilepsy, and they found the strongest EEG response to the 14 Hz frequency in both groups (with weaker responses to 4 and 30 Hz). This activity was localised in the occipital lobe and right thalamus for the control group, and in the occipital lobe and the hypothalamic region inferior to the left caudate nucleus in the patient group (da Silva et al., 1999). Pastor and colleagues (2003) also used PET imaging to identify a pattern of activation in the occipital (visual) cortex representing resting cerebral blood flow activity that was specifically responding to the SSVEP. This combination of neural imaging techniques can provide better information about the localisations of activity associated with SSVEP changes.

A thorough review by Norcia and colleagues (2015) describes the history of SSVEP research and the development and use of more complex stimuli or paradigms beyond flashing lights, such as pattern reversals (Zheng et al., 2020), flashing words (Montani et al., 2019), images (Minami et al., 2020; Mora-Cortes et al., 2018), colours (Adam et al., 2020), faces or social scenes (E. R. Davis, 2022; Gruss et al., 2012; Wieser et al., 2016), and even images of the participant's own body (Henn et al., 2022; Voges et al., 2019; Voges et al., 2020). Signal sensitivity increases when multiple stimuli are used together (Norcia et al., 2015).

### 2.2.1 NuroChek: SSVEP in concussion

The SSVEP may be a rapid way to assess concussive changes in sideline scenarios, particularly since the use of a VEP (rather than an auditory ERP) is sensitive to the many networks involved in vision and is more suited for loud outdoor environments. To explore a concussion assessment method using SSVEP, Fong and colleagues (2020) used a 14-channel EEG headset and two screens (within a headset-like Google Cardboard frame) that alternated between black and white at a 15 Hz frequency. They determined that the optimum stimulus exposure time to elicit the signal was 30 seconds, and that a priming trial improved the quality of the SNR. Fong and colleagues (2020) identified this signal in 65 non-concussed rugby athletes at baseline (M = 4.80, interquartile range [IQR, for a confidence interval of 95%] = 4.07–5.68). During the study, 12 athletes sustained concussions and demonstrated a decrease in SNR when tested within 72 hours of the concussion (M = 2.00, IQR = 1.40–2.32). Eight of these athletes were available for follow-up once their concussion had resolved (up to 12 days post-injury); their SNR magnitudes had returned to their baselines (M = 4.82, IQR = 4.13–5.18). The differences between these time points were significant.

NuroChek is a portable SSVEP headset whose development was based on this preliminary work. Unlike other EEG/ERP systems, the design of reference electrodes filters out background noise and the use of saline-soaked foam in the electrodes decreases contact impedance, making it easier to use outside of a laboratory setting. The headset interfaces with an iPad (via Bluetooth and NuroChek app) for immediate results, and the batteries of both devices can facilitate a testing session of over 5 hours. Subsequent research validated the EEG quality of the headset against a Grael EEG generator (Fong et al., 2021), and it was approved by the FDA as an EEG device in April 2020. NuroChek was found not to be affected by physical exercise or mental exertion, either in amateur boxers or in people running on a treadmill, or in participants performing a Stroop

inhibition task (Salazar et al., 2021). The NuroChek app automatically performs all processing to calculate the SNR and displays it as both a visual EEG pattern and an SNR value.

### 2.2.2 Use of the 15 Hz frequency

The specific electrophysiological activity at the 15 Hz frequency studied by Fong and colleagues (2020) theoretically represents an aspect of normal communication in specific regions of the brain; in this case, the occipital region located at the back of the head, where many visual signals are processed. In the event of concussion, regional damage can alter or terminate normal brain activity in this pathway, temporarily causing the 15 Hz signal (the neural mirroring of the frequency of the flashing light) to be undetectable or less distinguishable from noise (like nearby brain activity or twitching muscles). Upon recovery from the concussion, normal regional activity resumes and the signal returns to its baseline strength. The 15 Hz frequency falls into the beta band (12–30 Hz), which is characterised by its relationship with alertness or consciousness. Beta band frequencies have shown alterations after concussion, and these are associated with cognitive changes (Coenen & Reinsberger, 2023; Franke et al., 2023). Outside of electrophysiology, when examining cerebral blood flow after mTBI using rs-fMRI blood-oxygen-level-dependent (BOLD) imaging, Tan and colleagues (2023) reported diminished bilateral occipital activation within 12 hours of sustaining a concussion. However, it is not yet understood specifically what neural activity is represented by the 15 Hz signal, or its role in concussive damage and recovery.

Other studies have examined the 15 Hz frequency as a dynamic measure of alertness or consciousness. Pastor and colleagues (2003) found an occipital pattern of resting cerebral blood flow activity that corresponded to the strobing light stimulus; when compared to the EEG data, the occipital 15 Hz activity and a frontal 25 Hz activity demonstrated the highest amplitudes in reaction to the strobing light. Stimuli at 15 Hz and 10 Hz generated higher SNRs when a participant focused on an external stimulus, as opposed to the internal stimulus of counting one's own heartbeats (Kritzman et al., 2022). Takahashi and Tsukahara (1998) studied patients with epilepsy and determined that the target responses were most frequently generated by stimuli at 15 Hz and 20 Hz; however, since they did not include a control group, the signal strength was not described comparatively. The stimulus-evoked 15 Hz activity was also significantly lower in a population with dementia when compared to a control population (Tobimatsu, 2002; Tobimatsu et al., 1994). These studies seem to indicate that the 15 Hz activity is highly

reactive to external stimuli in a healthy population, and support that it may be sensitive to changes in normal brain processing.

## 2.3 Relationship between electrophysiology and concussive damage

### 2.3.1 Over time

An important question for athletes is, what does a lingering electrophysiological deficit mean? Does it mean an athlete is at increased risk of further injury, or worse symptoms? Does it represent symptoms the athlete is concealing, or unresolved cognitive deficits? Or does it mean that neural recovery necessitated long-term changes or adaptations in relevant networks? While many researchers have found evidence of long-term electrophysiological alterations that persist years to decades after injury, few of them have tried to articulate the nuanced line between persistent-but-subtle damage and benign-but-permanent changes, such as re-routing of networks (Clayton et al., 2020; Fickling, Poel, et al., 2021). In some cases, these electrophysiological alterations persist for so long that they are considered permanent reorganisations (Broglio et al., 2011; N. S. King, 2014). For example, different patterns of electrophysiological activity are still seen in retired athletes when compared to control adults (De Beaumont et al., 2009; Fratantoni et al., 2017; Ruiter et al., 2019). Some researchers have even hypothesised that concussion exacerbates or imitates the natural aging process (Broglio et al., 2011; Ledwidge & Molfese, 2016; Thériault et al., 2009), which can also account for electrophysiological differences between age groups. These are important considerations when interpreting electrophysiological changes after injury, especially those that are not accompanied by cognitive or functional deficits.

In addition to acute post-concussive changes (X.-P. Chen et al., 2006; Clayton et al., 2020; Fickling et al., 2019), post-injury ERP assessments can indicate persistent electrophysiological differences during and after recovery. The domain of attention (measured by P300) is particularly important to athletes because it protects them from injury, or re-injury (Fickling et al., 2019; Gosselin et al., 2006). Nandrajog and colleagues (2017) found that the P300 amplitude of concussed participants was significantly lower than control participants both within a week of injury and again at 2–3 months post-concussion, but the amplitudes of the concussed group were not significantly different from each other between the two time points. The P300 component has shown decreases at 5–6 weeks post-concussion (Gosselin et al., 2006; Sicard et al., 2021), and lower P300 amplitude has been observed in concussed-and-symptomatic participants within six months of their injury when compared to control groups (Lavoie et al., 2004). Similarly,

Zhao and colleagues (2018) saw lower N200 and P3b amplitudes in participants up to a month after their concussion when compared to a healthy control group, and Gosselin and colleagues (2006) saw lower N100 and P200 amplitudes at 6 and 15 weeks post-concussion. The findings that these deficits persisted beyond the return-to-baseline for symptoms and cognitive measures lends support to the idea that concussion may take more time to resolve than symptomology and cognition alone suggest (Kara et al., 2020; Nandrajog et al., 2017).

While some ERPs have shown correlations with symptom severity (Dupuis et al., 2000; Lavoie et al., 2004; Sicard et al., 2021; Thériault et al., 2009), the relationship is not yet well understood. When examined by field position, the ERP decreases seen by Richards (2017) were only correlated with severity of symptoms reported in one of three groups (the linemen, who receive the most subconcussive impacts by nature of their positions). De Beaumont and colleagues (2007) did not find injury severity (recorded as loss of consciousness or post-traumatic amnesia) to be correlated with changes to P300 amplitude. The differences in brain network activation seen by Reches and colleagues (2017) between the concussed and non-concussed participants could be related to symptom severity, or they may represent other non-related changes from baseline. Thus, some ERPs may be related to the severity of symptoms, or alternately to a third underlying process that causes both the ERP change and the symptoms (Donchin, 1981). Since recovery of symptoms or cognitive deficits does not always correlate to recovery of ERP deficits (Broglio et al., 2009; Clayton et al., 2020; Fratantoni et al., 2017; Gosselin et al., 2012; Hudac et al., 2018; Kozak, 2018; Ledwidge & Molfese, 2016; Olson et al., 2018; Ozen et al., 2013; Thériault et al., 2011), the addition of an ERP protocol to recovery assessments may be useful in tracking these post-injury changes, especially when considering an athlete's RTP (Broglio et al., 2011).

Although ERPs can show persistent alterations over time, the time since injury does not widely correlate with ERP changes (Boshra et al., 2019; Dupuis et al., 2000; Hudac et al., 2018; Lavoie et al., 2004; Ledwidge & Molfese, 2016; Moore, Broglio, et al., 2014), though they may still be related (Folmer et al., 2011). In one study using a working memory task (Gosselin et al., 2012), time since injury was correlated with larger N350 amplitude (in the left anterior region only), and while time since injury did not correlate with overall symptomology, more severe depressive symptoms were correlated with a smaller P300. Differences may be present over longer periods of time, as Theriault and colleagues (2009) saw significant differences in P3a and P3b between a recently-concussed group (within 5–12 months) and control group, but did not detect the same

difference between the control group and a group who were concussed 22–60 months prior. De Beaumont and colleagues (2007) also saw a trend between changes to P300 amplitude and time since last concussion, especially in athletes who had sustained multiple concussions. Time since injury is an important piece of the puzzle when using electrophysiology to better understand concussion recovery, and it can provide important clues about the persistence of post-injury changes.

### 2.3.2 Factors that affect electrophysiology

#### 2.3.2.1 Historical concussions

Sometimes the neural injury or compensatory changes made to neural networks from a historical concussion can persist beyond recovery and become permanent, independent of cognitive functioning (X.-P. Chen et al., 2006; Gaetz & Weinberg, 2000; Sicard et al., 2021). Despite no discernible cognitive deficits years after a concussion, these individuals may still exhibit differences in ERPs that indicate persistent or chronic concussion-induced change (Broglio et al., 2009; Carrier-Toutant et al., 2018; De Beaumont et al., 2007; Hudac et al., 2018; Ledwidge & Molfese, 2016; Olson et al., 2018; Ozen et al., 2013). Such differences can exist even if the previously concussed individual never complains of any symptoms, but they are often greater if an individual is more symptomatic (Thériault et al., 2009). Decreases in amplitude after a concussion are interpreted as fewer available cognitive resources or inefficiency in allocating them (Broglio et al., 2011; Guth et al., 2018; Ozen et al., 2013), while increases are interpreted as the recruitment of extra cognitive resources to meet the increased demands, often despite equivalent performances on neuropsychological measures (Hudac et al., 2018; Ledwidge & Molfese, 2016; Olson et al., 2018). Such changes to networks or processing strategies can act as a neural marker for concussion history (Ledwidge, 2018; Ledwidge & Molfese, 2016; Olson et al., 2018; Reches et al., 2017), and can even be seen in athletes who retired 30 years ago or more (De Beaumont et al., 2009; Fratantoni et al., 2017; Ruiter et al., 2019).

P100 is an early ERP component associated with interpreting visual stimuli. While some studies using P100 have found recovery during the sub-acute period (X.-P. Chen et al., 2006; Papathanasopoulos et al., 1994), others have reported mixed results in the years after injury. Using a facial expression recognition task, Carrier-Toutant and colleagues (2018) saw decreased P100 amplitude in those who experienced a concussion an average of two years prior, when compared to the non-concussed group. Moore and colleagues

(2014) also found comparatively lower[9] P100 amplitude in university athletes who had sustained a concussion an average of 6.7 years earlier, although the reduction was not correlated with time since injury. In contrast, Hudac and colleagues (2018) found higher P100 and P300 amplitudes in participants with a history of one to four concussions (an average of three years post-injury) when compared to the control group. Alterations to P100 might be rehabilitative after concussion with an optometric exercise regimen (Freed & Hellerstein, 1997).

The most significantly altered component in long-term concussion is P300, and a strong body of evidence supports decreased P300 amplitude in individuals with a concussion history at two years or more after injury, with or without corresponding symptoms or cognitive deficits (Broglio et al., 2009; Brush et al., 2018; Cavanagh et al., 2019; De Beaumont et al., 2007; De Beaumont et al., 2009; Moore, Hillman, et al., 2014; Moore et al., 2017; Ozen et al., 2013; Parks et al., 2015). While those with a previous concussion often exhibit smaller ERPs, some studies (Hudac et al., 2018; Ledwidge & Molfese, 2016; Olson et al., 2018) have found larger ERPs in the concussion history groups than in the never-concussed groups. Ledwidge and Molfese (2016) saw higher N200 and P3b amplitudes in participants at an average of four years post-injury when compared to a non-concussed group (despite equivalent cognitive performances), which they attributed to an increase in resource allocation for context updating. Higher amplitudes of P100 and P300 found by Hudac and colleagues (2018) were similarly attributed to permanent compensatory strategies of attentional allocation. N200 has also shown evidence of long-term impairment, often as higher amplitude than control groups (Broglio et al., 2009; Moore, Hillman, et al., 2014; Moore et al., 2015; Olson et al., 2018). Olson and colleagues (2018) saw increases of the N200 component in athletes with a history of concussion at an average of 30 months post-injury, despite performing equivalently with the non-concussed group on the cognitive measures. The differences in direction of change may be due to the use of different methods used to elicit the components or inconsistencies in the post-injury intervals across studies.

Repeated concussions can cause long-term and potentially cumulative electrophysiological changes (Broglio et al., 2011; Carrier-Toutant et al., 2018; De Beaumont et al., 2007; Gaetz et al., 2000; Gosselin et al., 2010; Pearce et al., 2021; Pontifex et al., 2009; Sicard et al., 2021; Slobounov et al., 2009; Thériault et al., 2009; Thériault et al., 2011). Thériault and colleagues (2009) found decreased amplitudes of

[9] Lower than non-concussed control participants with similar demographic characteristics.

P3a and P3b in asymptomatic athletes with a history of multiple concussions when compared to a control group, but only in the recently concussed group (within one year) and not in the long-term group (two or more years); this led them to conclude the P3 attenuation may be transient. Thériault and colleagues (2011) further found that a history of three or more concussions (at an average of 22.6 months since the last concussion) was correlated with significantly lower amplitudes of the sustained posterior contralateral negativity component, when compared to no concussion history and one to two previous concussions (with an average of 27 months since the last concussion); this decrease persisted even when they controlled for post-concussion symptoms. Similarly, participants in another study (Moore et al., 2017) with an average of two years since their last concussion demonstrated a correlation between lower N100 and estimated number of previous concussions. Multiple concussions could also cause unique interactions between electrophysiology and other types of post-injury changes. Pontifex and colleagues (2009) found an inverse relationship between number of previous concussions sustained by participating athletes and ERP amplitude during a flanker task (a measure of inhibition and processing speed). Sicard and colleagues (2021) found decreased P3b amplitude in symptomatic athletes with a history of multiple concussion, which correlated inversely with the number of previous concussions and was also related to increased depressive symptoms. Repeated concussions may amplify the electrophysiological evidence of these subtle-but-persistent changes for years after the last injury.

Though many studies have found evidence of persistent electrophysiological changes in individuals with a history of concussion, the consequences of these differences are not clear. Future research is needed to understand the relationship between the duration and severity of these changes over time, and to determine other effects or deficits that are associated with these changes. Sensitivity to previous concussion is a concern for methods that will be used in concussion assessment, and it is important to understand any effects they may have on electrophysiological readings.

#### 2.3.2.2 Sex differences

As Fong and colleagues (2020) studied an all-male population, no studies have yet examined sex differences in concussion using SSVEP. Additionally, very few studies have examined the electrophysiological effects of concussion by sex using ERPs (Baker, 2008; Carrier-Toutant et al., 2018; Covassin et al., 2018). A thesis by Baker (2008) found greater sex differences in P300 amplitudes and latencies in non-concussed athletes than concussed athletes when using auditory ERPs, but these differences were not discussed

in depth. Only one ERP measure (P300 amplitude on the right side) was significantly different between concussed female and male college athletes during cognitive tasks (Baker, 2008). Carrier-Toutant and colleagues (2018) fitted previously-concussed and never-concussed participants with EEG caps and then asked them to identify facial expressions on cards (angry, happy, or neutral) as quickly as possible; they found that female and male athletes with an average of two years since their concussion demonstrated a suppression of the visual P100 signal in the right hemisphere, but not the left. Female athletes outperformed male athletes, in the concussed groups and overall, at identifying facial expressions while the concussed male athletes showed a suppressed N100 amplitude that was not seen in the concussed female athletes (Carrier-Toutant et al., 2018). Because of the differences in these methodologies and groups of interest, it is difficult to interpret how the interaction of concussion history and sex may present in electrophysiology.

Outside of concussion, many studies have found larger SSVEP responses in female participants when compared with male participants. Wada and colleagues (1994) studied sex differences in photic stimulation at 10 Hz, and they found that female participants exhibited higher amplitudes than the male participants across the EEG spectrum. Skosnik and colleagues (2006) used a flickering light on a computer screen to study cannabis use and sex differences, and they found that female participants had stronger SSVEP signal amplitude than male participants overall. When examining patients with and without schizophrenia, Krishnan and colleagues (2005) found sex differences in SSVEPs; specifically, female participants had stronger signal amplitudes than male participants at different sites along the sagittal midline plane of the skull (Oz and Fz sites), but they found no interactions between sex and the groups with or without schizophrenia. Similarly and also in patients with schizophrenia, Wada and colleagues (1995) found larger amplitudes in female than male participants at the Oz site during an eyes-closed flickering light, but no interaction between sex and schizophrenic condition. These SSVEP differences may be due to anatomical (thickness of skull/biological layers) or functional (hormonal/metabolic) differences between females and males (Hausinger & Pletzer, 2021; Hu et al., 2013; Skosnik et al., 2006; Wada et al., 1994).

Using oddball paradigms, ERP components reveal other patterns of sex differences. For example, Gölgeli and colleagues (1999) used an auditory oddball paradigm and found that male participants demonstrated higher amplitudes of joint components N100–P200 and N200–P300 than female participants. Vaquero and colleagues (2004) used a visual oddball paradigm to study sex differences in visual attention and found sex differences in

many of the components they studied; while they similarly reported that male participants had higher amplitudes of P100 and P300 than female participants, they found that female participants presented a regionally (left temporal) higher N100 amplitude than male participants. They additionally reported a more temporal/parietal/posterior localisation for P300 in female participants, and a more central/parietal localisation for P300 in male participants, which may indicate that women and men employ different attentional and information processing strategies (Vaquero et al., 2004). Also using a visual oddball paradigm, Guo and colleagues (2019) studied sex differences in several ERP components of migraineurs, and while they found no sex differences in the healthy controls, they did find sex differences in the migraineurs: female participants demonstrated lower ERP amplitudes and more impairment of visual attention than the male participants. Further, semantic processing tasks in other studies have elicited higher N400 amplitudes in female participants, suggesting that language processing and semantic priming take slightly different forms in female and male brains (Daltrozzo et al., 2007; Wirth et al., 2006). More research is needed to understand the electrophysiological differences between brains of different sexes during different tasks, especially when considering the use of electrophysiology as an objective concussion assessment method.

## 2.4 Advantages and limitations of SSVEP/ERP use

### 2.4.1 Advantages

Physiological assessment methods to assess concussive damage objectively (such as the SSVEP, ERP, and EEG) would be considerably superior to the current methods of symptom reporting and clinical assessment because it would directly assess neural damage, rather than estimating it from subjective methods that can easily be manipulated. ERP technology can be quite portable and deliver rapid results. Although many ERPs are collected with a 64- or 128-channel electrode net, significant changes can be identified using a single electrode site (Lesiakowski et al., 2018; Nandrajog et al., 2017). ERPs are not vulnerable to habituation, rehearsal, or a practice effect (Donchin, 1981). They provide a measure of neural activity that is reliably associated with the external stimuli (Norcia et al., 2015), and while some EEG-based concussion assessment methods are affected by exercise (Devilbiss et al., 2019), the SSVEP calculated by NuroChek is reported not to be affected by physical or mental fatigue: Salazar and colleagues (2021) found no difference in participants who were tested before and after physical or mental exertion (boxing, running, and performing a Stroop inhibition task, respectively).

ERPs can also measure electrophysiological changes across time, which makes them useful for evaluating recovery (Broglio et al., 2011; Folmer et al., 2011), specifically to identify persistent damage in otherwise asymptomatic patients. When concussed but asymptomatic athletes (Gosselin et al., 2006; Kontos et al., 2016; Lavoie et al., 2004) and subconcussed athletes (Moore et al., 2017) have been compared to concussed-and-symptomatic and healthy control athletes, their electrophysiological profiles more closely resemble the symptomatic athlete than the healthy athlete. These lingering physiological deficits have important implications for considering an athlete's brain health, as well as the overall definition of concussion itself (Kozak, 2018).

When compared to other neurophysiological measures, the SSVEP, ERP, and EEG are less expensive to perform than common imaging methods (fMRI, MRI, DTI) and are relatively non-invasive, especially when compared to the pursuit of biomarkers of concussive changes in CSF or blood. The objective nature of this assessment method could also help a patient claim necessary aid if significant impairment can be demonstrated (Nandrajog et al., 2017). SSVEPs are specifically useful in populations who are unable to provide subjective information, like infants or individuals in comas (Norcia et al., 2015). ERPs can also be used to assess function and estimate prognosis of coma patients (Duncan et al., 2003; Folmer et al., 2011; Mazzini, 2004). While damage from moderate/severe TBIs is better determined by other methods like traditional imaging, ERPs may be specifically useful in mild TBIs because of the subtlety of the damage (Dockree & Robertson, 2011).

Many visual pathways in the frontal and temporal lobes can be vulnerable to concussive damage because these regions sustain high amounts of impacts in sport (Molloy et al., 2017; Rizzo et al., 2016). This could mean that methods using visual stimuli are particularly sensitive to concussive damage. Other vision problems after concussion can include blurred or double vision, convergence insufficiency, spatial deficits, weakening of focal muscles in eye, changes in eye alignment, uneven eye use, or eye strain (Armstrong, 2018; Norcia et al., 2015; Scheiman et al., 2017; Urosevich et al., 2018). Visual stimuli are also easier than auditory stimuli to isolate in sideline scenarios with loud background noise. Gaetz and Weinberg (2000) found the visual oddball paradigm to be more sensitive to post-concussive deficits than the auditory oddball, and other researchers have found that the visual oddball paradigms may also be specifically sensitive to the differences between symptomatic and asymptomatic concussed athletes (Dupuis et al., 2000; Gosselin et al., 2006; Lavoie et al., 2004).

The shorter time of administration also makes SSVEP more appropriate for sideline use. For a rapid assessment, the concentrated stimulus exposure of the SSVEP is superior to the traditional ERPs, which use shorter exposure periods and measures brain activity across regions in real time, producing a signal with more background "noise" in the signal. Two trials of the NuroChek headset can be performed in under five minutes; in contrast, the original 18-minute audio protocol used by Clayton and colleagues (2020) was shortened to four minutes to keep athletes from falling asleep during the test.

### 2.4.2 Limitations

The specific relationship between the different aspects of concussive damage is still unclear. Electrophysiological, cognitive, and symptom recovery do not always correlate with each other, and recovery of one does not mean that recovery of the others can be assumed. Because electrophysiological processes are invisible, they can only be approximated by abstract associations with cognitive domains. Many studies have found ERP deficits with no corresponding neurocognitive deficits, but this does not definitively mean the ERP deficits are evidence of prolonged concussion physiology. ERPs may be associated with symptoms or cognitive deficits to some degree (Dupuis et al., 2000; Lavoie et al., 2004; Reches et al., 2017; Richards, 2017; Sicard et al., 2021), and time since injury may also be correlated with ERP results (De Beaumont et al., 2007; Folmer et al., 2011; Reches et al., 2017), though many studies have not found this (Boshra et al., 2019; Dupuis et al., 2000; Hudac et al., 2018; Lavoie et al., 2004; Ledwidge & Molfese, 2016; Moore, Broglio, et al., 2014). The practical implications of these invisible cognitive deficits are not yet well understood (Broglio et al., 2011), and the variety of methods used in ERP research makes interpretation of each study nuanced, and it is difficult to apply their specific broadly (Brush et al., 2018; Folmer et al., 2011).

Many factors can affect the signal strength of the SSVEP or ERP. SSVEP magnitude can be affected by distraction, such as when the participant's attention is directed inward to counting their heartbeats (Kritzman et al., 2022). ERP amplitude can also be affected by many individual factors, including age (Baillargeon et al., 2012; Gaetz & Weinberg, 2000; Mitchell et al., 1987), skull or hair thickness (Adrian & Matthews, 1934), genetics (Guth et al., 2018), history of mood disorders (Campanella et al., 2012; Olson et al., 2018; Sumich et al., 2014), or migraines (Guo et al., 2019; Kontos et al., 2016), and sensory function or medications taken (Folmer et al., 2011). EEG can also be affected by metabolic factors such as blood sugar (An et al., 2015). Further, components like P300 are non-specific markers of cognitive function (Cavanagh et al., 2019; Clayton

et al., 2020; Polich, 2007) and can be affected by testing modality or stimulus used (Duncan et al., 2003). Additionally, because of differences in neural organization and activation, sex differences in SSVEP/ERP are not well understood (Gasbarri et al., 2006; Krishnan et al., 2005; Skosnik et al., 2006; Wada et al., 1995; Wada et al., 1994).

Lastly, electrophysiology is only one piece of the puzzle. When ERP/EEG signals are measured on the scalp (through the resistance of the skull), they can provide excellent temporal resolution, but poor spatial resolution concerning the precise source of signal (Brush et al., 2018; Olson et al., 2018). As Adrian and Matthews (1934) described the shortcomings of using surface electrodes: *"It can give a bird's-eye view, so to speak, of the cortical activity, showing the average potential changes of large areas but nothing of the local detail"* (p. 376). In contrast, SSVEPs have better spatial resolution and poorer temporal resolution because of the periodic and time-locked nature of exposure to the stimulus (Norcia et al., 2015), which concentrates the signal. However, the resulting SNR value is only a measure of signal intensity. ERPs should not be used alone as an assessment measure, but should be considered as a tool to guide decision-making (Gosselin et al., 2006) and used in combination with other behavioural or functional assessment tools (Reches et al., 2017; Slobounov et al., 2012).

## 2.5 Summary and gap in research

Accurate identification of concussion and early access to treatment leads to better recovery outcomes (Barnhart et al., 2021; Eagle, Collins, et al., 2020; Forrest et al., 2018; Kontos et al., 2020) and reduces the risk of subsequent damage. Unidentified concussions are a primary concern for athletes, as a second impact while an individual is still symptomatic (or even asymptomatic but still vulnerable) could cause severe brain damage or death (Bey & Ostick, 2009; Wetjen et al., 2010). In addition, recovery from concussion cannot be assumed upon self-reported symptom resolution and return to neuropsychological baselines alone; the physiological damage must heal as well.

Despite the growing body of knowledge on the dangers of concussion, second impacts, and the importance of complete recovery (Christoforou et al., 2020; McCrea et al., 2015; McCrory et al., 2017), there remains no widely viable option for rapid and objective screening for concussion or tracking recovery. An objective, validated, and reliable tool for diagnosing concussion would be of great relevance to athletes, those managing their care, and the field of sport-related concussion as a whole. Such a measure could also offer guidance on return to "normal" activities, or help to justify an individual's eligibility for medical benefits or treatment.

Electrophysiology, or the study of electrical activity in the brain, shows some non-invasive utility in identifying regional or temporal changes to neuroelectric communication networks. Electrophysiological changes or deficits have been detected in athletes who have recovered from cognitive and physical symptoms of their concussion (Clayton et al., 2020), or when previously concussed athletes are compared to never-concussed control participants (Broglio et al., 2009; Fratantoni et al., 2017; Ledwidge & Molfese, 2016; Olson et al., 2018; Ozen et al., 2013; Thériault et al., 2011). ERPs remain sensitive to persistent changes after a person has demonstrably recovered from concussion, and they may be useful in estimating symptom severity and predicting outcomes from concussion (Cavanagh et al., 2019). Concussed and control participants often show electrophysiological differences despite equivalent performances on neurocognitive assessments; this may be an indication that concussed brains recruit additional resources to mask the power deficiency, and it may also explain why functional resolution of symptoms is often faster than physiological recovery from the injury (Teel et al., 2014). Similarly, athletes with a history of concussion can show a different electrophysiological activation pattern than control athletes with no history of concussion, suggesting that they rely on different resources or networks than uninjured brains (Hudac et al., 2018). It is not yet clear what percentage of people with previous concussions exhibit the changes discussed in this review, or the ranges of severity.

One electrophysiological method uses a flickering visual stimulus to generate an SSVEP, measured in the form of an SNR, to determine relative signal strength of the target brain activity (Fong et al., 2020; Kritzman et al., 2022; Norcia et al., 2015; Salazar et al., 2021). SSVEP may be useful in the assessment of concussion: in a study using a flickering light on a smartphone LCD display in a Google Cardboard headset frame and an EEG cap, Fong and colleagues (2020) measured the baseline SNR of 65 non-concussed athletes. When the athletes were routinely tested within 48 hours of a match, 12 athletes were identified as being concussed because they demonstrated alterations in the induced brain activity; these alterations were no longer present when 8 of the 12 athletes that were available were retested following recovery. Visual stimuli have the added advantage of being easier to isolate in realistic testing scenarios like a sideline, although the sideline noise can still cause interference in SSVEP tests by increasing background activity.

## 2.6 Current studies

Steady-state visual-evoked potentials may be useful in the assessment of concussion. With flashing lights and occipital surface electrodes, the NuroChek system

was designed as a non-invasive method of rapid concussion testing (Fong et al., 2020; Fong et al., 2021). While the SNR has shown itself to be sensitive to the presence or absence of concussion, its utility and limitations are still largely unknown. The present studies seek to examine the SNR as a neural marker of concussive damage, and to evaluate the utility of the NuroChek headset system as a supplementary assessment and monitoring tool for use during the acute and recovery phases of concussion. The first study focuses on assessment of athletes with concussion and repetitive impact exposure. The second study focuses on the electrophysiological differences in non-concussed athletes by concussion history, sex, and repetitive impacts. This research also examines the effects of concussion history and sex on the SNR. The final discussion chapter evaluates the NuroChek system for its use in concussion assessment of athletes by the criteria of overall accuracy (validity + reliability) and accessibility of use.

This research includes two studies that examine the SNR in athlete populations by differential degree of head injury:

- **Study A: Changes to SNR in concussed male athletes** focuses on the assessment of concussion and recovery of concussive damage in male rugby athletes by SNR.

- **Study B: SNR and concussion history, gender, and repetitive impacts** focuses on the analysis of SNR data from non-concussed participants, particularly regarding concussion history and sex. It then examines the effects of repetitive impacts sustained acutely by combat athletes, and over time in rugby athletes.

To evaluate the NuroChek system for its use in concussion assessment and management, the specific **aims** of these studies are to:

1. Determine if the NuroChek system and SNR variable can assess concussion (or repetitive impacts) **acutely**.
2. Establish how the NuroChek system and SNR variable may change during concussion **recovery** and the remainder of the season (in concussed and non-concussed athletes).
3. Identify any effects that **history of concussion** or **sex** may have on SNR magnitude or trajectories in non-concussed athletes and control participants.
4. Identify any effects that **repetitive impacts** may have on SNR magnitude or trajectories in non-concussed athletes.

# Chapter 3

# Methods and Materials

This chapter contains details of the methods and measures used across all studies. The three participant populations are described in detail below, followed by a description of the NuroChek system and headset, including the primary outcome variable and the studies using it that have already been published. The other cognitive measures used are also described, as is the testing protocol and timeline. Finally, the statistical approach section describes the analyses used to make comparisons between and within groups.

## 3.1 Participants

Data were collected from three participant populations: rugby athletes, combat athletes, and non-athlete control participants. Ethical approval, sample sizes, and demographic information are reported for each group. Participants were excluded if they were under 17 years or reported epilepsy, history of seizures, history of fits or unexplained fainting, light sensitivity, uneasiness about the flashing lights, a current migraine, or legal blindness.

### 3.1.1 Rugby athletes

Approval was obtained from the University of Waikato Human Research Ethics Committee (2019#10) in March 2019 (Appendix 9.1.1) and from the Medical & Science Advisory Panel for NZ Rugby (Appendix 9.1.2); an out-of-scope letter obtained from the Health and Disability Ethics Committee is also attached (Appendix 9.1.3). Athletes were recruited from nine rugby teams in the Bay of Plenty Rugby Union: two academy-level, five community, and two semi-professional teams.

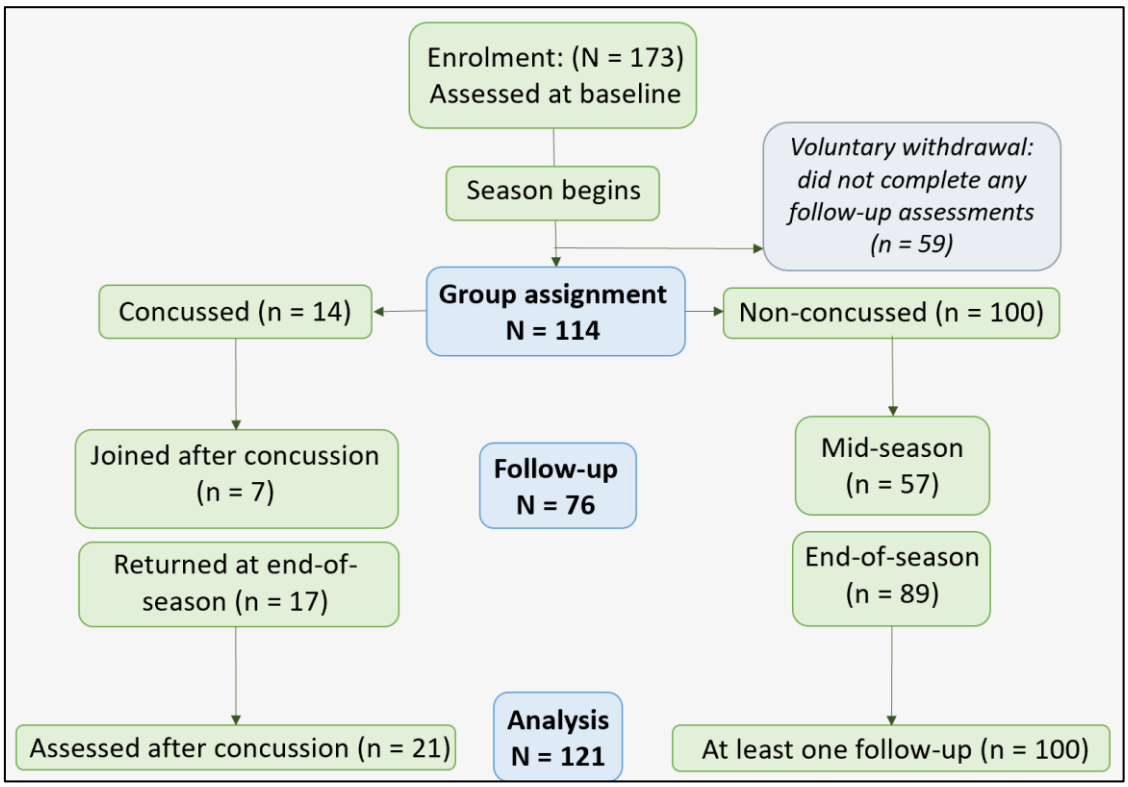
Table 3.1: Demographic information of rugby athlete by time point.

| | **Overall N=** | **BL N=** | **MS N=** | **EOS N=** | **Age M (SD)** |
|---|---|---|---|---|---|
| All | 121 | 114 | 66 | 106 | 23.05 (5.34) |
| Concussed | 21 | 14 | 9 | 17 | 23.33 (3.84) |
| Non-concussed | 100 | 100 | 57 | 89 | 22.99 (5.62) |
| Female | 36 | 36 | 17 | 30 | 23.11 (5.28) |
| Male | 85 | 78 | 49 | 76 | 23.02 (5.39) |
| Previous concussion | 79 | 72 | 48 | 67 | 23.24 (5.37) |
| No concussion history | 42 | 42 | 18 | 39 | 22.69 (5.33) |

*BL- baseline; MS- mid-season; EOS- end-of-season; M- mean; SD- standard deviation.*

In total, 121 rugby athletes consented to participate and were assessed with the headset at least twice during the season.[10] Table 3.1 presents the demographic and concussion history information for the groups at each time point, and Figure 3.1 summarises the participants' entry and exit points from the study. The distribution of age ranged from 17–38 years and showed a unimodal bias toward younger age, with an overall average age of 23.05. Ethnicity was reported only in the second year of data collection, by 53 of the 124 athletes. When multiple ethnicities were reported (n = 21), priority was assigned to Māori, then NZ European, then Pasifika identities. These athletes reported their ethnicities as Māori (n = 36; 67.9%), NZ European (n = 10; 18.9%), Pasifika (n = 3; 5.7%), and other European (n = 4; 7.5%).

Figure 3.1: Participant totals by entry and exit points.




Twenty-one male athletes were determined to be concussed by the team physiotherapist during the study, constituting 24.7% of the male population and 17.4% of the study population. The average age of the concussed athletes was 23.3 years, and all but two reported at least one previous concussion. The diagnosis of concussion was confirmed by a doctor in five athletes. Nineteen of these athletes completed at least two post-injury assessments, though not all of them completed the end-of-season assessment. Nine athletes joined the study after their concussion and did not have a baseline; two of

[10] Some athletes (23 male and 6 female) participated in both years of the study; they are included twice in this total and are examined in more detail in section 5.3.3.3.2.

these athletes sustained two concussions each during the season and were assessed several times after each injury.

Of the athletes tested at baseline, 100 did not sustain a concussion, and returned for at least one other time point (at mid-season or end-of-season). These athletes were asked verbally to report any big hits, suspected concussions, or other head injury at the follow-up assessment points. In addition to the primary groups of concussed or not, the non-concussed rugby athletes were further divided into more specific impact exposure groups based on these reports. To examine the electrophysiological effects of repetitive impacts over a season, they were coded into four groups: a confirmed concussion, an undiagnosed concussion or a big hit followed by concussion symptoms, regular impact exposure, and limited impact exposure. The shortest season was in the female semi-professional athletes, who were tested 6–8 weeks apart. The longest duration between baseline and end-of-season was eight months, seen in the male club and academy athletes.

### 3.1.2 Combat athletes

Approval was obtained from the University of Waikato Human Research Ethics Committee (2021#86) in December 2021 (Appendix 9.1.4). Combat athletes were recruited from local gyms at which clients practiced sparring, with and without head impacts. Boxers receive many punches to the head over a round of sparring, while participants of Brazilian Jiu Jitsu (BJJ) do not. Instead, BJJ requires slow, controlled movements designed to decrease the momentum of one's opponent, and hits to the head during a sparring session are not common.

Combat athletes (with and without exposure to repetitive impacts) were assessed before and after a sparring round, 20 of whom provided electrophysiological data. The impact group consisted of 11 boxers, and 7 of the no-impact athletes were recruited from BJJ; the remaining athlete participated before and after a cardiovascular "drill bootcamp" solo workout program. The boxers reported training an average of 21 times per month, while the BJJ athletes reported training an average of 14 times per month. Other characteristics of the 19 athletes can be found in Table 3.2. Ages ranged from 21–54 years, for an overall average age of 31.8 years. Ethnicities were again NZ-prioritised, and these athletes reported their ethnicities as NZ European (n = 10; 52.6%), Māori (n = 4; 21.1%), Latin American (n = 3; 15.8%), Asian (n = 1; 5.3%), and other European (n = 1; 5.3%).

Table 3.2: Demographics of combat athlete groups.

| | N= | Age M (SD) | CH n= |
|---|---|---|---|
| Overall | 19 | 31.76 (9.42) | 7 (36.8%) |
| Impacts | 11 | 29.18 (8.98) | 7 (63.6%) |
| No impacts | 8 | 35.31 (9.40) | 0 |
| Female | 7 | 36.96 (7.52) | 3 (42.9%) |
| Male | 12 | 28.72 (9.34) | 4 (33.3%) |

*CH- concussion history.*

### 3.1.3 Non-athlete control group

Approval was obtained from the University of Waikato Human Research Ethics Committee (2021#08), and amended in April 2022 (Appendix 9.1.5). A group of 17 non-athlete control participants were recruited from Tauranga noticeboard groups on social media. Due to recruitment difficulties and a limited timeline, this group only completed the headset assessment at one time point. The demographic information of these participants is reported in Table 3.3. Ages ranged from 20–39 years, with an overall average age of 30.9 years. Ethnicities were again NZ-prioritised, and were reported as NZ European (n = 7; 41.2%), other European (n = 4; 23.5%), Māori (n = 3; 17.6%), Asian (n = 2; 11.8%), and Latin American (n = 1; 5.9%).

Table 3.3: Demographic information of control participants.

| | N= | Age M (SD) |
|---|---|---|
| All control | 17 | 30.87 (6.44) |
| Female | 6 | 31.16 (7.60) |
| Male | 11 | 30.70 (6.08) |
| No concussion history | 7 | 31.22 (6.78) |
| Previous concussion | 10 | 27.60 (11.34) |

## 3.2 Materials

Participants completed the demographic questionnaire, then underwent the NuroChek protocol and a cognitive measure. Due to a protocol change in the cognitive measures used by the NuroChek team,[11] rugby athletes in 2020 were tested using the King–Devick test (K-D), and in 2021 using the Sport Concussion Assessment Tool, version 5 (SCAT-5). Athletes in the repetitive impact study were assessed with the symptom inventory and digit span subtests of the SCAT-5, as well as the Trail-Making Test form B (TMTb). The non-athlete control group completed all included measures (NuroChek, all SCAT-5 subtests, K-D, and TMTb).

[11] See Section 8.5.2.1 for more information on this change.

### 3.2.1 Screening and demographic questionnaire

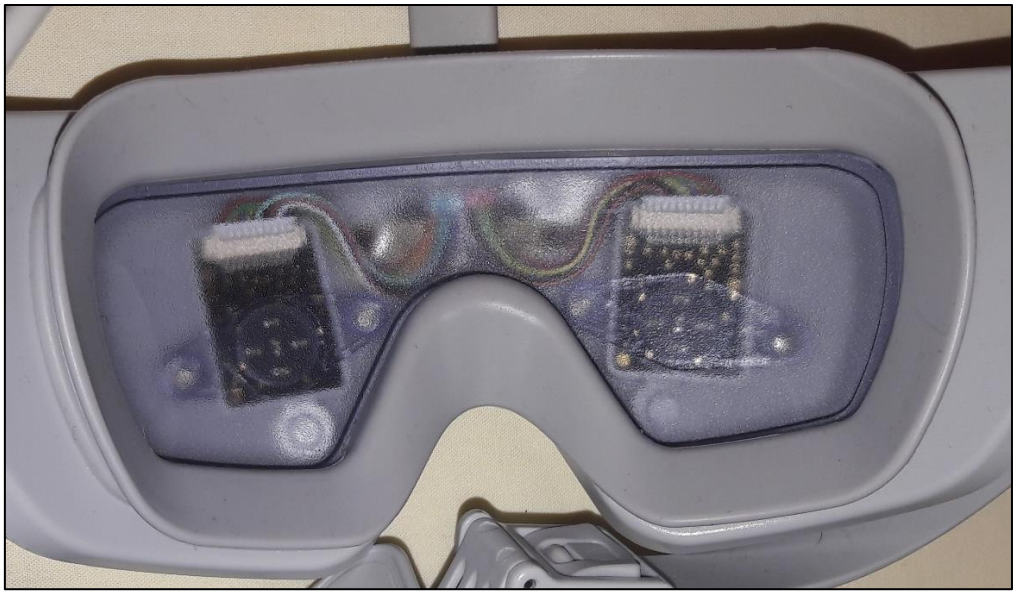
At the first assessment point, participants completed a demographic form (Appendix 9.2.2) that contained the screening criteria and questions about gender, age, previous concussions, ethnicity, and if English was their first language. Female participants in the second year reported any use of hormonal contraceptives and the first day of their last period.

### 3.2.2 NuroChek headset

The NuroChek headset was developed following a pilot study using an EEG headset and a 15 Hz flickering light on a smartphone LCD display inside a Google Cardboard frame; Fong and colleagues (2020) successfully generated a corresponding spike of 15 Hz activity in the occipital region of 65 non-concussed athletes. All participating athletes were assessed within 48 hours of a match, and 12 athletes with medically diagnosed concussions demonstrated alterations of the evoked brain activity. Eight of these athletes were retested following their return to full contact practice, (at least 12 days after injury), and the activity had returned to its baseline strength. After this proof-of-concept, the current headset design was developed, with a visor to administer the visual stimulus and a back panel with occipital target electrodes and two reference/ground points (to control for "background noise" of nearby but unrelated cortical activity). When compared to a clinical-grade Grael EEG amplifier with the standard 128 channels, it performed equivalently (Fong et al., 2021). This design obtained FDA approval for use as an EEG device in April 2020. Readings were found to be uninfluenced by the acute effects of physical or mental fatigue (Salazar et al., 2021). Three headset units were used sequentially during this study.

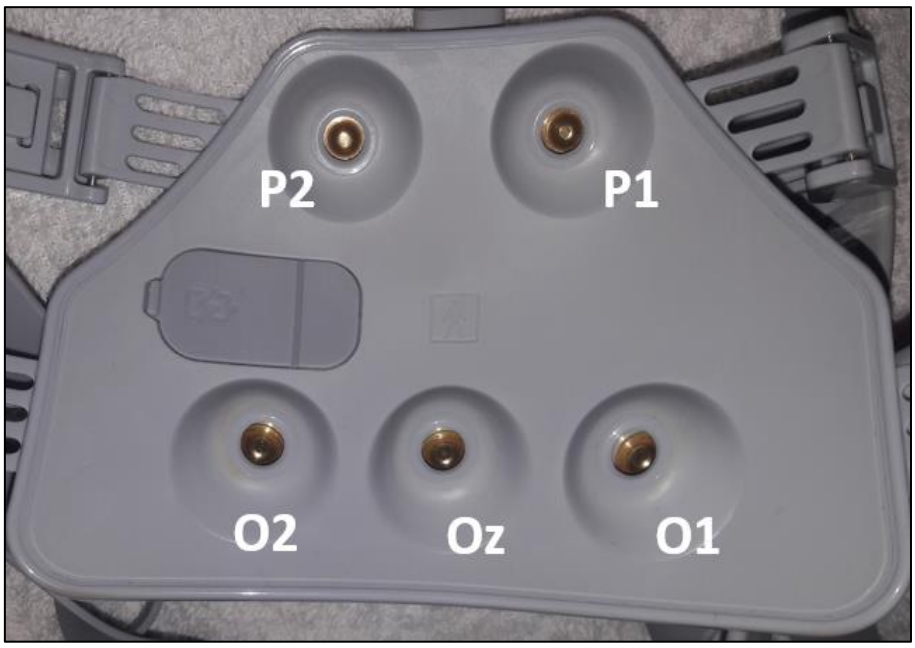
Figure 3.2: NuroChek EEG headset.

Figure 3.3: The inside of the NuroChek visor.



The headset is pictured in Figure 3.2. A visor houses LEDs that flicker at a rate of 15 Hz directly into the participant's eyes (Figure 3.3), and the EEG electrodes on the back panel send the evoked signals and background activity to the NuroChek app (run on a dedicated iPad), which transforms the signals and calculates the SNR. From left to right, the bottom row of target electrodes at the O2, Oz, and O1 positions are located below the ground (P2) and reference (P1) electrodes (Figure 3.4). Data from the NuroChek headset and app are stored in the encrypted and secure online database OpenClinica. Participant confidentiality was preserved by assigning all participants a unique code under which their data was stored in the app, so that no identifying information was entered into the NuroChek app.

Figure 3.4: NuroChek electrode locations.

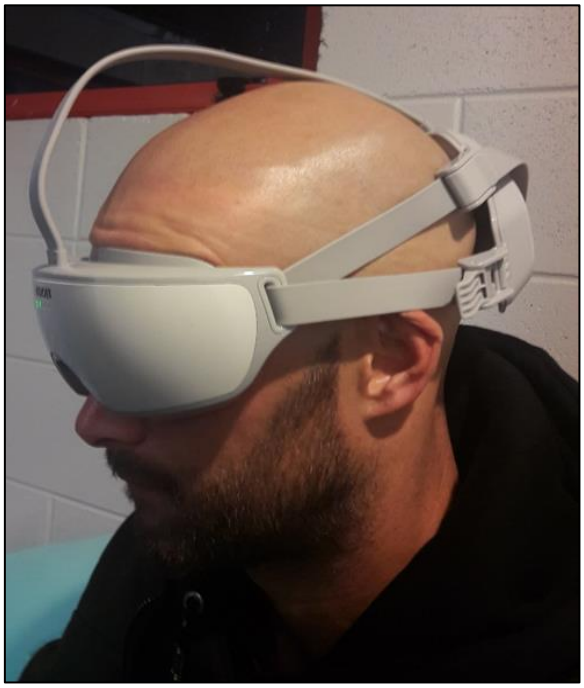


#### 3.2.2.1 Protocol

Foam cylinders were inserted into the electrode holes and moistened with medical-grade saline (0.9%). The headset was fitted to the participant, with the Oz electrode positioned one finger width directly above the occipital inion, the maximal localization for the target activity (Figure 3.5). Athletes received the following instructions:

> The lights will flash for 30 seconds, then a brief pause, then another 30 seconds. Then I will take the headset off and re-fit it, then I will run it again for another set of two. Look as close to the lights as you can without giving yourself a headache, and try not to move or talk while the test is running, unless you need me to stop the test.[12]

Figure 3.5: Headset fitted to participant.



The test began when all three electrodes were conductive with minimal impedance (as indicated by the app), and was comprised of an initial 30-second exposure to the flashing light to prime the participant, 10–15 seconds of rest, and then a 30-second exposure during which the signal was recorded and analysed. The headset was then removed, the foam cylinders were remoistened, and the headset was refitted (improving the placement if needed). A second trial set was run to obtain two readings for each

[12] If they asked, I told them it was okay to blink, and if they started talking, I asked them to remain silent until the test was over.

participant's time point; a third trial was run only if both previous trials had high impedance or a visually noisy signal (including a harmonic artefact). The highest trial at each time point was used for data analysis.

#### 3.2.2.2 Signal-to-noise ratio variable

The peak (magnitude) at 15 Hz represents the amount of target activity detected, and its relative strength is interpreted as a signal-to-noise ratio (SNR). The SNR is thought to be a marker of normal brain activity or regional communication that is sensitive to concussive damage and can indicate relative changes over time. The NuroChek app calculates the ratio of signal strength by dividing the evoked 15 Hz signal peak by that of the "noise," or the remaining activity detected by the P1/P2 electrodes. By this reasoning, a higher SNR should indicate a healthy individual, while a lower SNR with a reduced or no accompanying peak should indicate a concussed individual.

The NuroChek software automatically uploads the reading and calculates the SNR, displaying it and the corresponding EEG pattern 15–60 seconds after the test was completed. The calculation is described by Salazar and colleagues (2021, p. 3, emphasis added):

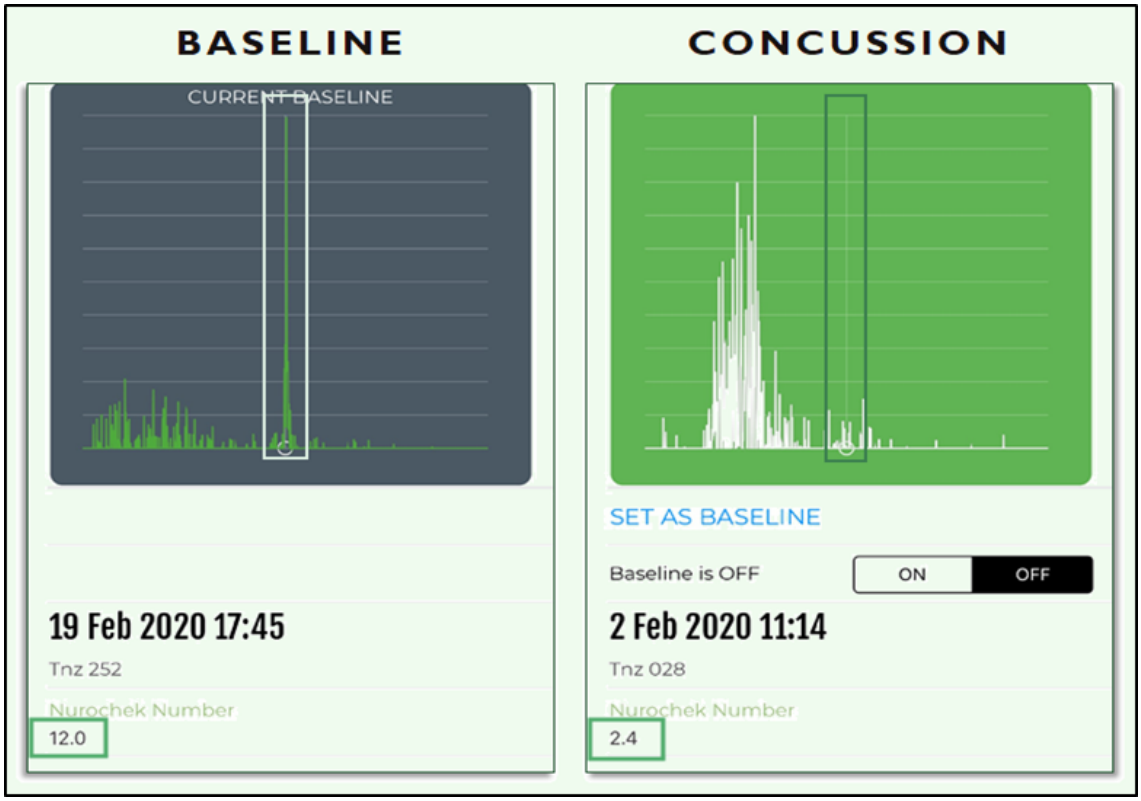
> These recordings were filtered using a 5–35 Hz third-order Butterworth bandpass filter before being normalized by dividing each channel's amplitude by its mean amplitude and multiplying by the mean amplitude of all three recording channels. The signals were then transformed into the frequency domain for analysis using a fast Fourier transform (2n+2 padding). The spectral resolution of the transformed signal was 0.01 Hz. The spectra of the three recording channels were then summed and SSVEP results were reported as the SNR, **where the signal is amplitude at 15 Hz, and the noise is mean amplitude across the 5–35 Hz window**. All processing was performed automatically by the NuroChek [software].

An example of the output from the NuroChek software can be found in Figure 3.6, which compares the baseline SNR[13] of a healthy athlete with the highest trial of an athlete who had an active concussion at baseline. The target 15 Hz portion of the EEG pattern is inside the vertical boxes, and the calculated SNR is highlighted in the boxes below. The baseline on the left shows an SNR of 12.0, accompanied by a high magnitude of the 15

[13] Called the "NuroChek Number" in this screenshot from a previous version of the software.

Hz activity (within the vertical box), while the concussed athlete on the right shows an SNR of 2.4 with no accompanying 15 Hz activity.

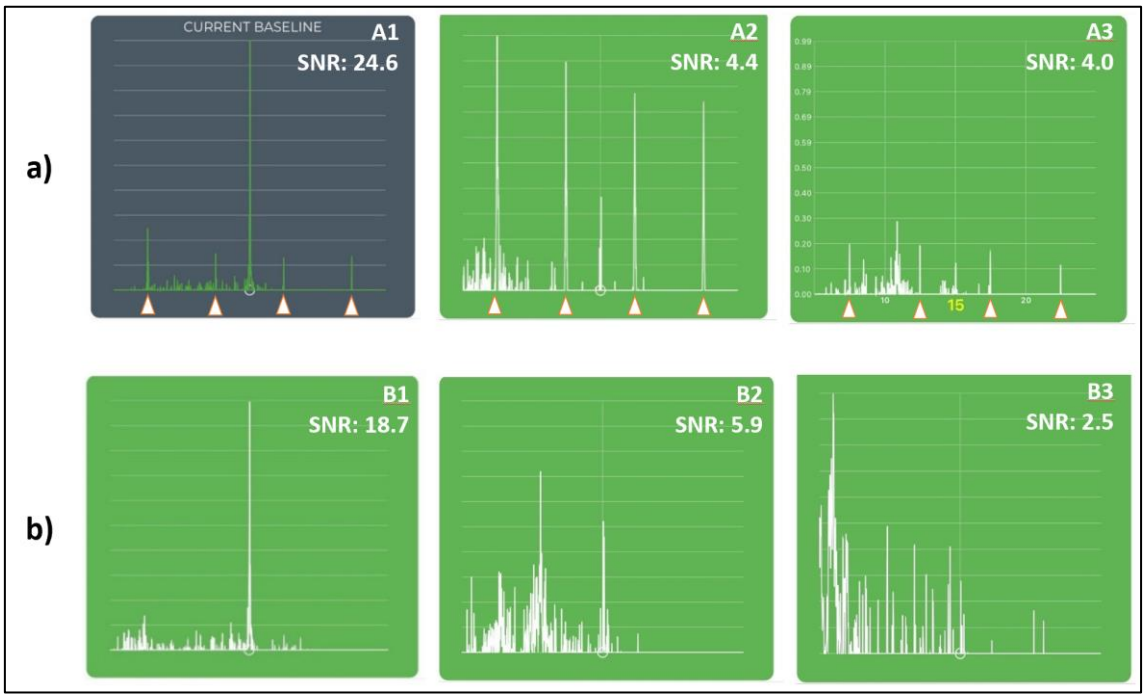
Figure 3.6: Comparison of output from a non-concussed participant and a concussed participant.




*The target magnitude is highlighted in the vertical box, and the SNR is highlighted in the bottom left box. (Note that the vertical axis scales represent SNR magnitude and are not equivalent.)*
*SNR- signal-to-noise ratio; images taken from the NuroChek app.*

In addition, the EEG patterns presented along with the SNRs were manually coded for the presence or absence of a harmonic artefact. The artefact was found within the "noise" spectrum of the EEG reading, and its magnitude occurred at variable proportion to the magnitude of the SNR, potentially decreasing the ratio by increasing the noise. In some athletes this artefact could be eliminated through fitting improvement or using more saline, but in other athletes it appeared at almost every assessment point. Figure 3.7 presents examples of SNRs with (a) and without (b) this 4-toothed harmonic pattern.

Figure 3.7: Examples of extracted EEG magnitude-spectrum signals from different participants with (a) and without (b) the harmonic pattern.

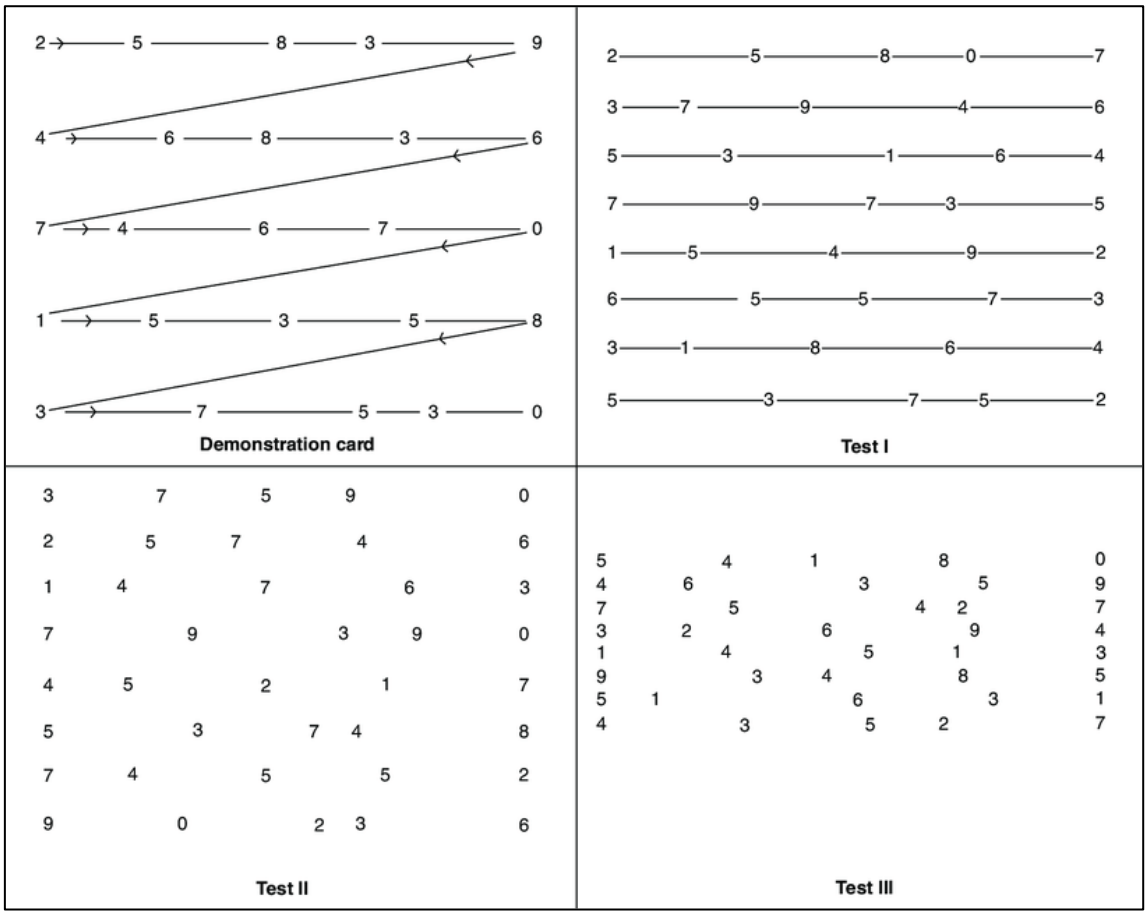



*The harmonic pattern is highlighted by arrows under the horizontal axis.*
*(Note that the vertical axis scales represent SNR magnitude and are not equivalent.)*
*SNR- signal-to-noise ratio; images taken from the NuroChek app.*

### 3.2.3 King-Devick test

Originally developed to screen for reading disorders (A. King, 1976), the King–Devick (K-D; Figure 3.8) is a rapid verbal number-naming test that can be used in concussion assessment (Galetta, Brandes, et al., 2011; D. King et al., 2015; Legarreta et al., 2019; Molloy et al., 2017; Rizzo et al., 2016). Participants received the standard instructions of the K-D test: *"Read the numbers as quickly as you can; if you make a mistake, go back and correct it. There will be 3 cards, and we will go through them twice."* Difficulty increased as the orientation of the numbers changed across the three cards, and the score was the total completion time. Once a participant satisfactorily completed the demonstration card, the K-D was administered until the athlete completed it twice with no errors; the fastest total time was assigned as the participant's baseline score. The K-D can be administered on an iPad screen or paper cards (K. M. Breedlove et al., 2019), and may detect deficits in vision or oculomotor function, attention, visual processing, and language (Clugston et al., 2019; Galetta, Barrett, et al., 2011; Gallagher et al., 2021; Moody et al., 2019).

Figure 3.8: The demonstration trial and three test trials of King-Devick.




The King-Devick test was used for all athletes in 2020, and for the semi-professional athletes in 2021. In the 2020 season, all K-D tests were conducted on a standard-size iPad held at comfortable reading distance (~30 cm) from the participant's eyes, and the results were stored within the K-D app. In the 2021 season, A4 paper cards were used and the times were recorded manually using a stopwatch app. Both methods are considered similarly reliable (r = .827 and r = .834, respectively) by Breedlove and colleagues (2019), though they used spiral-bound cards instead of A4 sheets.

The K-D can be used supplementally in sideline assessment, as it is quick, inexpensive, requires minimal expertise to administer, and is not affected by physical exertion (Galetta, Brandes, et al., 2011; Legarreta et al., 2019; Molloy et al., 2017; Rizzo et al., 2016). King and colleagues (2012) found the K-D to be useful in identifying witnessed and unwitnessed concussions when used after every match. It has up to a 23% rate of false negatives and a 27–33% rate of false positives (K. M. Breedlove et al., 2019; Harris et al., 2021; Molloy et al., 2017): Breedlove and colleagues (2019) examined the K-D's sensitivity and found that 27% of non-concussed athletes performed slower in year two than year one, M (SD) = 3.2 (± 3.9) seconds. Fuller and colleagues (2019) found the

K-D to have 39.2% specificity, but other researchers place it between 69–94% (Harmon et al., 2022; Harris et al., 2021; D. King et al., 2015; Molloy et al., 2017; Moody et al., 2019). Test-retest reliability across trials falls between 87–97%, and inter-rater reliability is similarly high at 88–95% (Galetta, Barrett, et al., 2011; Heick et al., 2016; D. King et al., 2015; Nowak et al., 2020; Walsh et al., 2016). The K-D does not correlate with many commonly-used baseline tests, possibly because it measures a domain that is not currently assessed by any other sideline test (Clugston et al., 2019; Galetta, Brandes, et al., 2011). Completion times of the K-D are not thought to be affected by non-acute history of concussion, but may be affected by age and sex (K. M. Breedlove et al., 2019; Gallagher et al., 2021; Gunasekaran et al., 2020; Heick et al., 2016; Moran & Covassin, 2017). The K-D is estimated to identify 53–86% of concussions post-match if used by itself, but its sensitivity may improve to over 89% when used with other sideline measures such as a symptom inventory and a balance assessment (Daly et al., 2022; Fuller et al., 2019; Harris et al., 2021; Legarreta et al., 2019; Marinides et al., 2014; Molloy et al., 2017; Moody et al., 2019).

The average baseline time in athletes is reported to be 40–50 seconds (K. M. Breedlove et al., 2019; Clugston et al., 2019; Fuller et al., 2019; Galetta, Barrett, et al., 2011; Gallagher et al., 2021; Gunasekaran et al., 2020; D. King et al., 2015; Molloy et al., 2017; Nowak et al., 2020; Rizzo et al., 2016; Walsh et al., 2016). A concussion can increase an athlete's completion time on the K-D by 4–10 seconds more than their baseline (Galetta, Barrett, et al., 2011; Galetta, Brandes, et al., 2011; D. King et al., 2015), whereas the performance of non-concussed athletes may improve by 2–5 seconds because of the practice effect (K. M. Breedlove et al., 2019; Galetta, Brandes, et al., 2011; Gunasekaran et al., 2020; Heick et al., 2016). An uncorrected error may also indicate the athlete has sustained a concussion (Harris et al., 2021). The utility of K-D peaks immediately post-injury, and may "rapidly dissipate" in the hours and days/sub-acute and chronic periods following concussion (Moody et al., 2019; Silverberg et al., 2014); because of this, some have posited that, despite the practice effect, the K-D may have better use in evaluating recovery than as a sideline assessment tool (Fuller et al., 2019; D. King et al., 2015; Marinides et al., 2014; Rizzo et al., 2016). Due to individual variation in reading speed, this test is not particularly useful with normative data or when a baseline is not available (Gallagher et al., 2021; Silverberg et al., 2014).

### 3.2.4 Sport Concussion Assessment Tool

The Sport Concussion Assessment Tool (SCAT-5; Appendix 9.2.3) combines elements of other common concussion assessment measures (Maddocks et al., 1995; McCrea et al., 2003; Riemann & Guskiewicz, 2000), including screens for symptoms, orientation, memory, concentration, balance, and gross neurological function. Administration of all subtests takes 10–15 minutes. The rugby athletes in the second year completed all subtests of the SCAT-5 at each assessment point (as did the non-athlete control participants), while the combat athletes completed only the symptom inventory and the digit span (to reduce assessment duration). The current SCAT-5 is the fifth version developed by the International Consensus on Concussion in Sport (McCrory et al., 2017); since it was developed unconventionally (by collaboration), the sections have been psychometrically evaluated separately. The SCAT-5 is not sensitive to concussion symptoms in the long term, and some domains begin to lose sensitivity quickly (McCrory et al., 2017).

#### 3.2.4.1 SCAT-5 subtests

The symptom inventory covers 22 symptoms with a 7-point Likert scale of severity for each, for a total severity score out of 132. Athletes were instructed to rate the symptoms as they were currently experiencing them. Many repetitive impact studies also include a symptom inventory (Broglio, Williams, et al., 2017; Caccese et al., 2018; Kieffer et al., 2021; Manning et al., 2020; Pearce et al., 2021). A thesis by Robinson (2019) examines the psychometrics of the SCAT-5 symptom inventory, as compared to the Rasch model. He determined it was reliable (but not valid), and somewhat redundant; specifically, 8 of the 22 symptoms had inconsistencies or needed clarity: dizziness, blurred vision, balance, feeling "slowed down," feeling "in a fog," not feeling "right," confusion, and feeling more emotional (Robinson, 2019). The person separation index, a measure of reliability that *"reflects the rating scale's ability to differentiate between different levels of the underlying construct"* (Robinson, 2019, p. 18), was reported to be above .80 and thus is considered highly reliable for at least 4 levels of the underlying construct (Robinson, 2019). In addition, Tucker and colleagues (2021) found that only 65.2% of athletes reported no symptoms at baseline testing; the most commonly reported by the remaining athletes were fatigue, neck pain, trouble sleeping and nervousness/anxiety. They also found that use of the SCAT-5 increased symptom reporting over that of the SCAT-3 (Tucker et al., 2021).

The five questions in the orientation subtest (date, time, day of week, month, and year) are selected from the Maddocks questions. Of these, the day and date are the most difficult for athletes immediately after concussion, though non-concussed athletes may also struggle with the correct date (Maddocks et al., 1995).

The verbal memory subtest is composed of an immediate recall score and a delayed recall score. This test required participants to listen to a list of 10 words, then repeat back as many as they could. The list was repeated three times for three trials of immediate recall, then the participants were prompted after 5–10 minutes to recall as many words from the list as they could for the delayed recall trial. The SCAT-5 provides three alternate forms of the 10-word trials (McCrory et al., 2017).

The concentration subtest reflects the scores on the digit span test and the task of reciting the months backwards. The digit span subtest is a measure of working memory and information manipulation, and has 6 alternate forms. Participants received the standard instructions (McCrory et al., 2017): *"I am going to read a string of numbers and when I am done, you repeat them back to me in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7."* Participants have two chances to recite the span correctly at each length, for a total of four lengths and four potential points. Being unable to complete the 4-digit span (i.e., scoring 1 point or less) is considered atypical (Tucker et al., 2021). Many concussion studies have used the digit span subtest, alone or as part of the SCAT (Cavanagh et al., 2019; Kozak, 2018; Miller et al., 2007; Ozen et al., 2013; Richards, 2017). Matser and colleagues (2000) performed neuropsychological assessments of boxers before and after a competitive match or a bag punching control task, and found that the control group scored significantly higher on the digit span than the competitive match group. Its use in repetitive impacts is not particularly common, but it was included because concentration was a domain of particular interest.

The neurological subtest asks participants to read aloud, report neck pain or double vision, touch their finger to their nose with their eyes closed, and walk 10 steps in a straight line. It is followed by the balance subtest, which requires participants to maintain three poses with their eyes closed and hands on their hips (standing on both feet, standing on the non-dominant foot, and a tandem pose with the non-dominant foot behind the dominant foot. The balance subtest was modified by the third International Conference on Concussion in Sport to be performed on flat ground (McCrory et al., 2009), whereas the original Balance Error Scoring System (BESS) is performed on a foam surface (Riemann & Guskiewicz, 2000). The modified version (m-BESS) is considered a

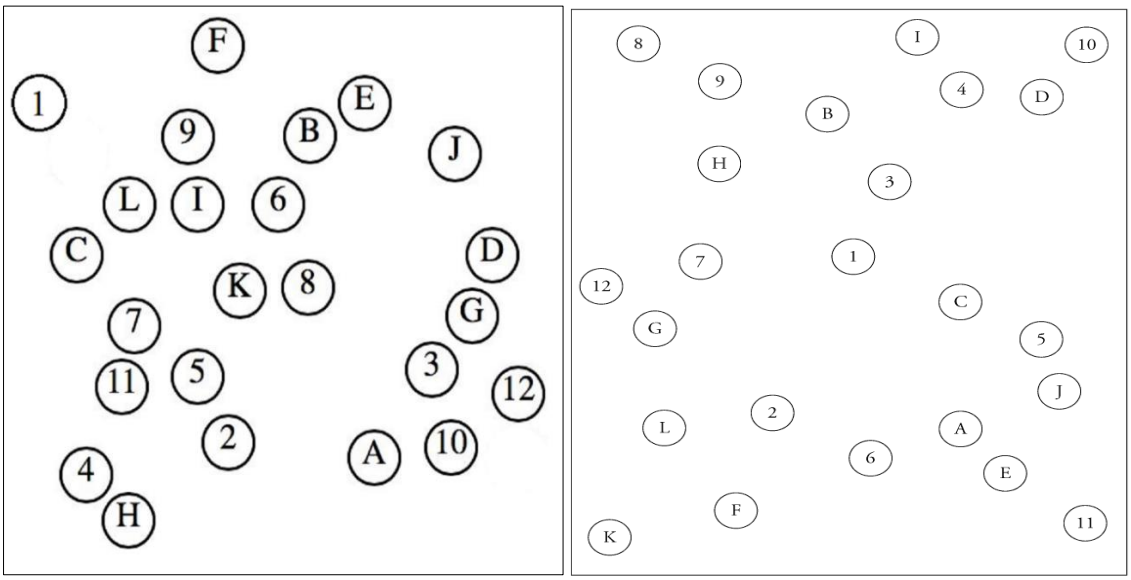
rudimentary standardised measure of postural stability (Iverson & Koehle, 2013) with an intraclass reliability of between r = .60–.88 and an inter-rater reliability of r = .97. The m-BESS loses sensitivity as one recovers (Iverson & Koehle, 2013), as early as three days post-injury (Riemann & Guskiewicz, 2000).

### 3.2.5 Trail-making Test

The Trail-Making Test (Reitan, 1958) is a measure of visual attention and psychomotor speed that is also used frequently used in concussion research. Athletes received an A4 sheet with a map of circles enclosing letters and numbers, and instructions to connect the circles in one continuous line, alternating between letters and numbers. (For example, *"Start with 1, then go to A, then to 2 and continue to alternate, and let me know when you get to L."*) The primary score for this test is completion time (though errors are also recorded), so lower scores indicate better performance. To control for the practice effect, two forms of the test were used, and the order the athlete received them was randomised (Figure 3.9).

Only form B (TMTb) was used because switching/cognitive flexibility is a domain that may be measurably affected by repetitive impacts; McAllister and colleagues (2012) compared repetitive impacts in contact and non-contact athletes and found a trend of poorer post-season performance by the contact athletes on the TMTb over a season. They also found that the athletes with more exposure to repetitive impacts demonstrated more impairment on the TMTb (McAllister et al., 2012). The constructs of working memory, information manipulation, visual searching, and switching may account for 48% of the variance of TMTb scores, making it a partially valid measure of these domains (Sánchez-Cubillo et al., 2009). One study reported that healthy professional American football athletes completed the TMTb in 55–60 seconds, comparable to the average of the general population (Lovell & Solomon, 2011), while another reported the average time for older adults to be 77.6 seconds (Sánchez-Cubillo et al., 2009).

Figure 3.9: Versions of the TMTb used.




*TMTb- Trail-Making Test form B; images published by (Eriksson, 2014; Reitan, 1958).*

## 3.3 Procedure

### 3.3.1 Rugby athletes

I met with the club coaches and physiotherapists, and attended pre-season meetings for participating teams (when possible) to introduce this study to the athletes and ask for their participation. At baseline, the participant read the study information sheet and asked any questions, then signed an informed consent form and completed the demographic questionnaire. Once their answers were checked for any exclusion criteria, they were assigned a unique participant code and I began the headset protocol. Assessments were performed in a quiet room or corner of the field, which took 15–20 minutes. During the mid-season and end-of-season assessments, participants were asked to report any possible concussions, head knocks, lingering headaches, or any other concussion symptoms they might be experiencing. At all time points, athletes completed the NuroChek assessment and a cognitive measure (K-D in 2020; SCAT-5 in 2021). Athletes were then thanked for their participation, given the information sheet with my contact information, and were told when to expect the next assessment. The headset was cleaned with antibacterial wipes after each participant, and the headset and iPad were charged as needed. During and after the season, athletes received a reminder text the day before their scheduled assessments, and up to three attempts were made to reschedule missed appointments.

Figure 3.10: Testing timeline for concussed and non-concussed athletes.

| | Baseline | Mid-season | | | | | End-of-season |
|---|---|---|---|---|---|---|---|
| Concussed | X | INJURY <72 hours | Day 4-5 | Day 6-10 | Day 11-15 | Day 16-20 | X |
| All rugby | X | X | | | | | X |

The testing timeline for the season is represented in Figure 3.10. Efforts were made to assess concussed athletes as soon as possible after injury. During the season I emailed the coaches or physiotherapists of the participating teams every Monday to ask about any injuries in the games over the weekend. When the coach or team physiotherapist reported a concussion to me, I contacted and assessed the participant as soon as possible (ideally within 72 hours after their injury), then again at 5, 10, 15, and 20 days post-injury. In some cases, post-injury testing coincided with trainings because this was easiest for the athletes, so these athletes were assessed on days 12 and 17 instead of on day 15, for example. Because of timeline inconsistencies, the time points should be interpreted as an upper range, as "10 days" represents 6–10 days, and "20 days" represents 16–20 days. Most of the athletes who sustained concussions were recruited and completed baseline testing during the pre-season training, although some entered the study after sustaining their injuries (Figure 3.1).

In addition to the post-injury tests, I assessed all available rugby athletes at mid-season (across one month) and at the end-of-season (which occurred in the last 2–3 weeks of the season to prevent post-season attrition). Due to incidental issues with equipment or scheduling, some athletes were not assessed until a month after the end-of-season.

### 3.3.2 Combat athletes

Combat athletes were recruited before their sparring session. Recruitment included explaining the study, reading the study information sheet, and asking any questions. The athlete completed the informed consent, demographic form, and symptom inventory while I sanitised and prepared the NuroChek headset. After two trials of NuroChek, the athlete completed the digit span and TMTb subtests. The athlete then participated in a round of sparring that either included repetitive impacts (boxers) or did not include repetitive impacts (BJJ/cardio), and lasted between 30–60 minutes. Once they finished their training session, the athletes reported back to me, where they again completed the symptom inventory, NuroChek trials, digit span, and TMTb. The athlete was then thanked for their participation and given the information sheet to take home.

### 3.3.3 Non-athlete control group

Non-athlete control participants were provided a verbal description of the study and an information sheet to read, and they were prompted to ask any questions they might have. Participants then completed the informed consent and demographic forms and were fitted with the NuroChek headset. After the NuroChek protocol, they completed all subtests of the SCAT-5, the K-D and the TMTb. The athlete was then thanked for their participation and given the information sheet to take home. Due to scheduling difficulties and a limited timeline, these athletes were only assessed at a single time point.

## 3.4 Design and statistical approach

This research includes two studies that examine the SNR by differential degree of head injury (from Section 2.6):

- **Study A: Changes to SNR in concussed male athletes** focuses on the assessment of **concussion** and recovery of concussive damage in male rugby athletes by SNR.

- **Study B: SNR and repetitive impacts** focuses on the assessment of subconcussive injury from **repetitive head impacts** sustained acutely by combat athletes, and over time in rugby athletes. This study also includes data collected from non-athletes for comparison differences by **sex** or **concussion history** in each of these populations.

The **aims** of these studies are to:

1. Determine if the NuroChek system and SNR variable can assess concussion (or repetitive impacts) **acutely**.
2. Establish how the SNR variable and cognitive factors (measured by the SCAT-5 or K-D) may change during concussion **recovery** and the remainder of the season (in concussed and non-concussed athletes).
3. Identify any effects that **sex** or **history of concussion** may have on SNR magnitude or trajectories in non-concussed athletes and control participants.
4. Identify any effects that **repetitive impacts** may have on SNR magnitude or trajectories in non-concussed athletes.

At least two SNR readings were taken from each participant at each time point and the higher of these was selected to represent the time point in the dataset. All data were double-checked before beginning the analyses. Rugby athletes were excluded if they did not complete any assessments after the baseline. Of 173 rugby athlete participants

with baselines, 59 did not return for another assessment (Figure 3.1); this high rate of attrition was largely due to Covid-related factors.

All three studies have elements of within-groups design and between-groups design, since the data were compared within the athletes over time and between athlete groups at each time point. The groups were determined by concussion status or degree of repetitive impact exposure during the season, sex, and history of previous concussion. Time points are classified as baseline (BL), post-injury (PI), mid-season (MS), and end-of-season (EOS).

Statistical analyses were performed using SPSS 28.0 (IBM Corp., 2022). The data were not normally distributed in most conditions, so most data have been analysed using non-parametric tests instead of transforming the data. Mann–Whitney tests or Kruskal–Wallis ANOVAs were used to examine differences between groups at each time point, and Wilcoxon signed-rank tests or Friedman's ANOVA were used to compare changes within groups over time. Chi-squares or McNemar's tests were used to examine associations between groups. In some cases where the datasets did not show normality violations, parametric repeated-measure ANOVAs were used to compare the changes and interactions between groups over time, and corrected test values were reported when Levene's equality of variance was violated. Results where $p \leq .100$ are included in the tables, while the results are discussed as significant when $p \leq .050$ or the effect size was greater than .500.

The use of some statistics differed by sample size, and the reporting of effect size depended on the test used. When $N < 50$, the Shapiro-Wilk test of normality and Hedge's g correction to effect size were reported; The Kolmogorov-Smirnov normality test and Cohen's d as effect size were reported when $N \geq 50$. The effect size for Kruskal–Wallis ANOVAs was reported as eta-squared, and the Bonferroni correction was applied to the p-values of the pairwise comparisons. Kendall's W was reported as the effect size for Friedman's ANOVA, and partial eta-squared or Pillai's V was reported for the repeated-measures ANOVAs. Effect sizes for Wilcoxon signed-rank and Mann-Whitney tests were reported using the formula $r = \frac{z}{\sqrt{N}}$. Cramer's V was reported as the effect size for the Chi-squares. All effect sizes were reported as small (0.1–0.3), moderate (0.3–0.5), or large (>0.5) except for Cohen's d, which was interpreted as small (0.2–0.5), moderate (0.5–0.8), or large (>0.8).

All raw data are available upon request to the author.

# Chapter 4

# Study A: Changes to SNR in Concussed Male Rugby Athletes

## 4.1 Introduction and rationale

As described in Sections 2.6 and 3.2.2, the NuroChek system is a promising method of objective concussion assessment. It is portable and uses a non-invasive flickering visual stimulus to generate a steady-state visually evoked potential (SSVEP), which is measured in the form of a signal-to-noise ratio (SNR): the relative signal strength of the target brain activity against background noise. While the SNR has shown itself to be sensitive to the presence or absence of concussion (Fong et al., 2020; Fong et al., 2021; Salazar et al., 2021), its utility and limitations are still largely unknown. This study examines Aims 1 and 2 in male rugby athletes who sustained a concussion.

### 4.1.1 Research questions

This study addresses two research questions:

1. Does the SNR change after acute concussion?
2. Does the SNR change during recovery (sub-acutely and over a season)?

## 4.2 Methods

### 4.2.1 Participants

Twenty-one male athletes were diagnosed with concussion by the team physiotherapist during the study, and concussion was confirmed by a medical doctor in five cases. The average age of the concussed athletes was 23.3 years (SD = 3.84), and all but two reported at least one previous concussion. Of these, 57.1% (n = 12) were assessed within 3 days post-injury, and a further 14.3% (n = 3) were assessed by 5 days post-injury. Nine athletes joined the study after their concussion and did not have a baseline; two of these athletes sustained two concussions each during the season and were assessed several times after each injury. In total, 19 athletes completed at least two post-injury assessments, and 17 completed the end-of-season assessment. The 85 non-concussed male rugby athletes were also included in this study as a comparison group. Overall, 21 concussed and 85 non-concussed male athletes were included in this study.

### 4.2.2 Procedure and design

Participants completed the informed consent (Appendix 9.2.1.1 or 9.2.1.2) and demographic forms (Appendix 9.2.2.1 or 9.2.2.2) at baseline, then an assessment with the NuroChek headset and a cognitive measure: either the King-Devick (K-D; Figure 3.8 and section 3.2.3) or the Sport Concussion Assessment Tool (SCAT-5; Appendix 9.2.3 and section 3.2.4) at each time point. Due to slow or unreliable wi-fi/hotspot connections at some rugby fields, some participants completed the symptomology portion first (or in very few cases, the full SCAT-5) while the NuroChek app loaded. This study has elements of both a within-groups and a between-groups design: pre-season baseline data were compared to data collected post-injury and at the end-of-season, and data from the concussed and non-concussed athletes were compared to each other by time point.

#### 4.2.2.1 Timeline

The testing timeline for the season is presented in detail in Section 3.3.1. Most of the athletes were recruited and completed the baseline testing during the pre-season training, although some were concussed at baseline, and others entered the study after their injuries. Efforts were made to assess concussed athletes as soon after injury as possible. Ideally, concussed participants were assessed within 72 hours after their injury, then again at 5, 10, 15, and 20 days post-injury. In addition to the post-injury tests, non-concussed athletes were assessed at mid-season when possible, and all available athletes were assessed again at the end-of-season. Season lengths ranged from 2–11 months; the average length of a season for these athletes was 3.8 months, but due to Covid-related pauses during both years, the average time between baseline and end-of-season for these athletes was 5.5 months.

### 4.2.3 Statistical approach

This study uses data from the concussed and non-concussed male rugby athletes. Only male data was used because of potential sex differences in SNR, which are examined in *Study B: SNR and concussion history, sex, and repetitive impacts.* The pre-season baseline SNR of the concussed athletes was compared to SNR data collected post-injury and at the end-of-season, and SNR data of all male rugby athletes were compared by concussion status at baseline and end-of-season. Power analyses showed that for a power of .80, I would need at least 7 concussions, $F = 0.8463$ ($p < .05$). If 7 concussions represented 10% of my participants, I would need at least 70 participants.

To examine SNR changes acutely after concussion (Research Question 1), the Wilcoxon signed-rank test was used to compare the concussed athletes' baseline SNR to their post-injury (up to 5 days) and post-season SNR. The athletes' baselines were first compared to their first post-injury assessment (3–5 days post-injury), then specifically at 3 days post-injury only. The baseline and post-injury values were also compared to the end-of-season SNRs.

To examine the SNR trajectory during and after recovery (Research Question 2), data from non-concussed male athletes were compared to the concussed males at baseline and end-of-season. Mid-season SNR was not included because of the different points at which concussions were sustained during the season, and none of the concussions were sustained within 21 days of the end-of-season assessment. Because of no normality violations or outliers at baseline or end-of-season, a repeated-measures ANOVA was run to compare the athletes' end-of-season SNRs of the concussed and non-concussed groups to their baselines, and to examine the interaction of concussion status and time.

## 4.3 Results

### 4.3.1 No difference between baseline and post-concussion SNR

Of the 21 male athletes who sustained a concussion (confirmed by the team physiotherapist), 19 of these were assessed at least once post-injury. Wilcoxon tests compared the concussed athlete's baseline SNR to their post-injury (up to 5 days) and post-season SNR; these are reported in Table 4.1. To examine the effects of time after injury, comparisons were made at the first post-injury assessment (3–5 days post-injury) and specifically at 3 days post-injury only (rows 1–2). The baseline and first post-injury SNRs were also compared to their SNRs at the end-of-season (rows 3–4). None of these comparisons were statistically significant, and none showed large effect sizes.

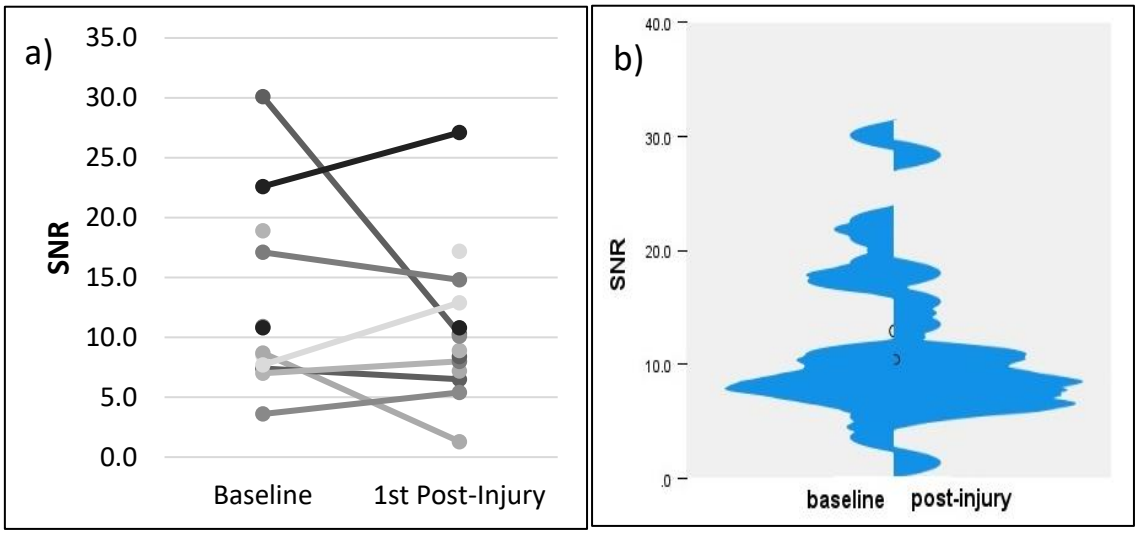
Table 4.1: Comparison of SNRs over time in concussed athletes.

| | T1 | T2 | test | stat | p | effect size | z score | N = | T1 M (SD) | T2 M (SD) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | BL | 1st PI | Wilcoxon signed-rank | 16.000 | 0.779 | -0.099 | -0.280 | 8 | 12.84 (7.80) | 10.46 (5.99) |
| 2 | BL | 3d PI | Wilcoxon signed-rank | 11.000 | 0.612 | -0.192 | -0.507 | 7 | 12.78 (7.79) | 10.35 (6.26) |
| 3 | BL | EOS | Wilcoxon signed-rank | 37.000 | 0.552 | -0.165 | -0.594 | 13 | 12.84 (7.80) | 10.57 (3.30) |
| 4 | 1st PI | EOS | Wilcoxon signed-rank | 76.000 | 0.363 | 0.235 | 0.909 | 15 | 10.05 (5.63) | 11.30 (4.66) |

*BL- baseline; EOS- end-of-season; PI- post-injury; T- time; M- average; SD- standard deviation.*

The baseline and post-injury SNRs for each participant are represented in Figure 4.1, in which (a) indicates the direction of change and (b) indicates the distribution and mean at each time point. In athletes who were assessed at baseline and within five days of their concussion, the relationship is represented by a line. Athletes who were only present at one assessment are represented by a single dot: 28.6% (n = 6) were not assessed within the first 5 days post-injury, and 33.3% (n = 7) did not have a baseline SNR at the time of injury. Of note are the three concussed athletes whose SNR increased after injury (relative to baseline), in addition to the three athletes who show sharp decreases and the two athletes who show little change from their baselines.

Figure 4.1: Comparison of baseline and first post-injury SNR for each concussed athlete, in (a) a line chart and (b) a violin plot.

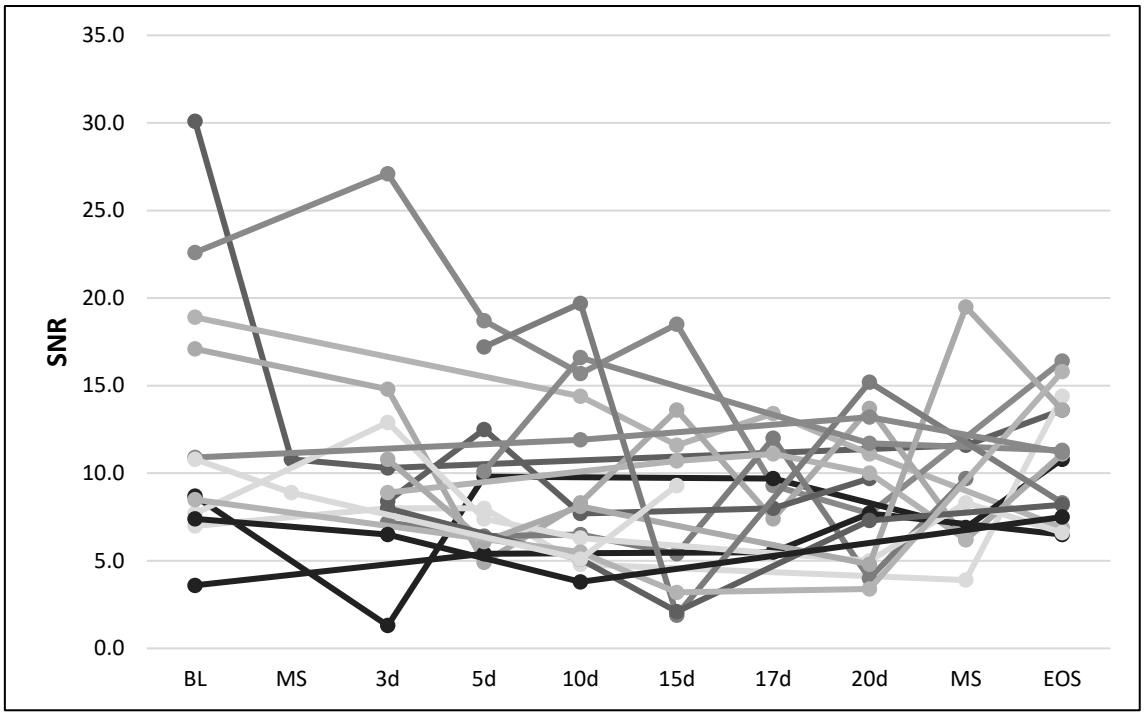



*SNR- signal-to-noise ratio.*

### 4.3.2 Inconsistent SNR behaviour during concussion recovery

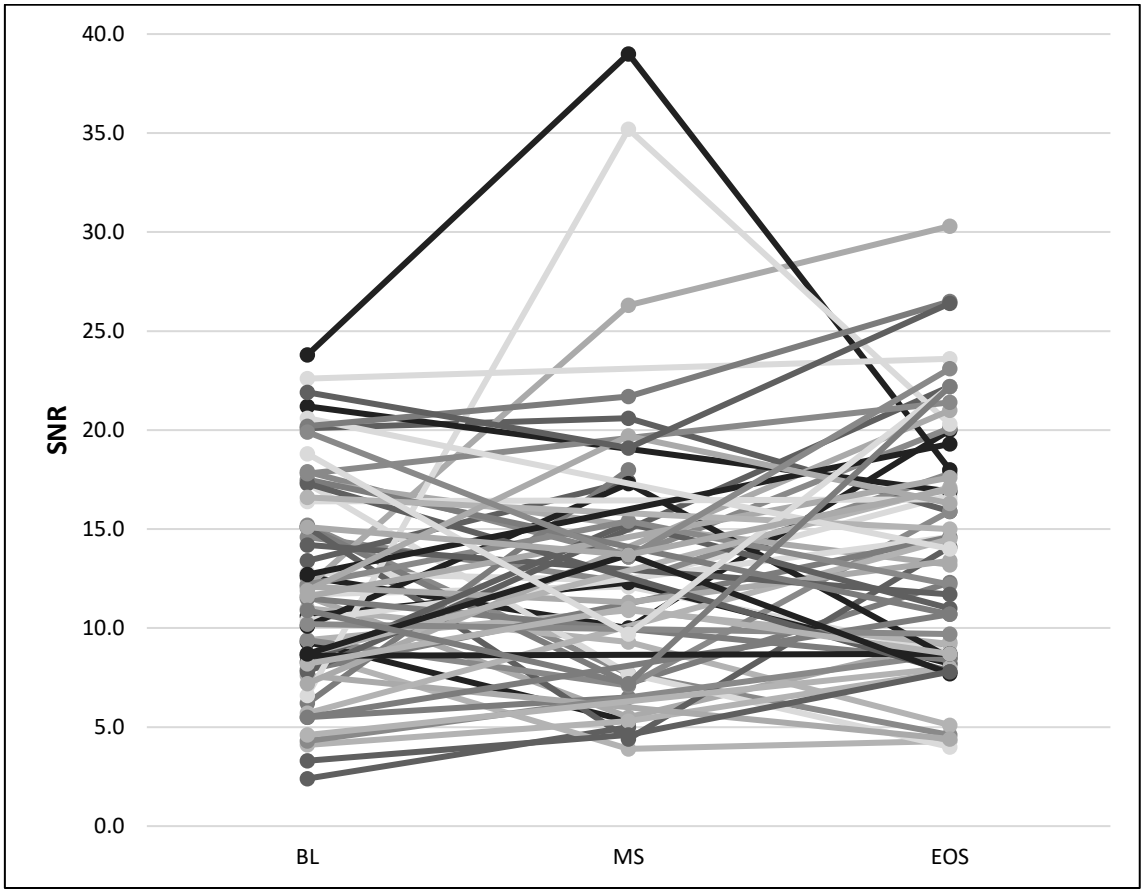
The post-injury data of the concussed athletes were analysed to examine changes up to three weeks post-injury. Since these data had a small sample size and inconsistencies in follow-up points, they were analysed statistically when possible, and visually or comparatively otherwise. Two athletes (one semi-professional and one club) sustained two concussions over the course of the season: only their first concussion was included in the concussed analyses, and the second concussions are discussed comparatively as case studies (Section 4.3.4). Figure 4.2 shows the post-injury SNR trajectories of the athletes who sustained a concussion during the season, while Figure 4.3 shows the trajectory of SNR at three time points for the athletes who did not sustain concussions. The SNRs of the concussed athletes show a greater range at baseline than at any other time point, while the SNRs of the non-concussed athletes show the greatest range at mid-season.

Figure 4.2: SNR post-injury trajectories of concussed athletes over time.




*SNR- signal-to-noise ratio; BL- baseline; MS- mid-season; EOS- end-of-season.*

Figure 4.3: SNR trajectories in non-concussed athletes over time.

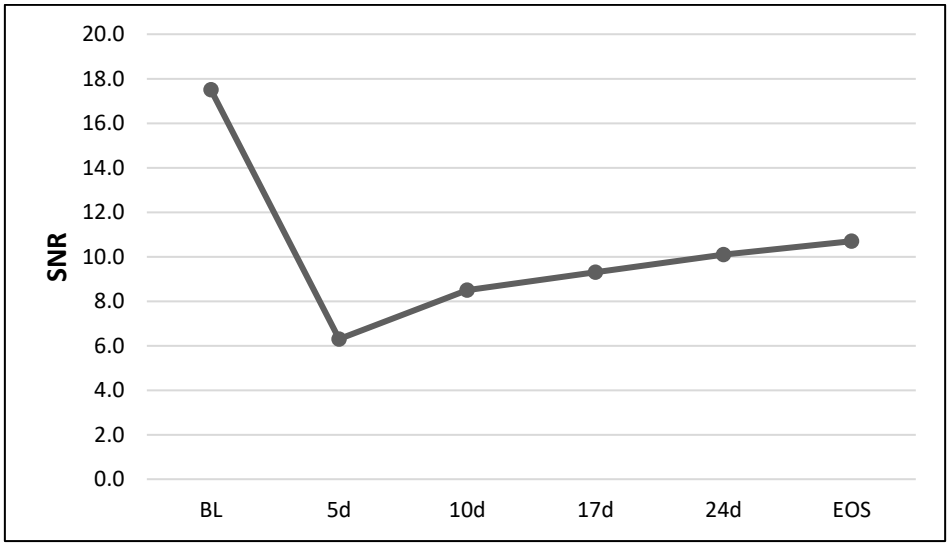



*SNR- signal-to-noise ratio; BL- baseline; MS- mid-season; EOS- end-of-season.*

For comparison, Figure 4.4 illustrates the recovery trajectory of a male athlete who sustained a suspected concussion and was tested multiple times post-injury, but

while the physiotherapist ultimately determined that he had not actually sustained a concussion, he was still held out of play with an arm injury. His SNR declined after his injury, and while it did increase after 5 days, it did not return to baseline by the end-of-season.

Figure 4.4: SNR trajectory of a non-concussed participant who was monitored post-injury.




*SNR- signal-to-noise ratio; BL- baseline; EOS- end-of-season.*

### 4.3.3 Inconsistent timeline for return-to-baseline of SNR

The SNR of the concussed athletes followed one of three recovery patterns: it either returned to baseline quickly post-injury, returned to baseline by the end-of-season, or never returned to baseline. Of the 14 athletes with baseline SNR data,[14] the SNR never returned to its baseline value in 5 athletes (35.7%), while it was higher at a post-injury time point than at baseline in 6 athletes (42.9%); of these six, three were higher at the first assessment point (3 days post-injury). The SNR did return to baseline by the end-of-season in a further three athletes (21.4%). Two athletes who had participated in 2020 (but who did not provide baselines for 2021) were assessed after they sustained concussions in 2021, so their baseline SNRs from 2020 were used.[15] These returned to baseline within five days. Only one of these six took ten days to return to his baseline SNR, but that was also his first post-injury time point.

To examine the SNR's return-to-baseline and determinations of recovery, the post-injury SNRs of concussed athletes are reported in Table 4.2, including the number of days after concussion that the final data point was taken. An SNR equal to or higher than the athlete's baseline is denoted in underline and bold. A green box (or x) represents

[14] The remaining seven athletes were recruited into the study after their injury, and thus did not provide baseline data for comparison.
[15] The SNR was not significantly different across years (Section 5.3.3.3.2)

when the athlete returned to play, and a red box in italics denotes that the athlete did not return during the season. Three athletes returned to play within one week, six athletes returned within two weeks, and two more athletes returned within three weeks. Three athletes had returned by the mid-season and another three by end-of-season, while two athletes did not RTP for the remainder of the season. The RTP timelines for athletes 17, 20, and 21 are unknown. The two mid-season columns note when the athlete sustained his concussion during the season, and the empty grey boxes represent missing data.

Of the nine athletes with available baseline and post-injury data, four of these demonstrated an SNR that met or exceeded their baseline at RTP, while another four returned to play before their SNR returned to baseline, and one showed a return-to-baseline after RTP. A further two never returned to play and RTP for one more was unknown, but these three did demonstrate a return-to-baseline in SNR. The time between the date of concussion and the last assessment point is reported in the final column (the end-of-season was used for all but athletes 7 and 9, whose time after is calculated from the mid-season time point).

Table 4.2: SNRs of concussed athletes at post-injury assessment points.

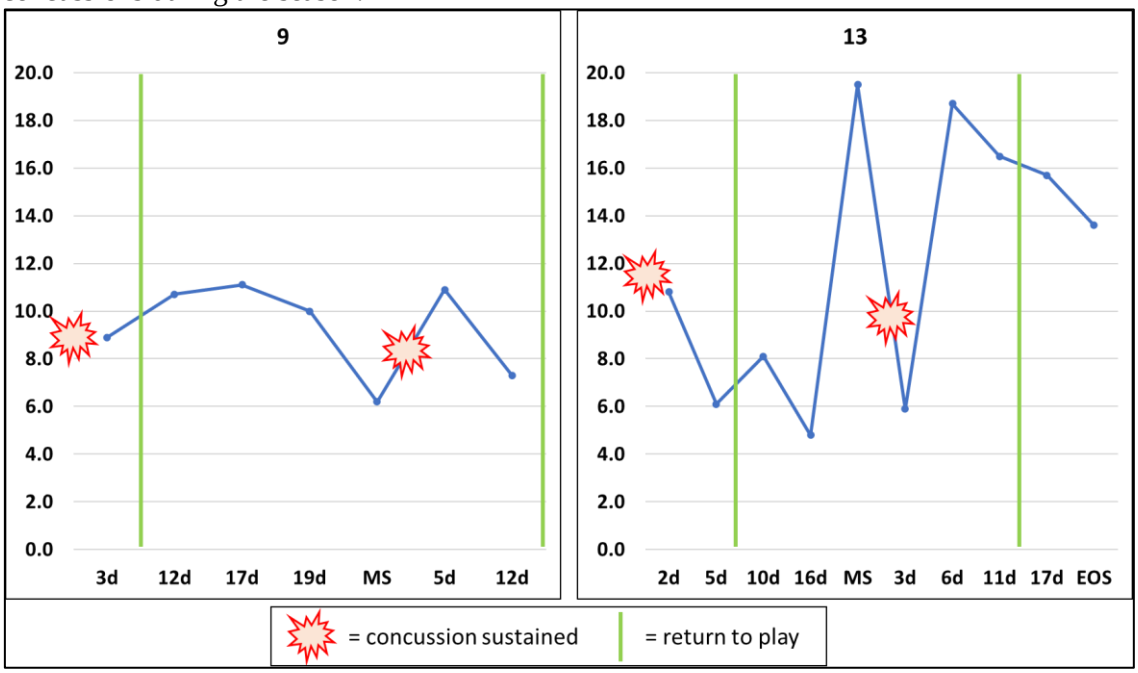
| pt # | BL | MS | 3d | 5d | 10d | 15d | 17d | 20d | MS | EOS | days after |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 30.1 | 10.8 | 10.3 | | | | | | 11.6 | 13.6 | 184 |
| 2 | 18.9 | | | | 14.4 | 11.6 | 13.4 | 11.1 | | 6.9 | 131 |
| 3 | 22.6 | | **27.1** | 18.7 | 15.7 | 18.5 | 9.3 | 7.7 | | 16.4 | 143 |
| 4* | 8.7 | | 1.3 | **9.8** | | | 9.7 | | 6.9 | 10.8 | 193 |
| 5 | 7.0 | | **8.0** | **8.0** | 4.8 | | | | 3.9 | *14.4* | 124 |
| 6 | 17.1 | | 14.8 | 4.9 | 8.3 | 13.6 | 7.4 | 13.7 | 6.2 | 11.1 | 159 |
| 7* | | | 7.2 | 6.4 | 6.5 | 5.4 | 12.0 | 4.0 | 9.7 | | 87 |
| 8* | | | 8.4 | 12.5 | 7.7 | | 8.0 | 9.7 | | | |
| 9 | | | 8.9 | | | 10.7 | 11.1 | 10.0 | 6.2 | | 45 |
| 10 | | | | 10.1 | 16.6 | | | 11.7 | | 11.3 | 38 |
| 11 | 3.6 | | | **5.4** | | | **5.5** | **7.7** | | **6.5** | 54 |
| 12 | 7.7 | | **12.9** | 7.4 | 6.3 | | | 5.0 | **8.3** | 6.6 | 61 |
| 13 | | | 10.8 | 6.1 | 8.1 | | | 4.8 | 19.5 | 13.6 | 67 |
| 14* | | | | 17.2 | 19.7 | 1.9 | x | 15.2 | | 8.3 | 39 |
| 15 | | | 8.0 | | 5.1 | 2.1 | x | 7.3 | | 8.2 | 30 |
| 16 | 8.5 | | | | 5.5 | 3.2 | | 3.4 | x | **15.8** | 36 |
| 17 | 10.9 | | | | **11.9** | | | **13.2** | | **11.2** | 89 |
| 18 | 7.4 | | 6.5 | | 3.8 | | | | | ***7.5*** | 86 |
| 19 | 10.8 | 8.9 | | | 5.1 | 9.3 | | | | | |
| 20 | 5.4 | | | | | x | | | | **10.4** | 37 |
| 21 | 21.1 | | | | | | | | | 7.1 | 79 |
| M= | 12.84 | 9.85 | 10.35 | 9.68 | 9.30 | 8.48 | 9.55 | 8.89 | 9.04 | 10.57 | 88.53 |

*Pt #- participant number; *- diagnosis confirmed by doctor; BL- baseline; MS- mid-season; EOS- end-of-season; SNR- signal-to-noise ratio.*

### 4.3.4 No difference in SNR between the first and second concussions

Two rugby athletes (one club and one semi-professional) sustained two concussions during the season, but only the first concussion was included in the above analyses; because of the small sample size, the second concussions were not analysed statistically. Both athletes joined the study after their concussions, so baseline SNRs were not available for comparison of the first injury. The SNR trajectories for each twice-concussed athlete are presented in Figure 4.5 below.

Figure 4.5: Comparison of the SNR trajectories of athletes 9 and 13, who sustained two concussions during the season.




*SNR- signal-to-noise ratio; MS- mid-season; EOS- end-of-season.*

After Athlete 9's first concussion of the club season (represented as a burst icon), his SNR increased after his RTP at one week (represented as a vertical bar), then began to decrease at 19 days post-injury, until its lowest at mid-season. Following his second concussion (confirmed by a doctor), his first post-injury SNR had increased from mid-season, but showed another decrease at 12 days post-injury. He was unable to be reached for further post-injury or end-of-season assessments.

The SNR of the (semi-professional) Athlete 13 is much more variable, showing a decrease before RTP and then reaching its lowest at 16 days post-injury. His SNR exceeded his baseline by mid-season, then he showed a sharp decrease after his second injury. His SNR showed almost a full recovery by six days post-injury then again began to decrease before his RTP, though the end-of-season SNR was still higher than the first post-injury SNR and than the average of other concussed athletes at end-of-season.

No common pattern of SNR trajectory is apparent across these two athletes. Both waited one week until RTP for the first concussion and two weeks until RTP for the second, as determined by the physiotherapists. Both athletes recovered from their second concussion and returned to play before the season ended, though one did not provide end-of-season data. Without baselines and more consistent follow-up points, no meaningful pattern for second concussion can be determined.

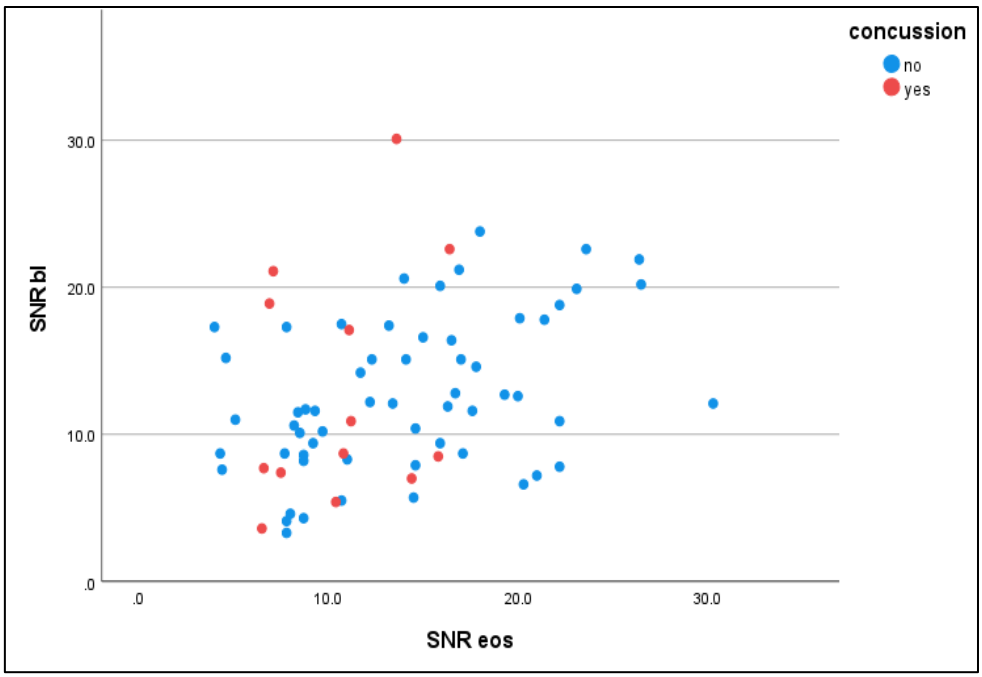
### 4.3.5 No differences in the SNR of concussed and non-concussed athletes over time

Data from 64 non-concussed male athletes were used as the comparison group for the concussed male athletes; for this group, the SNR average for baseline was 12.3 (SD = 5.3, n = 64); for mid-season was 13.1 (SD = 7.8, n = 40); and for end-of-season was 14.2 (SD = 6.2, n = 59; also reported in Table 5.1). When all male rugby athletes were compared at the end-of-season, those who sustained a concussion had a significantly lower SNR than those who did not, t(51.023) = -3.160, p = .001, d = -.629, CI = -5.8850–-1.13128, N = 76.

Because of no normality violations or outliers at baseline or end-of-season, a repeated-measures ANOVA was run to compare SNR in the concussed and non-concussed groups over time. Mid-season SNR was not included in the ANOVA because of the different points at which concussions were sustained during the season, and none of the concussions were sustained within 21 days of the end-of-season assessment. Supplemental Table 9.2 shows comparisons of the baseline and end-of-season scores between the male athletes who sustained a concussion over the season to those who did not. The interaction of the repeated-measures ANOVA was marginally significant, F(1) = 3.740, p = .057, Pillai's V = .051, while the main effects of concussion status and time were not statistically significant. None of the pairwise comparisons were statistically significant.

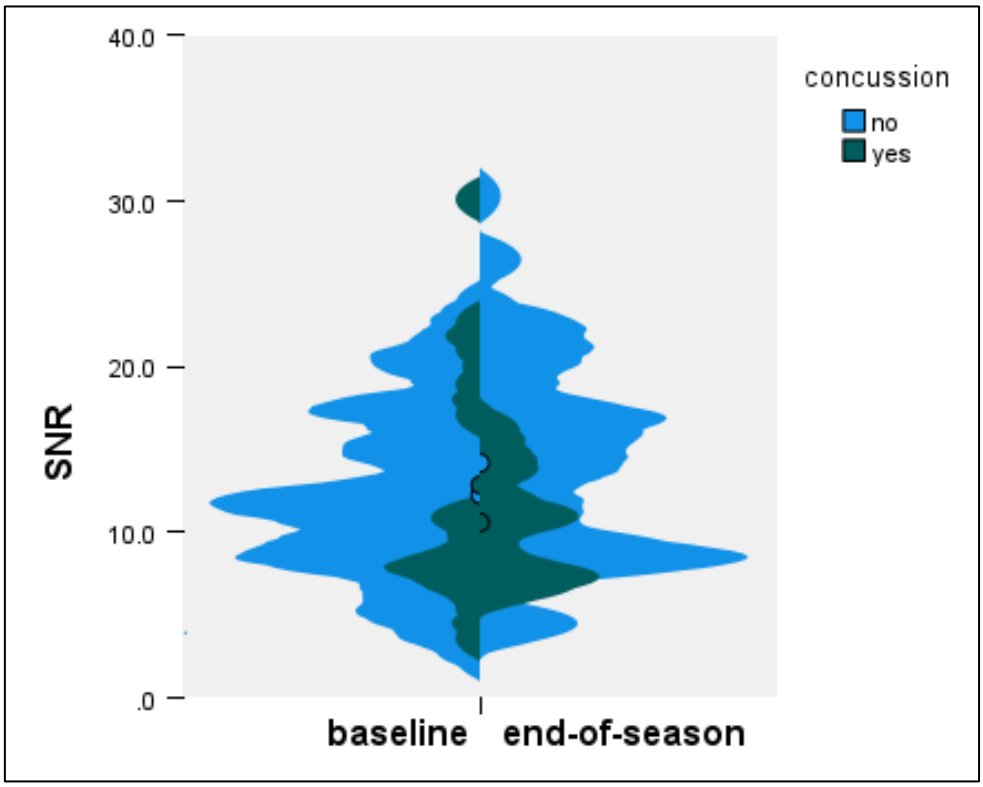
The SNRs over time are visualised in two figures below. Figure 4.6 shows the stability of SNR over time in male athletes, by concussion status. While some concussed athletes (in red) had high baseline SNRs (represented on the vertical axis), no concussed athletes had SNRs above 16.4 at the end-of-season, nearly the midpoint of the horizontal distribution. The lower maximal score for the concussed athletes is also visible in Figure 4.7, which indicates the SNR distributions at baseline and end-of-season in the concussed (green) and non-concussed (blue) athletes.

Figure 4.6: SNR trajectories of male athletes across time, by concussion status.




*SNR- signal-to-noise ratio; BL- baseline; EOS- end-of-season.*

Figure 4.7: SNR distributions of male athletes at each time point by injury status.




*SNR- signal-to-noise ratio.*

### 4.3.6 No significant cognitive changes after concussion from baseline

Analyses of the concussed athletes' cognitive scores by domain are reported in Supplemental Table 9.1. Several domains demonstrated violations of normality, likely because most participants got all five possible points for these domains, creating a ceiling effect. Due to these, some outliers, and the small sample size, non-parametric

comparisons were run. The King-Devick was used the first year, and the SCAT-5 was used the second year. Domains assessed include symptom number and severity, orientation, concentration, neurological symptoms (mainly neck pain), balance, and the K-D number-reading task. The domains of immediate and delayed verbal memory were unable to be analysed because of inconsistencies in baseline data collection, as some were obtained from the team physiotherapist, and the trials of five words were administered instead of the trials with ten.

Comparisons between the concussed athlete's baseline and first post-injury cognitive scores show no statistically significant differences in any domain. The only domain to show a trend (with a large effect size) towards increase over time was concentration, $W = 10.000$, $p = .059$, $r = .772$. Many other domains showed large effect sizes ($r > .500$) but non-significant p-values, likely due to the small sample sizes. Specifically, the orientation score decreased post-injury, the concentration score increased, and the symptom number and severity were reduced to zero by the end-of-season. While these domains showed indications of post-injury change, none of the changes were statistically significant.

### 4.3.7 No consistency between return to baseline of SNR and other determinants of recovery

The different recovery trajectories are broken down by RTP, return to SNR baseline, and return to baseline on the cognitive measure (the SCAT-5 or K-D); these timelines are compared for each concussed athlete in Table 4.3. No consistency was seen between the three measures for each athlete, and the time point at which each recovery landmark was met varies widely between athletes. Symptom number and severity returned to baseline or below between 5 and 15–17 days post-injury, respectively. Orientation also returned to baseline between 5–15 days. Concentration scores were met or exceeded by 3–5 days post-injury. Some neck pain (the only change in the SCAT-5 neurological domain) resolved by 3 days post-injury, while some resolved by mid-season or did not resolve. Balance either resolved between 3–10 days post-injury, or took longer (up to 20 days or until mid-season). Return-to-baseline for the King-Devick occurred in one athlete at 3 days post-injury and in the remaining five between 10-20 days. Note that the baselines for Athletes 4 and 11 were taken from the first year.

Table 4.3: Comparison of recovery across different measures.

| pt #[16] | RTP | SNR | Cognitive measure |
|---|---|---|---|
| 1 | by MS | never returned | return to all SCAT-5 @3 d |
| 2 | by 3 wks | never returned | return to all SCAT-5 @10 d |
| 3 | by 3 wks | higher @3 d | 3-17 days, depending on SCAT-5 domain |
| 4 | by MS | higher @5 d | |
| 5 | did not RTP | higher @3 d | return to all SCAT-5 @3 d, except neuro @15 d |
| 6 | by EOS | never returned | return to all SCAT-5 @3-5 d, except neuro @MS |
| 11 | by EOS | higher @5 d | |
| 12 | by 1 wk | higher @3d | faster K-D @3 d |
| 16 | by MS | returned by EOS | w/in 1s of K-D baseline @15 d, faster @20 d |
| 17 | *unknown* | higher @10 d | w/in 1s of K-D baseline @10 d, faster @20 d |
| 18 | did not RTP | returned by EOS | faster K-D @20 d |
| 19 | by 1 wk | never returned | faster K-D @10 d |
| 20 | by 2 wks | higher @EOS | faster K-D @EOS |
| 21 | *unknown* | never returned | K-D remained stable |

*Pt #- participant number; RTP- return-to-play; SNR- signal-to-noise ratio; BL- baseline; MS- mid-season; EOS- end-of-season; SCAT- Sport Concussion Assessment Test; K-D- King-Devick; neuro- neurological; d- days; wk(s)- week(s).*

When examined for correlations in all athletes overall, the SNR was weakly correlated with the K-D time at baseline, $\rho = .283$, $p = .010$, $N = 81$, CI = .062–.477. It was also negatively correlated with symptom amount, $\rho = -.306$, $p = .037$, $N = 47$, CI = -.551–-.012, and severity, $\rho = -.314$, $p = .032$, $N = 47$, CI = -.557–-.020. However, the SNR was not correlated with the K-D at any other time point, either overall or when examined by subgroups (concussed/non-concussed or female/male). Moreover, the post-injury SNR (within 2–5 days) was not correlated with the K-D, $\rho = .632$, $p = .368$, $N = 4$, CI = -.854–.992, or with the symptom amount, $\rho = .142$, $p = .715$, $N = 9$, CI = -.592–.747, or severity, $\rho = -.151$, $p = .698$, $N = 9$, CI = -.751–.586.

### 4.3.8 Cognitive differences between concussed and non-concussed athletes

Comparisons between the cognitive scores of concussed and non-concussed male athletes are reported in Supplemental Table 9.3. Mann–Whitney tests were run because of normality violations or outliers at one or both time points in all domains. Only two domains of the SCAT-5 show differences by concussion status: symptoms and orientation. When compared by injury group, the concussed athletes showed trends of lower symptom number and severity at baseline and end-of-season (rows 1–4) and higher orientation

[16] Athletes with no baseline SNR have been excluded from this table, and the baseline SNRs from the previous year were used for athletes 4 and 11.

scores (row 6), but none of these differences were statistically significant. The baseline and end-of-season K-D scores showed no between-groups differences. All effect sizes for these comparisons were moderate or small.

## 4.4 Conclusion

### 4.4.1 Summary

In total, 21 male athletes sustained a concussion during the study, constituting 24.7% of male participants and 17.4% of the study participants. This high proportion of male athletes who sustained a concussion is a biased representation of overall concussion prevalence because some of these athletes joined the study due to their concussion. Over 90% of these athletes had previously sustained at least one concussion, which is much higher than recent data from the ACC (Accident Compensation Corporation, 2022), which only shows that 32.8% of the 33,619 concussion claims from 2020–2021 were filed by patients with a history of concussion. This is likely because athletes would not have filed an ACC claim for their previous concussions; many of these athletes did not seek treatment for their qualifying concussion beyond that provided by the team physiotherapist. The ACC numbers also represent overall concussion claims (not specific to sport-related concussion). No reported concussions were sustained by female athletes, which is also inconsistent with the recent ACC data that shows 45.1% of the 33,619 claims were filed by female patients (Accident Compensation Corporation, 2022), including 11,940 sport-related concussions.

The concussed athletes showed no commonalities in post-concussive SNR changes, and the post-injury SNR was not significantly different from the baseline SNR (Table 4.3). The average SNR baseline for male athletes in this study was 12.8, and the average SNR within 3–5 days post-injury was 10.3 (Table 4.2). The average SNRs in my study by concussion status did not match those reported by Fong and colleagues (2020), who found the male athletes had an average non-concussed baseline of 4.80 (range: 4.07–5.68), and that the concussed athletes had an average SNR of 2.00 (range: 1.40–2.32). These are quite different from the averages seen in this study because they used a non-equivalent variable calculation in the previous iteration of their software. Perhaps the change in variable calculation unwittingly lost an element or construct that is sensitive to concussive injury.

Of the six athletes whose SNR exceeded their baseline during recovery, three demonstrated a higher SNR at day 3, two had higher SNRs by day 5, and the remaining SNR was higher at day 10. Time to RTP ranged from 10 days until the end-of-season

(Table 4.3), and the return-to-baseline exceeded the RTP in 60% of athletes (for whom this information was available), though the early assessment points (< 10 days post-injury) were missing for many concussed athletes. There was no clear pattern between return to baseline for SNR and the physiotherapist's determination that the athlete could RTP, which is consistent with the conclusion that there is no single recovery timeline for concussion (Kamins et al., 2017). This is important to consider when weighing the athlete's risk of re-injury against their return-to-baseline on a basic cognitive screen like the SCAT-5 (which also did not coincide with RTP in this study).

There was a marginally significant group × time interaction for SNR over a season between concussed and non-concussed athletes (Table 9.2). The SNR of the concussed male athletes was lower than the non-concussed male athletes by the end-of-season, though the SNRs for both groups were similar at baseline. The SNRs of the concussed athletes also showed a greater range at baseline than at the end-of-season (Figure 4.2), while the SNRs of the non-concussed athletes show little change in range across both time points (Figure 4.3). Athletes with concussions did not exceed an SNR of 16.4 by the end-of-season, while the maximal SNR for the non-concussed athletes was 34.4, equivalent to the range demonstrated at baseline. This "flattening" effect may indicate reduced electrophysiological activity weeks or months after the concussion.

No common features were observed across twice-concussed athletes (Figure 4.5). In addition to the two athletes with data for both injuries, another athlete sustained a previous concussion during the season (Athlete 14 in Table 4.2), but did not contribute data after this first injury. In total, these three athletes with second concussions in one season/year represent 14.3% of all participating concussed athletes. This rate is comparable to (if not slightly higher than) other studies which have reported 9–13.4% of athletes to sustain a second concussion within 12 months of the first (Brett et al., 2020; Nordström et al., 2014).

The SNR did not correlate with the cognitive measures at any time point beyond baseline. Though no cognitive domains changed significantly in the concussed athletes by the first post-injury assessment or the end-of-season (Supplemental Table 9.1), several domains showed non-significant changes or large effect sizes. Concentration scores showed a trend of increase in the concussed athletes at post-injury and the end-of-season, possibly due to the practice effect. Slight disorientation followed the concussion, but had recovered by the end-of-season. Lastly, the athletes who sustained concussions did not report any symptoms at the end-of-season, despite reporting a small amount at baseline; this effect is likely from non-reporting (due to a strong desire to return to play, rather than

a complete decrease of all symptoms). Symptom and orientation scores also showed trends of differences between the concussed and non-concussed athletes (Supplemental Table 9.3).

**Research Question 1:** Does the SNR change after acute concussion?

While the SNR does show change after concussion, the direction and degree of change show no consistent pattern.

**Research Question 2:** Does the SNR change during recovery, acutely and over a season?

The SNR demonstrated widely variable behaviour during recovery and did not return to baseline with any consistent pattern. While the SNR of the concussed athletes was less variable by the end-of-season, it was not significantly different to that of the non-concussed male athletes.

### 4.4.2 Limitations

Covid-19 lockdowns in 2020 and 2021 interrupted data collection at multiple points over two seasons, and caused much of the attrition seen, as athletes moved away, quit the team, had to work more, or their plans changed in another way due to the unpredictable stoppages of the season. As a result, the baseline data were separated from regular rugby play by three months in 2020.

Concussions reported in this study were determined by the team physiotherapists, and they were not all confirmed by a doctor. As a result, some athletes may not have sustained an actual concussion. For example, the physiotherapist reported that Athlete 18 may not have sustained a true concussion, though he was still included in this group because my notes indicated he acknowledged his injury as a concussion at the end-of-season assessment.

Inconsistent post-injury follow-up is a weak point of this study. The necessary preoccupation of the rugby organisation with Covid bubble sizes, testing, scanning in, changes to recommendations, and rushing to reschedule meant that my study was often unable to be prioritised, and that I did not always find out about a concussion within 72 hours. I struggled to complete all planned post-injury assessments, especially the first and second (<3 days and 3–5 days), as well as up to the full 20 days. The maximal number of time points (9) was only met for one concussed athlete, and the average number of data points (including baseline and end-of-season) was 5.5 across the concussed athletes. Additionally, several athletes joined the study after their concussions and did not provide

baseline data. Similar issues with inconsistent follow-ups were also acknowledged by Clayton and colleagues (2020).

Due to small sample size and inconsistent follow-up times, time since injury was not analysed as a post-injury factor in this study. Time since injury does not widely correlate with ERP changes (Boshra et al., 2019; Dupuis et al., 2000; Hudac et al., 2018; Lavoie et al., 2004; Ledwidge & Molfese, 2016; Moore, Broglio, et al., 2014). However, aspects or specific components may still be related (De Beaumont et al., 2007; Folmer et al., 2011; Gosselin et al., 2012; Thériault et al., 2009), and this is an interesting facet of electrophysiology in concussion assessment for further study.

This study also does not include any data on female athletes with concussions. It is unclear why no female athletes on the participating teams sustained concussions. Despite emailing every week during the season to ask about injuries, it is possible that injuries were not communicated to me. It is also possible that the female athletes use more effective injury-prevention strategies than the male athletes, as fewer of them reported big hits as well (see Section 5.3.3.3.1). In a related manner, SNR impedance also varied by hair length and thickness, and potentially head size as well.

### 4.4.3 Strengths

This study details the post-concussive trajectories of the SNR in 21 rugby athletes who sustained a concussion during their season. Despite the issues with Covid-19, the two seasons of this study yielded data from 121 total rugby athletes at two or more time points, which resulted in almost 10 athletes with concussions each year. While the post-injury trajectories were not complete or consistent enough for direct comparison, they provide a series of case studies to show how recovery activity of the SNR may look, and provide support for the need of multidimensional recovery assessment.

## 4.5 Take-home message

- Of 121 athletes, 21 male athletes sustained a concussion during the study (24.7% of male participants and 17.4% of the study participants).
- The average SNR baseline for male athletes in this study was 12.8, and the average SNR within 3–5 days post-injury was 10.3; the difference between these SNRs was not statistically significant.
- SNR magnitude did not correspond with return to baseline on the cognitive assessments or the physiotherapist's decision that the athlete can return to play.

# Chapter 5
# Study B: Changes to SNR in Non-concussed Athletes, by Concussion History, Sex, and Impact Exposure

## 5.1 Introduction and rationale

To understand the findings of the previous study, I investigated the context of what changes might be normal in non-concussed athletes. Two demographic factors commonly associated with electrophysiological differences are previous concussion history and sex, but these were not specifically mentioned in the other NuroChek publications (Fong et al., 2020; Fong et al., 2021; Salazar et al., 2021). Fong and colleagues studied an all-male population and did not report the concussion history of their participants (though participants with a recent concussion at baseline were excluded), and Salazar and colleagues used data from male and female athletes who had not had a concussion in the last year, but they did not report the results separately by sex or concussion history. Therefore, this study aims to understand what effects these two factors may have on the SNR.

As noted in Section 2.3.1, electrophysiological alterations after a concussion can become permanent, persisting for years despite no other symptoms or impairment (Broglio et al., 2009; Carrier-Toutant et al., 2018; X.-P. Chen et al., 2006; De Beaumont et al., 2007; Gaetz & Weinberg, 2000; Hudac et al., 2018; Ledwidge & Molfese, 2016; Olson et al., 2018; Ozen et al., 2013; Sicard et al., 2021). As measured by ERP, changes to electrophysiological networks or differences in processing strategies can act as a neural marker for concussion history (Ledwidge, 2018; Ledwidge & Molfese, 2016; Olson et al., 2018; Reches et al., 2017), and have been seen in athletes up to 50 years after retirement (De Beaumont et al., 2009; Fratantoni et al., 2017; Ruiter et al., 2019). Alterations have been seen in many components, including the P100, N200, and P300 (Broglio et al., 2009; Carrier-Toutant et al., 2018; Hudac et al., 2018; Moore, Hillman, et al., 2014; Moore et al., 2015; Olson et al., 2018; Yadav & Ciuffreda, 2015) and may be amplified in individuals with a history of multiple concussions (Broglio et al., 2011; Carrier-Toutant et al., 2018; De Beaumont et al., 2007; Gaetz et al., 2000; Gosselin et al., 2010; Pearce et al., 2021; Pontifex et al., 2009; Sicard et al., 2021; Slobounov et al., 2009; Thériault et

al., 2009; Thériault et al., 2011). The effect of concussion history on the SNR must be clarified to understand if it interferes with detection of current injury,

Beyond concussion, many studies have found larger SSVEP responses in female participants, when compared with male participants (Section 2.3.2.2). Wada and colleagues (1994) studied sex differences at 10 Hz with a flashing light stimulus, and found that female participants exhibited higher amplitudes than male participants across the EEG spectrum. Skosnik and colleagues (2006) used a flickering light on a computer screen to study cannabis use and sex differences, and found that female participants had stronger SSVEP signal amplitudes than male participants overall. Two further studies examining patients with schizophrenia (Krishnan et al., 2005; Wada et al., 1995) found larger amplitudes at the Oz site in female participants when compared to the male participants. In contrast, some ERP studies have found higher amplitudes in healthy male participants when compared to female participants (Bourisly & Pothen, 2016; Bourisly & Shuaib, 2018; Gölgeli et al., 1999), while others have found mixed results by sex (Nagy et al., 2003; Vaquero et al., 2004), which might be due to anatomical (thickness of skull/biological layers) or functional (hormonal/metabolic) differences (Hausinger & Pletzer, 2021; Hu et al., 2013; Skosnik et al., 2006; Wada et al., 1994).

Another factor that may affect the SNR of non-concussed athletes is exposure to repetitive impacts (Section 2.1.2). Rugby athletes sustain many impacts that do not result in concussion, but microscopic damage can accumulate over the season and may still affect the brain, as detected by ERP (Abbas et al., 2015; Clayton et al., 2020; Fickling, Poel, et al., 2021; Fickling et al., 2019; Fickling, Smith, et al., 2021; Richards, 2017; Wilson et al., 2015). Additionally, many boxers will sustain such impacts when fighting (not including the knock-outs that sometimes end a match). While the SNR showed no significant change in boxers before and after a match or in non-impact controls who performed equivalent exercise on a treadmill (Salazar et al., 2021), the effect of repetitive impacts in rugby athletes over a season on the SNR has not yet been examined.

This study focuses on Aim 3, which examines the electrophysiological differences of the three participant groups across the demographic factors of concussion history and sex. After determining the effects of these factors, this study examines the effects of repetitive impact on the athlete groups (Aim 4).

### 5.1.1 Research questions

This study addresses several research questions:

1. In non-concussed athletes and participants, is the SNR different across history of concussion?

2. In non-concussed athletes and participants, is the SNR different across sex?
3. Is the SNR affected by acute exposure to repetitive impacts?
4. Is the SNR affected by exposure to repetitive impacts over time?

## 5.2 Methods

### 5.2.1 Participants

This study includes participants from all three groups (rugby athletes, combat athletes, and non-athlete control participants), previously described in Section 3.1. Of the 121 rugby athletes, this study focuses on the 100 athletes who did not sustain concussions. This study also compares the baseline SNR data of the 19 combat athletes (impact and no-impact), and it examines data from a non-athlete control group of 17 participants. The SNR is reported for each participant group (by demographic and time point) below.

#### 5.2.1.1 Rugby athletes

The average SNRs of the rugby athletes by time point and demographic group can be found (in bold) in Table 5.1. Of the 121 rugby athletes, 22 of the 36 female athletes (61.1%) and 57 of the 85 male athletes (67.1%) reported a previous history of concussion, for an overall prevalence of 65.3%. The strongest signal was seen in a non-concussed male athlete at mid-season (39.0) and the weakest signal was seen in a male athlete after his concussion (1.3). The average age was 23, with little variation between concussion history or sex groups (Table 3.1).

Table 5.1: Average SNR of rugby athletes by demographic and time point.

| | | N= | SNR M | SD | SNR min | SNR max | SNR range[17] |
|---|---|---|---|---|---|---|---|
| Baseline | All | 114 | **10.573** | 5.713 | 2.4 | 30.1 | 27.7 |
| | **Non-concussed:** | 100 | **10.255** | 5.332 | 2.4 | 23.8 | 21.4 |
| | Female | 36 | **6.708** | 3.238 | 2.8 | 17.3 | 14.5 |
| | Male | 64 | **12.250** | 5.255 | 2.4 | 23.8 | 21.4 |
| | No concussion history | 40 | **10.535** | 4.943 | 3.2 | 22.6 | 19.4 |
| | Previous concussion | 60 | **10.068** | 5.609 | 2.4 | 23.8 | 21.4 |
| | | | | | | | |
| Mid-season | All | 66 | **10.814** | 7.444 | 1.9 | 39.0 | 37.1 |
| | **Non-concussed:** | 57 | **11.096** | 7.797 | 1.9 | 39.0 | 37.1 |
| | Female | 17 | **6.412** | 5.687 | 1.9 | 24.6 | 22.7 |
| | Male | 40 | **13.088** | 7.771 | 3.9 | 39.0 | 35.1 |
| | No concussion history | 17 | **10.788** | 5.615 | 2.1 | 21.7 | 19.6 |
| | Previous concussion | 40 | **11.228** | 8.619 | 1.9 | 39.0 | 37.1 |
| | | | | | | | |
| End- | All | 106 | **12.651** | 6.773 | 1.6 | 34.4 | 32.8 |

[17] For tables in this chapter, range = ($SNR_{max}$ – $SNR_{min}$).

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Non-concussed:** | 89 | **13.048** | 7.195 | 1.6 | 34.4 | 32.8 |
| | Female | 30 | **10.843** | 8.476 | 1.6 | 34.4 | 32.8 |
| | Male | 59 | **14.169** | 6.231 | 4.0 | 30.3 | 26.3 |
| | No concussion history | 37 | **12.316** | 7.559 | 2.8 | 34.4 | 31.6 |
| | Previous concussion | 52 | **13.569** | 6.952 | 1.6 | 30.3 | 28.7 |

*SNR- signal-to-noise ratio; SD- standard deviation; min- minimum; max- maximum.*

Rugby athletes were asked at the mid-season and end-of-season time points to report any suspected concussions or big head impacts sustained. To examine SNR trajectory in repetitive impacts over a season, 85 male athletes were coded into four groups, based on their level of impact exposure: 21 with a confirmed concussion; 10 who reported a big hit (e.g., blacking out briefly after a big hit and then continuing to play, sustaining a big hit and experiencing concussion symptoms in the following days, being cleared for concussion by the physiotherapist after a big hit, or an unreported injury that met the criteria for a concussion), 45 with regular repetitive impact exposure (active through the season, with no reported big hits or suspected concussions), and 9 with limited impact exposure (those who missed playing time for another reason, often a musculoskeletal injury). Self-reported impact exposure in the female athletes was not analysed due to small sample sizes.

#### 5.2.1.2 Combat athletes

Boxers (impact) and Brazilian Jiu Jitsu (no-impact) athletes were tested before and after a sparring session, and the average SNRs of these combat athletes can be found (in bold) in Table 5.2. The strongest signal was seen in a male boxer (27.9), and the weakest signal was seen in a female BJJ athlete (1.9). The average age was 32 (Table 3.2); on average, the no-impact athletes (35) were older than the impact athletes (29), and the female athletes (37) were older than the male athletes (29). None of the no-impact athletes reported a history of concussion, while seven impact athletes (63.6%) reported a history of concussion.

Table 5.2: Average SNR of combat athletes by demographic at both time points.

| | | **N=** | **SNR M** | **SD** | **SNR min** | **SNR max** | **SNR range** |
|---|---|---|---|---|---|---|---|
| Pre | All | 19 | **10.116** | 7.1310 | 1.9 | 27.9 | 26.0 |
| | Impact | 11 | **13.064** | 7.9736 | 2.4 | 27.9 | 25.5 |
| | No-impact | 8 | **6.063** | 2.7391 | 1.9 | 10.3 | 8.4 |
| | Female | 7 | **6.643** | 6.8024 | 1.9 | 21.6 | 19.7 |
| | Male | 12 | **12.142** | 6.7690 | 3.5 | 27.9 | 24.4 |
| | | | | | | | |
| Post | All | 19 | **10.737** | 5.6982 | 3.6 | 22.5 | 18.9 |
| | Impact | 11 | **12.327** | 6.4134 | 4.7 | 22.5 | 17.8 |
| | No-impact | 8 | **8.550** | 3.9104 | 3.6 | 15.1 | 11.5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Female | 7 | **10.186** | 5.9364 | 3.6 | 18.9 | 15.3 |
| | Male | 12 | **11.058** | 5.7968 | 4.7 | 22.5 | 17.8 |

*SNR- signal-to-noise ratio; SD- standard deviation; min- minimum; max- maximum.*

Combat athletes were recruited from local gyms whose clients participated in sparring, with and without head impacts. Boxers receive many punches to the head and body over a round of sparring, while BJJ athletes do not. Instead, BJJ requires slow, controlled movements designed to decrease the momentum of one's opponent, and impacts to the head or body during a sparring session are not common.

Twenty-four combat athletes with and without exposure to repetitive impacts were assessed before and after a sparring round, twenty of whom provided SNR data. The impact group consisted of 11 boxers, and 8 of the no-impact athletes were recruited from BJJ; the remaining no-impact athlete was tested before and after a cardiovascular "drill bootcamp" workout program. One female control athlete was further removed from SNR analyses because of an incorrect headset fitting at baseline. In total, 19 combat athletes were included in data analysis.

#### 5.2.1.3 Non-athlete control group

As a comparison for athletes with and without head impact exposure, a group of non-athletes were recruited from a local social media page and completed the headset assessment at one time point. The SNR averages and demographic information of these 17 non-athlete participants are reported in Table 5.3. The highest SNR was seen in a man with a previous concussion (28.4), and the lowest SNR was seen in a woman with no concussion history (2.2). The average age was 31 years, and the youngest subgroup was those with a previous concussion (Table 3.3).

Table 5.3: Average SNR of control participants by demographic group.

| | **N=** | **SNR M** | **SD** | **SNR min** | **SNR max** | **SNR range** |
|---|---|---|---|---|---|---|
| All control | 17 | **8.782** | 5.913 | 2.2 | 28.4 | 26.2 |
| Female | 6 | **6.783** | 4.6611 | 2.2 | 13.9 | 11.7 |
| Male | 11 | **9.873** | 6.4326 | 5.1 | 28.4 | 23.3 |
| No concussion history | 7 | **6.529** | 3.9373 | 2.2 | 13.9 | 11.7 |
| Previous concussion | 10 | **10.36** | 6.7165 | 5.1 | 28.4 | 23.3 |

*SNR- signal-to-noise ratio; SD- standard deviation; min- minimum; max- maximum.*

### 5.2.2 Procedure

Participants completed the informed consent (Appendix 9.2.1) and the demographic information forms (Appendix 9.2.2), then completed assessments with the

NuroChek system and the cognitive measures, which varied between participant groups. The athletes were then thanked for their participation and given the information sheet to take home. The rugby athletes were tested at baseline, mid-season, and end-of-season using the NuroChek headset and the SCAT-5 or the K-D, as described in Sections 3.3.1 and 4.2.2. The non-athlete control participants were tested at one time point, and completed assessments of the NuroChek, SCAT-5, K-D, and TMTb, as described in Sections 3.3.3. Details of the materials (Section 3.2) and procedure (Section 3.3) have been previously reported.

Combat athlete participants were recruited before their sparring session. They completed the symptom inventory of the SCAT-5 (Appendix 9.2.3 and Section 3.2.4), then completed two trials with the NuroChek system, the digit span subtest, and the TMTb (Figure 3.9 and Section 3.2.5). The athletes participated in a round of sparring that either included repetitive impacts (boxing) or did not (BJJ), which lasted between 30-60 minutes. Once they finished their training session, the athletes again completed the symptom inventory, NuroChek trials, digit span, and TMTb. The athletes were then thanked for their participation and given the information sheet to take home.

This study has elements of both a within-groups (across baseline, mid- and end-of-season) design for the rugby athletes and a between-groups (concussion history/none, female/male, and with/without repetitive impacts) design for the rugby athletes and non-athletes. This study also has elements of both a within-groups (before and after the sparring session) and a between-groups (with/without repetitive impacts, female/male, and concussion history/none) design for the combat athletes.

### 5.2.3 Statistical approach

This study examines Aims 3 and 4, and uses data from all three participant groups. First, the data from the non-athlete control participants were examined using a Kruskal–Wallis test for differences between the athlete groups, and Mann–Whitney tests were used to compare the effects of concussion history and sex.

Next, data from all participants were compared by concussion history and sex and analysed separately; between-group differences were examined at baseline (and at mid-season and end-season in the rugby athletes) using Mann–Whitney tests, and differences in SNR trajectory were examined over time for each factor in the separate athlete groups using Friedman's ANOVAs or Wilcoxon signed-rank tests (sample size and average SNR for each group are reported in Table 3.1). Finally, a Chi-square was used to determine any association between history of concussion and sex in all participants. The effects of

repetitive impacts were also examined by concussion history and sex, as well as in the whole participant population (unsplit) for an overall effect.

To examine the effects of concussion history on the SNR over time, Friedman's ANOVAs were run to compare the SNR at baseline, mid-season, and end-of-season in those with and without a history of concussion. The SNR was not compared by concussion history after immediate impact exposure in the combat athletes because the no-impact combat athletes all reported no concussion history, confounding this analysis. Comparisons of the cognitive measures over time were also analysed by concussion history in the rugby athletes. Finally, to examine the effect of impact exposure and concussion history at the end-of-season, Mann–Whitney tests were used to compare athletes with repetitive impact exposure to a limited impact exposure group comprised of athletes who missed playing time and the non-athlete control group (sample sizes for each group reported in Table 3.3).

The overall effect of sex was compared in all participant groups at baseline, then non-parametric comparisons by sex were run in the non-concussed rugby athletes between groups at each time point, and within groups over time. Signal quality was also compared between sex groups, specifically by presence or absence of the harmonic artefact (using Chi-square and Mann-Whitney tests), the test-retest reliability of the SNR over both trials (using Mann–Whitney and Wilcoxon signed-rank tests), and any effect for time of day (before or after noon) was examined using Mann–Whitney tests.

To analyse the data from the combat athletes (sample sizes for each group reported in Table 3.2), a Wilcoxon signed-rank test was used for the female athletes because normality violations and an outlier were only present at the SNR pre-round time point of the female group, and a paired t-test was used for the male athletes since they demonstrated no normality violations. To compare the effects of impact exposure and sex on the SNR at the end-of-season, female and male rugby athletes with regular impact exposure were compared to the limited impact exposure group of athletes who reported missing playing time and non-athlete controls. Analyses comparing impact exposure in the male rugby athletes were run using non-parametric tests because of normality violations and outliers. Because of the four different impact exposure groups (concussed, big hits, repeated impact exposure, and limited impact exposure), Kruskal-Wallis tests were run to compare the means of groups at each time point, and Friedman's ANOVAs or Wilcoxon signed-rank tests were run to identify changes in each impact exposure group during the season.

Lastly, the overall effect of repetitive impacts was examined (without being split by sex). This analysis examined Aim 4 and used the regular impact exposure data for all participants (end-of-season for rugby athletes and baseline for combat athletes and non-athlete controls), as well as data from combat athletes to identify any effects over time. A Mann–Whitney test was used to compare all participants by impact vs no impact exposure, and a repeated-measures ANOVA was used to compare the combat athletes by impact exposure before and after a sparring session, as well as the rugby athletes by regular vs limited impact exposure over a season (baseline, mid-season, and post-season). One no-impact female combat athlete was further removed from SNR analyses because of an incorrect headset fitting at baseline; a second no-impact female combat athlete experienced one minor head impact during her sparring session, but she was not excluded from the SNR analyses. To analyse the performance on cognitive measures by the combat athletes, Mann—Whitney and Wilcoxon signed-rank tests were run for the symptom inventory and the digit span, while the scores of the TMTb were standardised into t-scores, then compared by independent-sample and paired t-tests. Sample sizes of the cognitive measures for the limited-impact rugby athletes were not large enough to undertake statistical analyses between impact exposure groups of rugby athletes over time.

## 5.3 Results

### 5.3.1 No differences of SNR found in non-athlete control group

The SNRs of the non-athlete control group were examined by concussion history and sex for differences from the athlete group; these analyses are presented in Table 5.4. A Kruskal-Wallis test was used to compare the SNRs of the control participants to those of the athletes (rugby and combat), and Mann–Whitney tests were used to compare demographic factors within the control participants. When all participant groups were compared to each other at baseline, the SNRs were not significantly different (row 1). Differences by concussion history (row 2) or sex (row 3) were not present in the control group.

### 5.3.2 No significant differences in SNR across concussion history

When the SNRs of all participants were compared at baseline (N = 150), there was no overall difference for SNR between concussion history groups, U = 2929.500, p = .411, r = .067. However, because of previous research that reported an association between electrophysiology and concussion history, these were explored in more detail. Comparisons of impact exposure by concussion history included the rugby and non-

athlete participants, and concussion history was examined over time in the rugby athletes. Analyses on concussion history in the combat athletes over time could not be run because of a statistically significant overlap between impact exposure and concussion history, $\chi^2 = 8.061$, $p = .005$, Cramer's $V = .651$, and the sample size of the never-concussed boxers was too small to run analyses for the boxers only (Table 5.5).

Table 5.4: Comparisons of SNR in control group to other athlete participant groups (rugby and combat).

| | G1 | G2 | test | stat (df) | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | SNR BL | Athlete pt group | Kruskal-Wallis | 2.484 (2) | 0.289 | 0.016 | | 151 | | | |
| 2 | CH control SNR | No CH control SNR | Mann-Whitney | 49.500 | 0.161 | 0.343 | 1.416 | 11 | 10.09 | 6 | 7.00 |
| 3 | Female control SNR | Male control SNR | Mann-Whitney | 45.000 | 0.256 | 0.293 | 1.207 | 6 | 10.09 | 11 | 7.00 |

**- p < .05; **- p < .01; ***- p < .001; SNR- signal-to-noise ratio; CH & conc hist- concussion history; pt- participant; G- group.*

Table 5.5: Sample sizes of groups by impact exposure and concussion history for Chi-square.

| | Concussion history | No concussion history |
|---|---|---|
| Impact exposure | 7 | 4 |
| No impact exposure | 0 | 8 |

#### 5.3.2.1 No change in SNR over a season by concussion history

The comparisons between rugby athletes with a history of concussion and those who had never sustained a concussion at all three time points are reported in Table 5.6. Between-group comparisons were made using the Mann–Whitney test (rows 1–3), but the SNRs did not differ by concussion history at any time point. Friedman's ANOVAs were run to compare the changes in SNR over time by concussion history (rows 4–5); the SNR trajectory of those with a history of concussion showed marginally significant changes over time, but the SNR of the never-concussed athletes showed no change over time.

#### 5.3.2.2 Changes to cognitive measure scores by concussion history

The rugby athletes were compared by concussion history and the same non-parametric tests were re-run; only a few domains showed any differences, with most only

trending toward significance. The results with a significance of $p < .10$ are reported in Table 5.7.

Mann–Whitney tests were run to compare the scores of those with and without concussion history at each time point. A trend of higher concentration score was seen in the previously-concussed athletes when compared to the never-concussed athletes at baseline ($U = 265.000$, $p = .059$, $r = .307$), but not at any other time points; no other cognitive domains showed statistically significant between-group differences. To examine within-group differences over time, Friedman's ANOVAs were run for the three time points in each domain, and significant pairwise comparisons were reported. The domain of orientation showed statistically significant change over time in those with a history of concussion (row 1), but none of the pairwise comparisons were statistically significant. The King-Devick scores also showed a statistically significant change over time in those with a concussion history, specifically a significantly faster score from baseline to end-of-season (rows 2–3).

Table 5.6: Comparisons of SNR over time in non-concussed rugby athletes, by concussion history.

| | G1 | G2 | test | stat | p | effect size | z score | N = | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Conc hist BL | No CH BL | Mann-Whitney | 1113.000 | 0.540 | -0.061 | -0.612 | 100 | 60 | 49.05 | 40 | 52.68 |
| 2 | Conc hist MS | No CH MS | Mann-Whitney | 316.000 | 0.675 | -0.055 | -0.419 | 57 | 40 | 28.40 | 17 | 30.41 |
| 3 | Conc hist EOS | No CH EOS | Mann-Whitney | 1079.000 | 0.330 | 0.103 | 0.974 | 89 | 52 | 47.25 | 37 | 41.84 |
| 4 | Conc hist | BL, MS, EOS | Friedman's | 5.685 (2) | **0.058** | 0.089 | | 32 | | | | |
| 5 | No CH | BL, MS, EOS | Friedman's | .143 (2) | 0.931 | 0.005 | | 14 | | | | |

**- p < .05; **- p < .01; ***- p < .001; BL- baseline; MS- mid-season; EOS- end-of-season; CH & conc hist- concussion history; G- group.*

Table 5.7: Comparison of cognitive changes over time, by concussion history.

| | Group/ domain | time points | test | stat | p | effect size | z score | N = | BL mean rank | MS mean rank | EOS mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Conc hist orient | BL, MS, EOS | Friedman's | 8.909 (2) | **0.012*** | 0.262 | | 17 | 2.38 | 1.68 | 1.94 |
| 2 | Conc hist K-D | BL, MS, EOS | Friedman's | 7.194 (2) | **0.027*** | 0.212 | | 17 | 2.44 | 2.03 | 1.53 |
| 3 | | BL & EOS | pairwise | .912 | **0.024*** | **0.594** | 2.658 | | | | |

**- p < .05; **- p < .01; ***- p < .001; BL- baseline; EOS- end-of-season; CH & conc hist- concussion history; orient- orientation; concen- concentration; K-D- King-Devick.*

#### 5.3.2.3 Differences in SNR by concussion history and impact exposure over time

To examine differences in SNR by concussion history and impact exposure, the end-of-season data from the rugby athletes and the data from the non-athlete group were pooled together and compared; these results are reported in Table 5.8. The combat athletes were not included in these analyses because of the confounding overlap between concussion history and regular repetitive impact exposure (Table 5.5). Mann–Whitney tests compared those with concussion history to those with no previous concussions by impact exposure group, then compared the effects of impact exposure separately in those with and without a history of concussion. Of the participants with limited impact exposure (non-athletes or rugby athletes who missed more than three weeks of playing time), those with a history of concussion had significantly higher SNRs (with a moderate effect size) than the never-concussed participants (row 2), but no effect for concussion history was seen in those with regular impact exposure (row 1). Of the never-concussed participants, those with regular impact exposure had significantly higher SNRs (with a moderate effect size) than those with limited impact exposure (row 4), but no effect for impact exposure was seen in those with a concussion history (row 3).

A Chi-square compared the sex and concussion history of all participants at baseline (N = 161), but it was not significant, $\chi^2 = 1.591$, p = .207, Cramer's V = .099. Mann–Whitney tests were run at all three time points for the non-concussed rugby athletes (n = 100) to examine the interactive effects of concussion history by sex on the SNR (Supplemental Table 9.4), but none of the analyses showed any statistical significance or moderate to large effect sizes.

### 5.3.3 Differences in SNR across sex

#### 5.3.3.1 Overall lower SNR in female participants

Table 5.9 shows the overall sex comparisons between participant groups (rugby, combat, and non-athletes) at their baseline. The SNR was significantly different by sex with a moderate effect size (row 1); specifically, the SNR magnitude of the male participants was higher than that of the female participants. When separated by sex, the SNR did not differ significantly across binary impact groups (rows 2–3) in male or female participants. The comparison of SNR by sex in the non-athlete control group was not statistically significant (Table 5.4, row 3), but sex differences were found in both the rugby and combat athlete groups, and are discussed separately over time because of the difference in follow-up intervals.

Table 5.8: Comparisons of SNR by impact exposure and concussion history in rugby athletes and non-athletes at the end-of-season.

| | G1 | G2 | test | stat | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | CH regular impact | No CH regular impact | Mann-Whitney | 896.500 | 0.488 | 0.142 | 0.694 | 47 | 43.07 | 35 | 39.39 |
| 2 | CH limited impact | No CH limited impact | Mann-Whitney | 107.500 | **0.017*** | 0.487 | 2.386 | 15 | 15.17 | 9 | 8.06 |
| 3 | CH regular impact | CH limited impact | Mann-Whitney | 426.500 | 0.224 | 0.155 | 1.217 | 47 | 33.07 | 15 | 26.57 |
| 4 | No CH regular impact | No CH limited impact | Mann-Whitney | 254.000 | **0.004**** | 0.423 | 2.809 | 35 | 25.26 | 9 | 11.78 |

**- p < .05; **- p < .01; ***- p < .001; BL- baseline; MS- mid-season; EOS- end-of-season; CH- concussion history; G- group.*

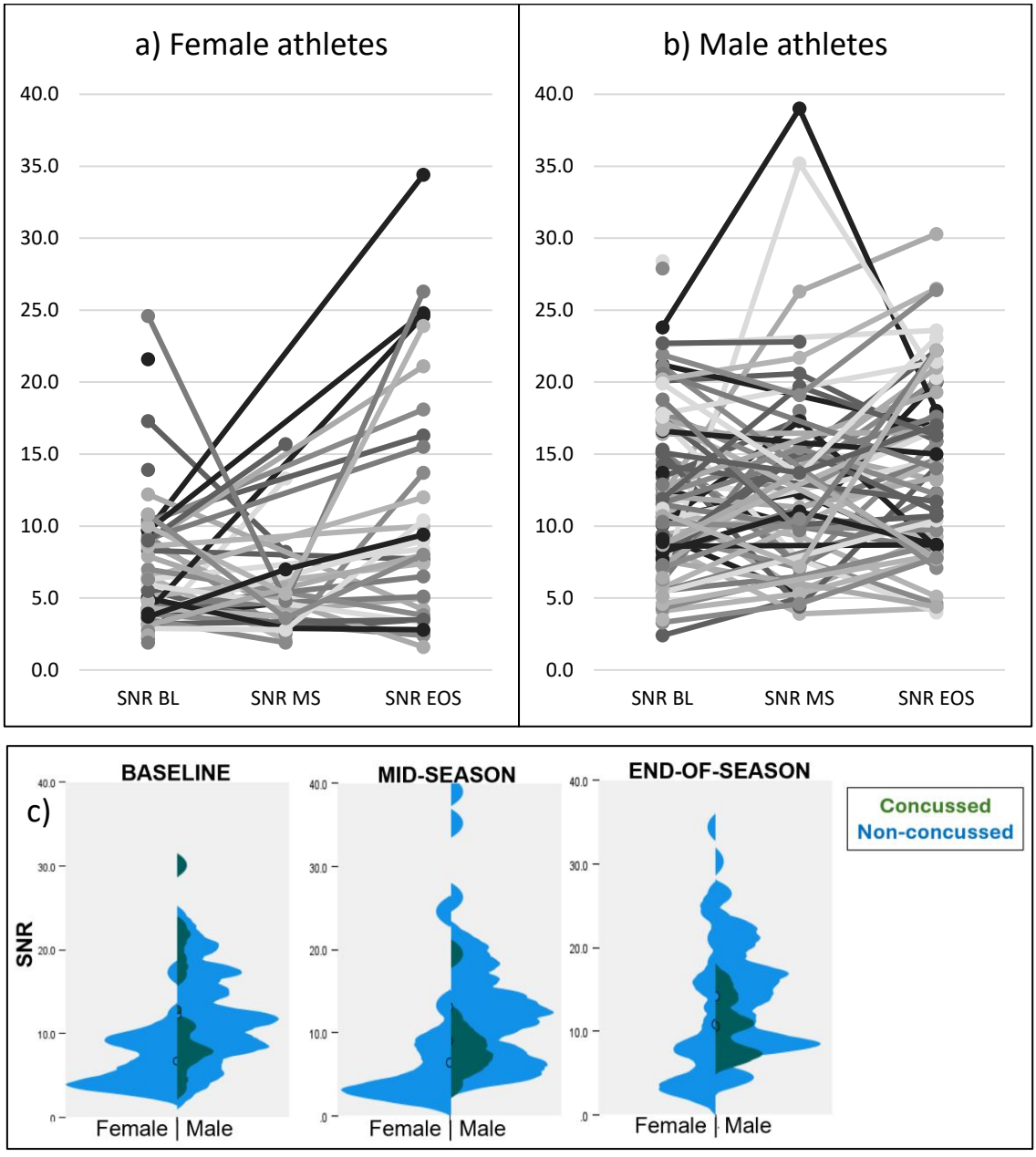
Table 5.9: Comparisons of baseline SNR in participant groups by sex.

| | G1 | G2 | test | stat | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Female | Male | Mann-Whitney | 4047.500 | **<0.001**** | 0.476 | 5.873 | 50 | 46.55 | 102 | 91.18 |
| 2 | Female | Pt group | Kruskal-Wallis | 1.208 (2) | 0.547 | 0.025 | | 50 | | | |
| 3 | Male | Pt group | Kruskal-Wallis | 5.813 (3) | 0.121 | 0.048 | | 102 | | | |

*SNR- signal-to-noise ratio; CH & conc hist- concussion history; BL- baseline; G- group.*

In addition to being lower overall, the SNRs of the female participants showed a generally lower distribution (Figure 5.1), which can also be seen in the range and standard deviation columns of Table 5.1–Table 5.3. While female participants did demonstrate high SNRs (i.e., above 4 standard deviations, or roughly 20.0) in some circumstances, the frequency of these events was low: one female athlete demonstrated SNRs higher than 20.0 at two time points (MS and EOS) and four more female athletes exhibited an SNR over 20.0 at the end-of-season, but no other female athletes exceeded a maximum SNR of 17.3 at baseline or 13.3 at mid-season. A direct comparison by sex for each time point is represented in (c).

Figure 5.1: Baseline SNR of all female (a) and male (b) participants, and season trajectories for the rugby athletes. (c) compares these distributions by sex and concussion status at each time point.




*SNR- signal-to-noise ratio; BL- baseline; MS- mid-season; EOS- end-of-season.*

#### *5.3.3.1.1 Harmonic artefact in female athletes*

A harmonic "echo" of the SNR was seen in many readings and created interference within the noise value of the SNR (Figure 3.7); after the first season of data collection, this artefact seemed to be more common in the female athletes than the male athletes. To test this, both trials of all SNR baseline data (rugby, combat, and non-athletes), as well as both trials of the mid-season and end-of-season data from the rugby athletes, were pooled to increase the sample for analysis of the harmonic pattern within the population (N = 791). Each SNR trial was manually coded for the presence or absence of the harmonic artefact that appeared in the EEG pattern at various magnitudes relative to the 15 Hz signal.

Though the group sizes were larger, the test of normality was violated in all conditions, so non-parametric analyses were used to study the prevalence of the harmonic pattern. A Chi-square test was used to analyse the association of the categorical variables of sex and harmonic presence. The harmonic pattern was present in 26.5% of readings taken from participants overall, representing 51.8% of the readings from female participants and 15.1% of readings taken from male participants. This proportion across sex was significantly different with a moderate effect size, $\chi^2 = 117.639$, $p < 0.001$, Cramer's $V = 0.386$ (Table 5.10).

Table 5.10: Sample sizes for Chi-square of harmonic presence by sex.

| Sex | Harmonic | No harmonic |
|---|---|---|
| Female | 128 | 119 |
| Male | 82 | 462 |

Mann–Whitney tests were then used to compare the harmonic and clear SNR magnitudes to each other (Table 5.11). The SNRs that presented with the harmonic pattern were significantly lower (with a small effect size) than the SNRs with no harmonic pattern in the EEG (row 1); this effect was more significant in male participants than female participants (rows 2–3).

#### *5.3.3.1.2 Higher SNR for female participants on second trial*

Since at least two trials were performed at each assessment point, these two time points from all participants (N = 162) were compared to each other to evaluate test-retest reliability. All second trials were performed within five minutes of the first. Wilcoxon signed-rank tests were used to compare the athletes who completed two trials. Friedman's

ANOVA was used to compare the few male athletes who contributed three readings (usually to improve the fitting), but the sample size of female athletes with three time points was too small for statistical analysis (n = 4). These results are presented in Table 5.12; because of sex differences (rows 1–2), reliability was also analysed separately by sex. The SNR was significantly higher at the second trial (with a moderate effect size) for the female participants (row 3), but statistically similar across both trials for the male participants (row 4). There were no statistically significant changes across the male participants who were assessed for a third trial (row 5).

Table 5.11: Comparisons of SNR by presence of harmonic pattern and sex.

| | G1 | G2 | test | stat | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | SNR harmonics | SNR no harmonics | Mann-Whitney | 38361.000 | **<0.001*** ** | -0.284 | -7.980 | 210 | 288.17 | 581 | 434.97 |
| 2 | Female SNR harmonics | Female SNR no harmonics | Mann-Whitney | 6691.000 | **0.099** | -0.105 | -1.649 | 128 | 116.77 | 119 | 131.77 |
| 3 | Male SNR harmonics | Male SNR no harmonics | Mann-Whitney | 12416.000 | **<0.001*** ** | -0.213 | -4.975 | 82 | 192.92 | 462 | 286.62 |

**- p < .05; **- p < .01; ***- p < .001; G- group.*

Table 5.12: Comparison of two SNR trials taken at each time point from all participants, by sex.

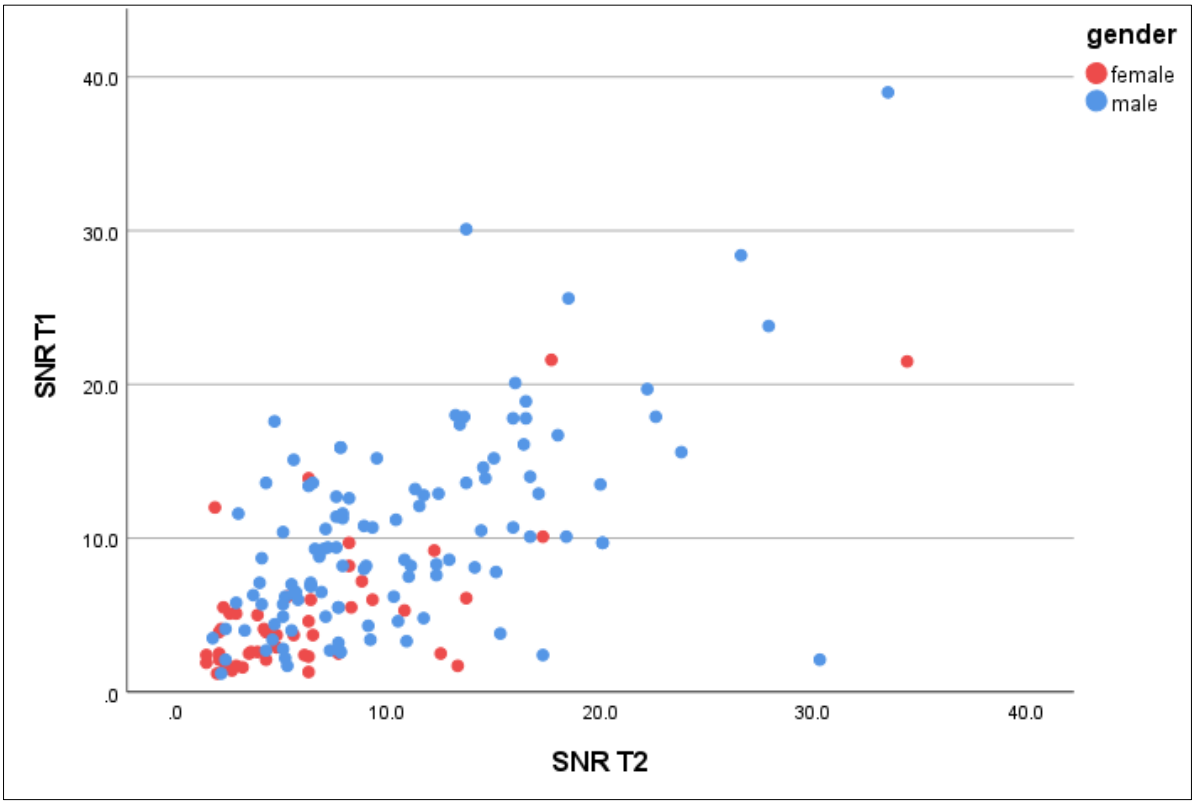
| | G1 | G2 | test | stat (df) | p | effect size | z score | Std error | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Female SNR1 | Male SNR1 | Mann-Whitney | 4371.000 | **<0.001*** ** | **0.835** | 5.844 | 274.223 | 49 | 48.4 | 113 | 95.68 |
| 2 | Female SNR2 | Male SNR2 | Mann-Whitney | 4118.500 | **<0.001*** ** | **0.703** | 4.923 | 274.221 | 49 | 53.95 | 113 | 93.45 |
| 3 | Female SNR1 | Female SNR2 | Wilcoxon signed-rank | 803.500 | **0.011*** | 0.362 | 2.535 | 94.483 | 49 | 5.03 | | 6.40 |
| 4 | Male SNR1 | Male SNR2 | Wilcoxon signed-rank | 3364.000 | 0.680 | 0.039 | 0.413 | 349.044 | 113 | 10.20 | | 10.58 |
| 5 | Male | SNR1, SNR2, SNR3 | Friedman's | 1.750 (2) | 0.417 | 0.109 | | | 8 | | | |

**- p < .05; **- p < .01; ***- p < .001; SNR- signal-to-noise ratio; SNR1- first trial; SNR2- second trial; G- group; Std- standard.*

To examine any effects that time of day may have had on the SNR, data were coded as being taken before or after noon, and these data were compared to each other (Supplemental Table 9.5), but there was no statistically significant effect for time of day (rows 1–2). Data were again split by sex and the same comparisons were run to see if SNR differed by time of day in each sex group. Higher SNR (with a moderate effect size) was seen in female participants on the second trial before noon, W = 365.000, p = .022, r = .399 (row 7). No other times of day showed statistically significant differences trials for the male or female participants (rows 3–6), and no other groups showed statistically significant changes between the two trials (rows 8–10).

The reliability of the SNR over two trials can also be seen In Figure 5.2, where the line y = x would indicate identical SNRs for both trials. In fewer than five instances, an athlete demonstrated an identical SNR in both trials during a testing session. While the maximal range for female participants is nearly that of the male participants, the SNRs of the female participants (in red) were more likely to be low for both trials (represented by the dense clusters in the bottom left), where the SNRs of the male participants (in blue) showed a less concentrated distribution with higher magnitudes.

Figure 5.2: SNRs of all participants across two trials, by sex.

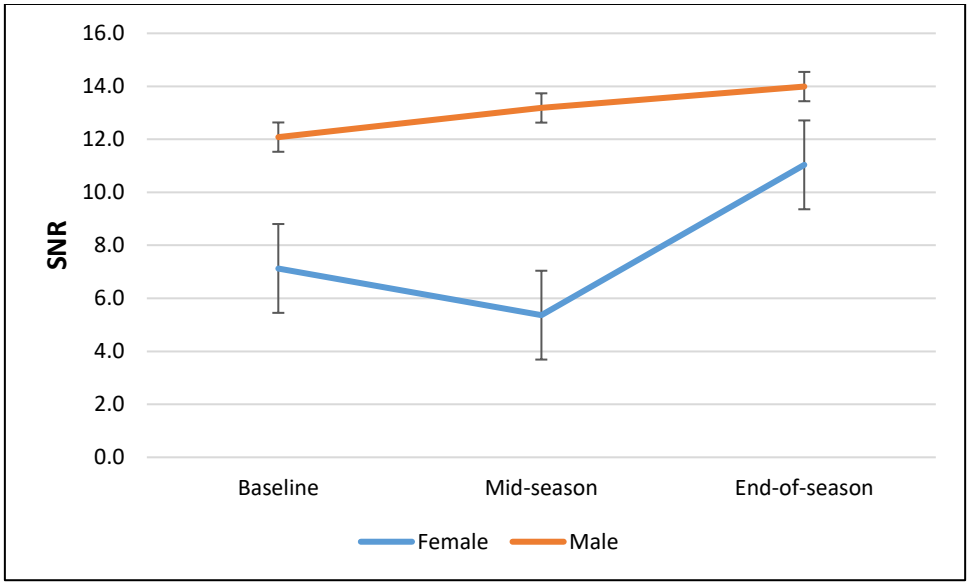



*SNR- signal-to-noise ratio; T1- first trial; T2- second trial.*

### 5.3.3.2 Increases of SNR over time in female rugby athletes

Nearly 30% of the 121 rugby athletes were female, allowing us to study sex differences with robust sample sizes. Comparisons of SNR by sex in non-concussed rugby athletes are reported in Table 5.13. Female SNRs were significantly lower than male SNRs at all three time points (rows 1–3), with large effect sizes for baseline and mid-season, and a small effect size for the end-of-season. When the SNR was compared over time in female and male athletes, the SNR of the female athletes showed a trend of increase (with a large effect size) from mid-season to the end-of-season (rows 4–5), but the SNR of the male athletes showed no change over time (row 6); these trajectories are visualised in Figure 5.3. This trend of increase in female athletes partially reduced the difference between sexes at the end-of-season time point (row 3).

Figure 5.3: SNR by sex across the season.




*SNR- signal-to-noise ratio.*

### 5.3.3.3 Differences in SNR by sex and impact exposure after a season of rugby

To examine the SNR by sex and impact exposure, female and male rugby athletes with regular impact exposure were compared to participants with limited impact exposure (those who reported missing playing time or the control participants); these analyses are reported in Table 5.14. Though they had similarly small effect sizes, female athletes with regular exposure demonstrated significantly lower SNRs than male athletes with regular exposure (row 1); however, no effect for sex was seen in those with limited exposure (row 2). Among males, athletes with regular exposure demonstrated significantly higher SNRs (with a moderate effect size) than participants with limited exposure (row 4), but no effect for degree of exposure was seen in the female participants (row 3).

Table 5.13: Comparisons of SNR over time in non-concussed rugby athletes, by sex.

| | G1 | G2 | test | stat | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Female BL | Male BL | Mann-Whitney | 429.500 | **<0.001*** ** | **-0.519** | -5.189 | 36 | 30.43 | 64 | 61.79 |
| 2 | Female MS | Male MS | Mann-Whitney | 120.500 | **<0.001*** ** | **-0.507** | -3.829 | 17 | 16.09 | 40 | 34.49 |
| 3 | Female EOS | Male EOS | Mann-Whitney | 573.000 | **0.007**** | -0.287 | -2.708 | 30 | 34.60 | 59 | 50.29 |
| | **group** | **time** | **test** | **stat (df)** | **p** | **effect size** | **z score** | **N =** | **BL mean rank** | **MS mean rank** | **EOS mean rank** |
| 4 | Female | BL, MS, EOS | Friedman's ANOVA | 5.636 | **0.060** | 0.256 | | 11 | 1.91 | 1.55 | 2.55 |
| 5 | | MS & EOS | pairwise | -1.000 | **0.057** | **-0.707** | -2.345 | | | | |
| 6 | Male | BL, MS, EOS | Friedman's ANOVA | 0.619 | 0.734 | 0.009 | | 35 | 1.99 | 1.91 | 2.10 |

**- p < .05; **- p < .01; ***- p < .001; BL- baseline; MS- mid-season; EOS- end-of-season; SNR- signal-to-noise ratio; G- group.*

Table 5.14: Comparisons of SNR at end-of-season by impact exposure and sex.

| | G1 | G2 | test | stat | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Female impact | Male impact | Mann-Whitney | 1029.000 | **0.008**** | 0.295 | 2.670 | 28 | 31.75 | 54 | 46.56 |
| 2 | Female limited impact | Male limited impact | Mann-Whitney | 87.000 | 0.159 | 0.288 | 1.409 | 8 | 9.63 | 16 | 13.94 |
| 3 | Female impact | Female limited impact | Mann-Whitney | 136.500 | 0.358 | 0.155 | 0.932 | 28 | 19.38 | 8 | 15.44 |
| 4 | Male impact | Male limited impact | Mann-Whitney | 624.500 | **0.007**** | 0.322 | 2.693 | 54 | 39.06 | 16 | 23.47 |

**- p < .05; **- p < .01; ***- p < .001; BL- baseline; MS- mid-season; EOS- end-of-season; G- group.*

#### *5.3.3.3.1 SNRs are higher after a season of repetitive impacts than a concussion in male rugby athletes*

Thirty-one athletes (female n = 7) reported impacts that did not result in a diagnosed concussion, and fifteen of these athletes (female n = 2) were cleared for concussion by the team physiotherapist. Twelve of these reported impacts that met the criteria for "big hits" (memorable hits that resulted in concussion symptoms such as visual disturbance or headache) and ten were included in this group for analysis (because of no comparison groups, the two female athletes were not included in these analyses).

To examine if self-reported degree of impact exposure affected the SNR, the male rugby athletes (n = 85) were coded into different impact exposure groups; the average SNR and ranges of each group at baseline and end-of-season can be found (in bold) in Table 5.15. Only the male athletes were included in these analyses because the groups of big hits and concussions were small or not represented in the female athletes.

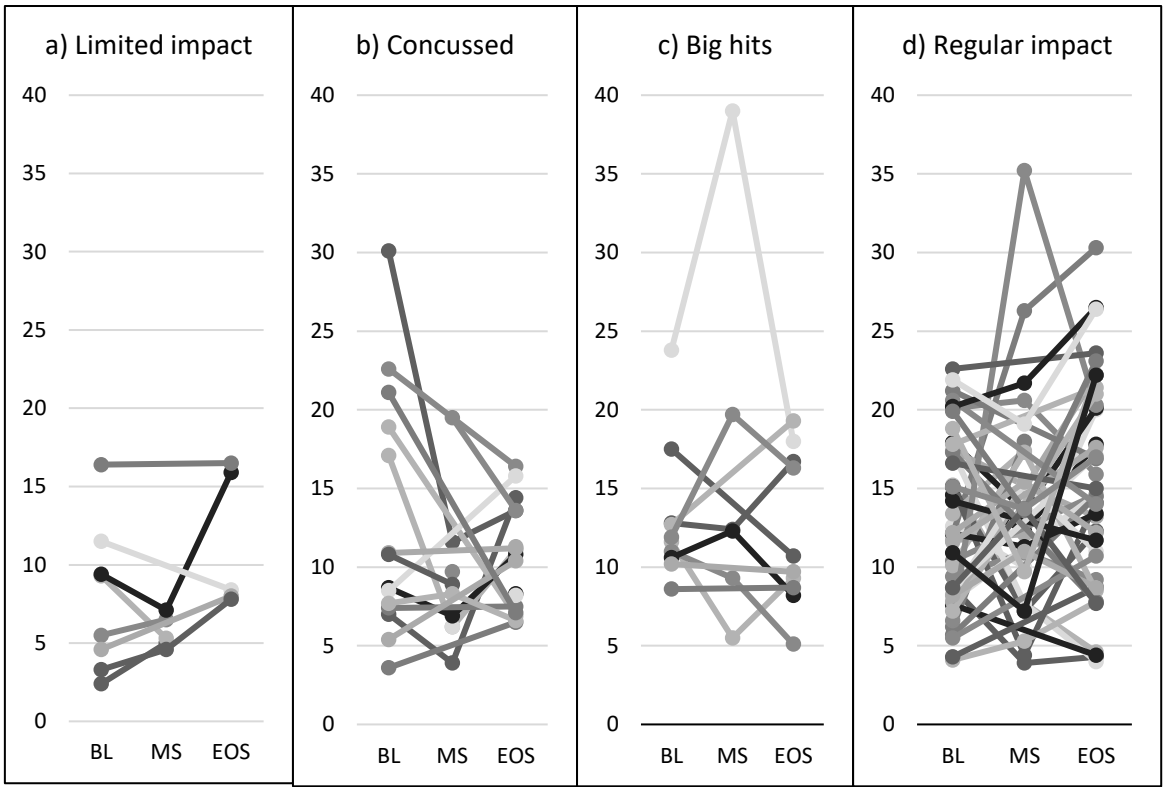
Table 5.15: Average SNR in male rugby athletes over time, by impact exposure group.

| | | N= | **SNR M** | SD | Min | Max | Range | CH %age |
|---|---|---|---|---|---|---|---|---|
| baseline | Concussion | 14 | **12.843** | 7.801 | 3.6 | 30.1 | 33.7 | 90.5 |
| | Big hits | 10 | **13.070** | 4.436 | 8.6 | 23.8 | 32.4 | 70.0 |
| | Regular impact | 45 | **12.962** | 5.213 | 4.1 | 22.6 | 26.7 | 53.3 |
| | Limited impact | 9 | **7.778** | 4.436 | 2.4 | 16.4 | 18.8 | 77.8 |
| | | | | | | | | |
| end-of-season | Concussion | 17 | **10.571** | 3.295 | 6.5 | 16.4 | 22.9 | |
| | Big hits | 10 | **12.200** | 4.907 | 5.1 | 19.3 | 24.4 | |
| | Regular impact | 43 | **13.364** | 5.884 | 4.0 | 30.3 | 34.3 | |
| | Limited impact | 6 | **10.167** | 4.892 | 4.4 | 16.5 | 20.9 | |

*SNR- signal-to-noise ratio; CH- concussion history.*

The trajectories of non-concussed athletes across three time points are broken down into four different groups, represented in Figure 5.4. There is no distinct pattern of trajectory seen in any group. The athlete in (c) with the highest SNR at mid-season reported a neck injury associated with the big hit, but no suspected concussion when asked at mid-season. The athlete in (d) with the highest SNR at mid-season sustained his impact after mid-season; this is also the highest SNR seen in the present study.

Figure 5.4: SNR trajectories in individual male rugby athletes by impact exposure (a–d).




*SNR- signal-to-noise ratio; BL- baseline; MS- mid-season; EOS- end-of-season.*

For statistical analysis, non-parametric tests were because of unequal group sample sizes, normality violations, and outliers. Kruskal-Wallis tests were used to compare the four athlete groups at baseline and end-of-season. Because of the small sample size for mid-season, it was not analysed by itself and was only used in Friedman's ANOVAs to compare the regular impact and big hits groups over three time points; instead, Wilcoxon signed-rank tests were used to compare the concussed and limited impact groups at baseline and end-of-season. Only the significant pairwise comparisons of the SNR between groups of different injury exposure over time are reported in Table 5.16, while mean SNR values for each group were reported in Table 5.14.

Baseline SNRs were significantly different between the male rugby athletes with regular and limited impact exposure (with a moderate effect size; rows 1–2), and at end-of-season between those with regular impact exposure and those who sustained a concussion (with a large effect size; rows 3–4). Differences between all four groups at each time point are visualised in Figure 5.5. None of the comparisons over time were significantly different in any of the impact exposure groups (rows 5–8).

Table 5.16: Comparisons of SNR trajectories across impact or injury exposure levels in male rugby athletes.

| | G1 | G2 | test | stat | df | p | effect size | z score | N = |
|---|---|---|---|---|---|---|---|---|---|
| 1 | DxLevel | BL | Kruskal-Wallis | 7.679 | 3 | **0.053** | 0.100 | | 78 |
| 2 | Limited impacts BL | Regular impacts BL | pairwise | -21.911 | | **0.049*** | -0.360 | -2.648 | 54 |
| 3 | DxLevel | EOS | Kruskal-Wallis | 10.160 | 3 | **0.017*** | 0.135 | | 76 |
| 4 | Concussion EOS | Regular impacts EOS | pairwise | -17.663 | | **0.031*** | **-0.677** | -2.792 | 60 |
| 5 | Big hits | BL, MS, EOS | Friedman's | 1.000 | 2 | 0.607 | 0.083 | | 6 |
| 6 | Regular impacts | BL, MS, EOS | Friedman's | 0.804 | 2 | 0.669 | 0.015 | | 27 |
| 7 | Limited impacts BL | Limited impacts EOS | Wilcoxon's signed-rank | 16.000 | | 0.249 | 0.471 | 1.153 | 6 |
| 8 | Concussion BL | Concussion EOS | Wilcoxon's signed-rank | 37.000 | | 0.552 | -0.165 | -0.594 | 13 |

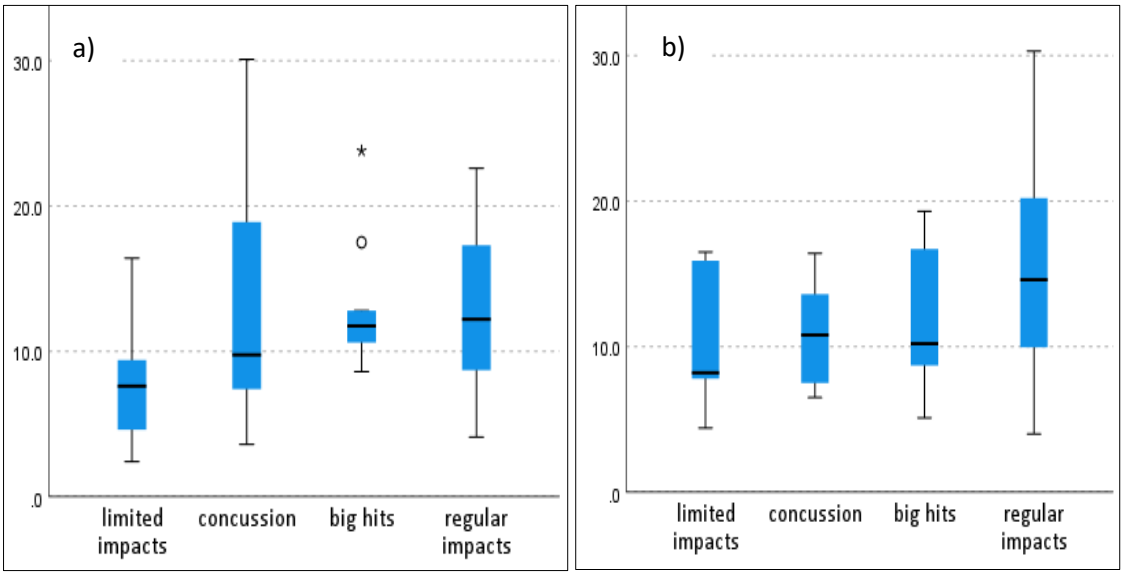
**- p < .05; **- p < .01; ***- p < .001; G- group BL- baseline; MS- mid-season; EOS- end-of-season; DxLevel- level of injury exposure.*

Table 5.17: Comparison between SNRs of athletes who reported untreated concussions.

| | Baseline | Follow-up | Time since | Symptoms reported |
|---|---|---|---|---|
| 1 | **12.8** | **12.4** | <10 weeks | 48 hr headache, then he felt fine |
| 2 | **10.2** | **9.7** | 5 weeks | Unobserved loss of consciousness after impact |
| 3 | **12.7** | **19.3** | *Unknown* | Left eye blacked out after being hit in the nose |

*SNR- signal-to-noise ratio.*

Figure 5.5: Average SNRs for the male rugby athletes by impact exposure group at baseline (a) and end-of-season (b).




When verbally screened for unreported or undiagnosed head injuries at the mid-season and end-of-season assessments, three male athletes (30% of the "big hits" group) admitted experiencing an impact that they believed was a concussion or that fit the description of a concussion (such as an unobserved loss of consciousness). Table 5.17 presents the SNRs of these athletes at baseline and at the closest time point after the reported injury; two athletes show small decreases while Athlete 3 showed an increase from baseline to end-of-season, but the time since injury was not reported for this athlete. Of the remaining seven athletes that sustained big hits, five were cleared by a physiotherapist and two did not seek treatment.

Additionally, several athletes reported visual disturbances after big hits (including Athlete 3 from Table 5.17), and they are examined in Table 5.18. Besides the SNR increases seen in Athletes 3 and 4, no common pattern is observed between them. Other symptoms reported after a big hit include feeling dazed or disoriented, headaches, and neck pain.

Table 5.18: Comparison of SNRs in athletes who reported visual disturbance after impact.

| | Baseline | Follow-up | Visual symptoms notes |
|---|---|---|---|
| 1 | **8.6** | **8.7** | A couple head knocks 6 weeks ago where he saw stars ago, but nothing diagnosed |
| 2 | **10.2** | **18.1** | Baseline was done post-impact because she lost vision, but she was cleared |
| 3 | **12.7** | **19.3** | Got hit in the bridge of his nose and his left eye blacked out, but he kept playing |
| 4 | **11.9** | **19.7** | A couple of "white flashes" on some impacts, but nothing diagnosed & no symptoms |

*SNR- signal-to-noise ratio.*

#### *5.3.3.3.2 Stability of SNR over two seasons across sex*

Twenty-nine athletes participated in both years of the study; 6 of these athletes were female (20.7%) and 6 of the 23 male athletes sustained a concussion during this study. To compare SNR by year at each time point, Wilcoxon signed-rank tests were performed separately between sexes; the results of these are reported in Table 5.19. The sample sizes were less than five for male and female athletes at mid-season and for female athletes at end-of-season, so these comparisons (as well as the Friedman's ANOVAs) also could not be run. The SNR averages were not significantly different between years at any time point (rows 1–3). However, when the data were analysed separately by sex, the comparison between baselines for the female athletes showed a large effect size for lower values in 2020, and the baselines for the male athletes showed a trend towards lower values in 2020 with a moderate effect size. These effects might have been statistically significant with a larger sample size.

Table 5.19: Comparisons of SNR in longitudinal participants at each time point.

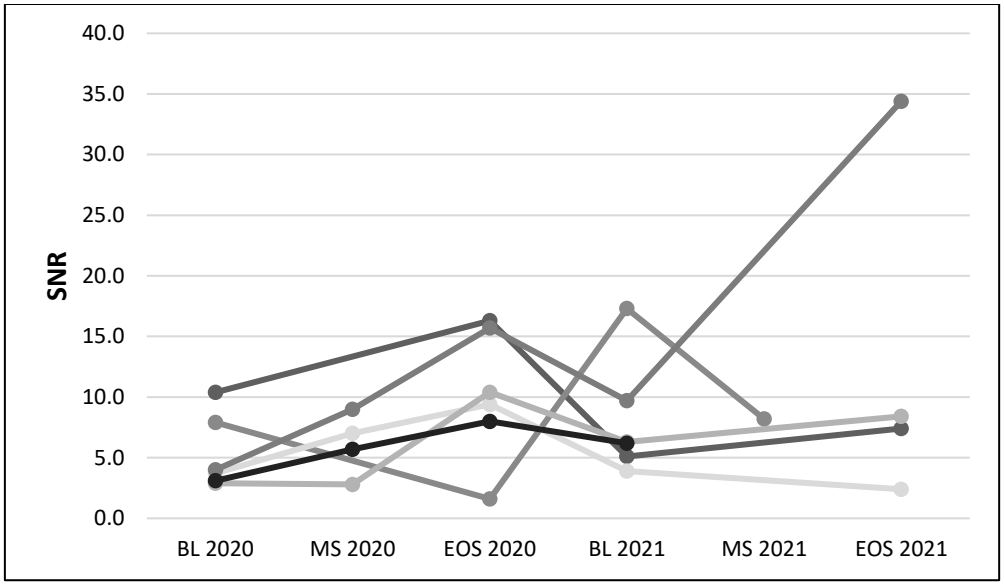
| | G1 | G2 | test | stat | p | effect size | z score | N = | T1 M (SD) | T2 M (SD) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Female BL 2020 | Female BL 2021 | Wilcoxon signed-rank | 17.000 | 0.173 | **0.556** | 1.363 | 6 | 5.33 (3.09) | 8.08 (4.91) |
| 2 | Male BL 2020 | Male BL 2021 | Wilcoxon signed-rank | 178.000 | **0.095** | 0.356 | 1.672 | 22 | 10.96 (5.95) | 13.58 (5.94) |
| 3 | Male EOS 2020 | Male EOS 2021 | Wilcoxon signed-rank | 63.500 | 0.490 | 0.185 | 0.691 | 14 | 14.75 (6.49) | 13.89 (6.40) |

**- p < .05; **- p < .01; ***- p < .001; SNR- signal-to-noise ratio; G- group; BL- baseline; MS- mid-season; EOS- end-of-season; CH & conc hist- concussion history.*

Figure 5.6 and Figure 5.7 represent the individual trajectories of the 6 female and 23 male athletes, respectively, who participated in this study for two years. With exception of the female outlier at the end-of-season 2021, the scores of the female athletes appear to be generally lower than those of the male athletes over two seasons.

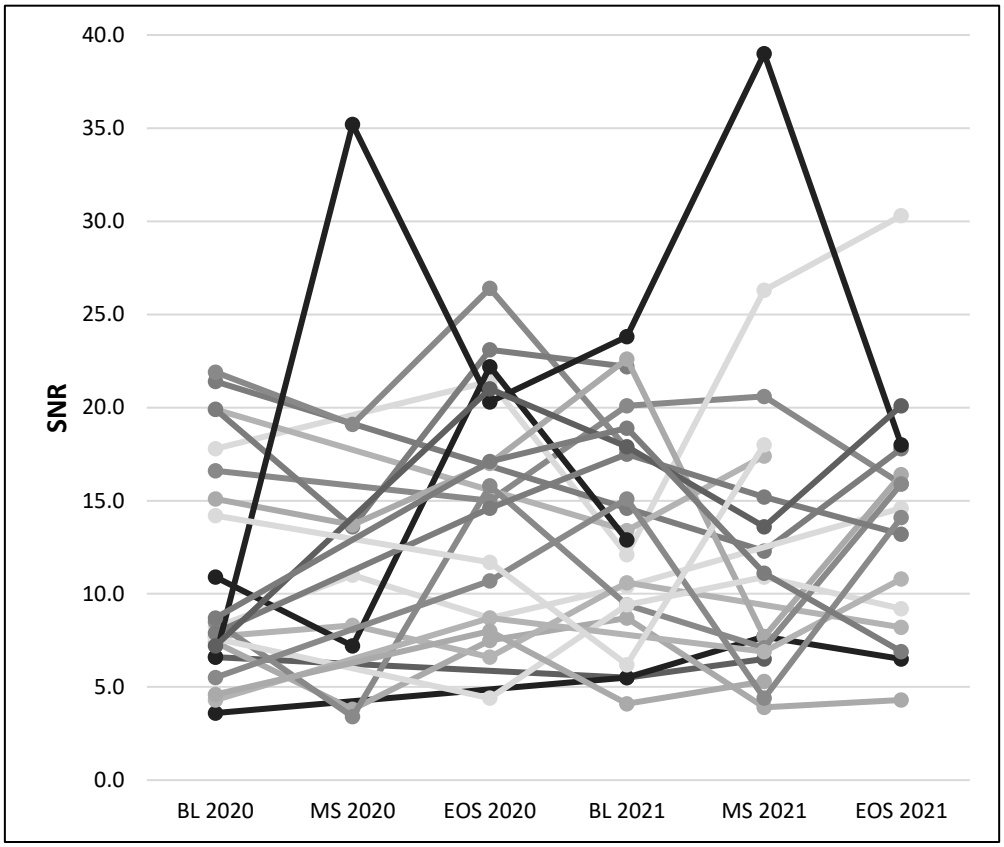
To examine the SNR activity for both years before and after the concussions, the trajectories of the concussed and non-concussed male athletes are further broken down over two years, shown in Figure 5.8. The mid-season data points are represented by the latest post-injury data for those who sustained concussions; in some cases, this time point is the highest SNR produced by the athletes, and in some cases, it is the lowest. No common features were observed for the concussions in either year or in the non-concussed athletes.

Figure 5.6: SNR trajectories of individual female athletes who participated both years.



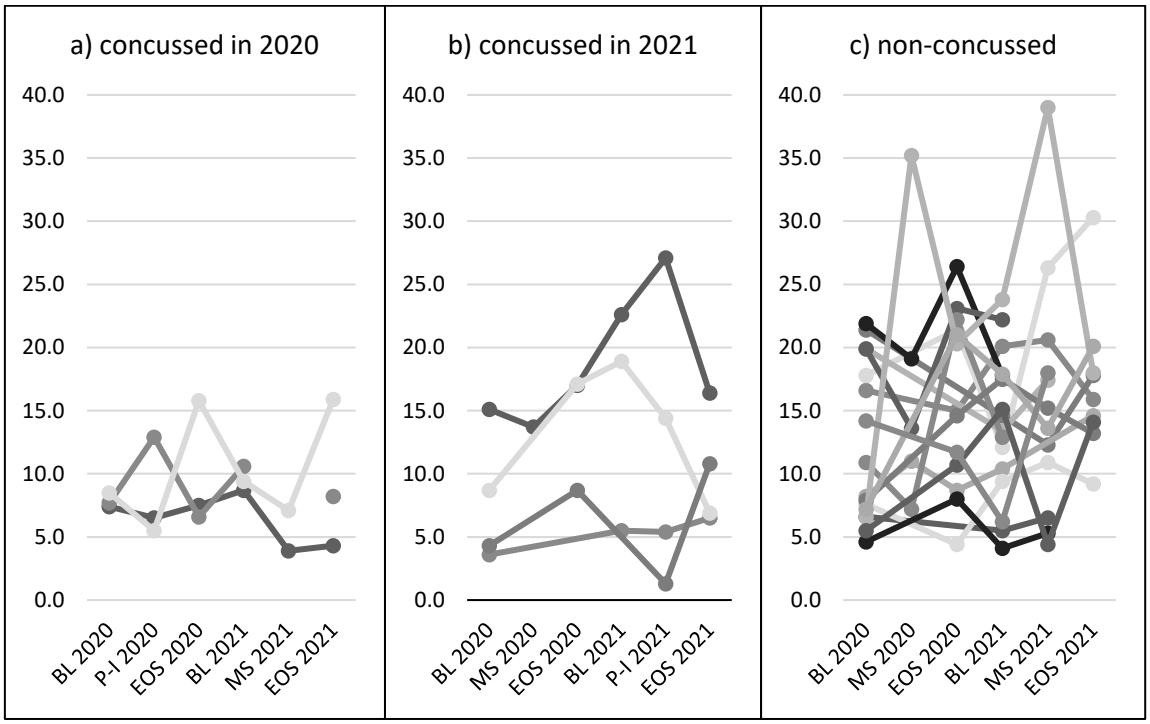

*SNR- signal-to-noise ratio; MS- mid-season; EOS- end-of-season.*

Figure 5.7: SNR trajectories of individual male athletes who participated both years.




*SNR- signal-to-noise ratio; MS- mid-season; EOS- end-of-season.*

Figure 5.8: Comparison of SNR trajectories over two years in concussed (a & b) and non-concussed (c) male athletes.




*SNR- signal-to-noise ratio; BL- baseline; P-I- post-injury; MS- mid-season; EOS- end-of-season.*

### 5.3.3.4 Increased SNR in female athletes after combat session

Sex was also analysed in a group of combat athletes. The SNRs of these athletes overall ranged from 1.9–27.9, and the average SNRs by impact exposure group and sex are reported (in bold) in Table 5.2. The no-impact group had a smaller range than the impact group at both time points, and the lowest SNRs at each time point were seen in the no-impact athletes. The SNR of the female athletes at baseline was also low, but with a wider distribution. Additionally, the lengths of the sparring sessions were significantly different between groups, with the no-impact group (M = 27.91 mins) sparring an average of 31 minutes longer than the impact group (M = 58.63 mins), $t(17) = -5.260$, $p < .001$, $d = -2.444$. Because of this difference, this choice of control group was not ideal, but it was driven by necessity and participant availability during the ongoing Covid protocols and intermittent stoppages.

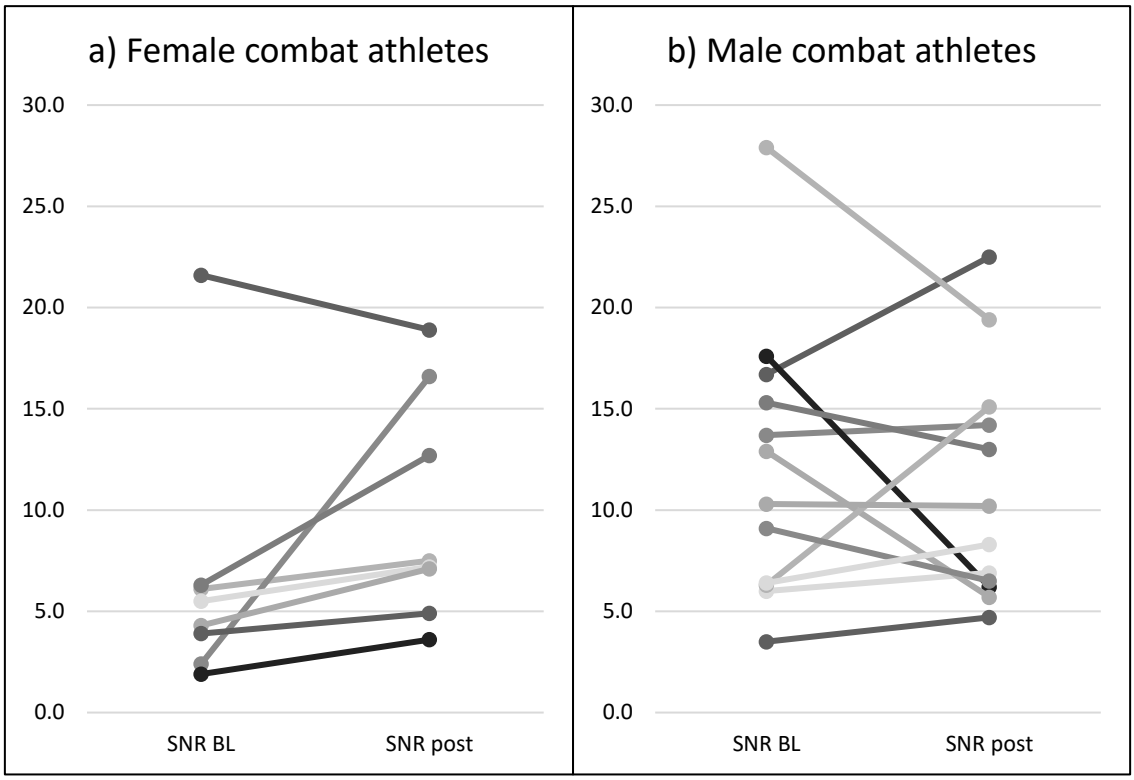
Differences in the SNR of combat athletes over time were analysed by sex group (Table 5.20), using parametric and non-parametric tests because of an outlier and normality violations that were only present at the SNR pre-round time point of the female group. The female no-impact athletes experienced a trend of increase in SNR with a large effect size during the session (row 1) that was not seen in the male athletes (row 2). The trajectories of individual athletes are represented by sex in Figure 5.9. Sample sizes were not large enough to analyse each sex group by impact exposure.

Table 5.20: Comparisons of SNR in combat athletes before and after a sparring round, by sex.

| | G1 | G2 | test | stat (df) | p | effect size | N = | T1 M (SD) | T2 M (SD) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Female SNR pre | Female SNR post | Wilcoxon signed-rank | 24.000 | **0.091** | **0.639**[18] | 7 | 6.64 (6.80) | 10.19 (5.94) |
| 2 | Male SNR pre | Male SNR post | Paired t-test | 0.648 [19] (11) | 0.265 | 0.174 | 12 | 12.14 (6.77) | 11.06 (5.80) |

**- p < .05; **- p < .01; ***- p < .001; G- group; pre- before the round; post- after the round.*

Figure 5.9: Comparison of SNR over time in individual female (a) and male (b) combat athletes.




*SNR- signal-to-noise ratio; BL- baseline; post- post-sparring.*

### 5.3.3.5 Cognitive and symptom changes by sex

Mann-Whitney tests and Friedman's ANOVAs were run on the non-concussed rugby athletes by sex to compare scores on the different cognitive measures, and the results with a significance of p < .10 are included in Table 5.21. Differences between the female and male groups were seen in symptoms, concentration, and the King-Devick, while within-group differences were seen in the male athletes in domains of orientation and concentration; no domains changed over time in female athletes. Female athletes showed a trend of reporting more symptoms at the end-of-season than the male athletes with moderate effect sizes (rows 1–2), although not at baseline. They also showed a trend of higher concentration scores than the male athletes at baseline (with a small effect size;

[18] Z-score: 1.690
[19] Mean differences: 1.08 (5.79)

row 3), and they completed the K-D significantly faster than the male athletes at baseline and end-of-season with moderate effect sizes (rows 4–5). Over time, the male athletes showed an increase in concentration and a marginally significant decrease in orientation (rows 6–7), but no pairwise comparisons were statistically significant.

Comparisons of cognitive measures were performed for the combat athletes, and the only statistically significant difference was an increase in digit span performance in the male athletes over time, $W = 40.500$, $p = .021$, $r = .667$. Mann-Whitney tests were used to examine the cognitive results of the non-athlete control participants at a single time point, but no cognitive domains showed differences by sex.

### 5.3.4 Effects of impact exposure on the SNR in combat athletes

The previous analyses (by concussion history and sex) showed effects in the rugby athletes for long-term impact exposure, so a Mann-Whitney test was run to compare all participants by impact vs no impact exposure (e.g., non-concussed rugby athletes at the end-of-season, combat athletes at baseline, and control participants); the impact athletes had significantly higher SNRs than the no-impact participants, $U = 2174.000$, $p < .001$, $r = .311$, $N = 125$.[20]

The female and male combat athlete data (including SNR and cognitive measures) were examined together over time for a main effect of impact exposure. When the data from all combat athletes (n = 19) were analysed by impact vs no impact exposure, the SNRs before and after the round had normal distributions and only one minor outlier, so parametric tests were used. Despite the normal distribution, the repeated-measures ANOVA showed significant violations of normality using Levene's test, and a near violation of the homogeneity of variance using Box's test, so partial eta-squared or Pillai's V were used as the effect size. The main effect for regular impact exposure was seen at both time points with a small effect size, $F(1, 18) = 5.021$, $p = .039$, $V = .228$, but no main effect for time or group × time interaction was seen. When the rugby athletes were compared over time without being split by sex groups (as discussed above), no main effect was seen for impact exposure and no statistically significant changes in trajectory were seen by impact exposure group; this is likely because of the different patterns observed in the male and female trajectories (Table 5.13 and Figure 5.3).

[20] Impact: n = 91, M (SD) = 13.35 (7.38), mean rank = 69.89; No impact n = 34, M (SD) = 8.47 (5.18), mean rank = 44.56.

Table 5.21: Comparisons of cognitive scores in rugby athletes over time, by sex.

| | **group 1** | **group 2** | **test** | **stat (df)** | **p** | **effect size** | **z score** | **G1 N =** | **G1 mean rank** | **G2 N =** | **G2 mean rank** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Female symx# EOS | Male symx# EOS | Mann-Whitney | 80.500 | **0.089** | -0.307 | -1.762 | 12 | 20.79 | 21 | 14.83 |
| 2 | Female sever EOS | Male sever EOS | Mann-Whitney | 79.500 | **0.082** | -0.313 | -1.800 | 12 | 20.88 | 21 | 14.79 |
| 3 | Female concen BL | Male concen BL | Mann-Whitney | 134.000 | **0.080** | -0.286 | -1.829 | 16 | 25.13 | 25 | 18.36 |
| 4 | Female K-D BL | Male K-D BL | Mann-Whitney | 852.000 | **0.006**** | 0.321 | 2.726 | 28 | 28.07 | 44 | 41.86 |
| 5 | Female K-D EOS | Male K-D EOS | Mann-Whitney | 820.000 | **0.004**** | 0.345 | 2.890 | 27 | 26.63 | 43 | 41.07 |
| | **group** | **time** | **test** | **stat (df)** | **p** | **effect size** | **z score** | **N =** | **BL mean rank** | **MS mean rank** | **EOS mean rank** |
| 6 | Male orient | Bl, MS, EOS | Friedman's | 5.429 (2) | **0.066** | 0.136 | | 20 | 2.33 | 1.78 | 1.90 |
| 7 | Male concen | Bl, MS, EOS | Friedman's | 7.292 (2) | **0.026*** | 0.182 | | 20 | 1.63 | 2.13 | 2.25 |

**- p < .05; **- p < .01; ***- p < .001; G- group; BL- baseline; EOS- end-of-season; symx#- symptom number; sever- symptom severity; orient- orientation; concen- concentration.*

#### 5.3.4.1 Cognitive and symptom differences after acute impact exposure

Differences on the symptom and cognitive measures between rugby athletes with regular and limited impact exposure could not be statistically analysed because of the small sample sizes of the limited-impact rugby athletes. Performance on the cognitive measures was compared between the impact and no-impact combat athletes. Cognitive scores were compared using non-parametric tests because of outliers and normality violations in the distributions. Additionally, the two forms of the TMTb used were found not to be equivalent: athletes completed form B in an average of 54.16 seconds, and form A in 72.54 seconds, $U = 116.00$, $p = .009$, $r = -.404$. The values for each time point were standardised into t-scores for each form, and the time points were compared by independent-sample and paired t-tests (using Hedges' d as the effect size). One outlier was removed from the TMTb for times of over two minutes at each trial.

The comparisons of scores on the SCAT-5 subtests (symptoms and digit span) and the TMTb are reported in Supplemental Table 9.6. The impact group reported a significantly higher symptom amount (rows 1–2) and severity (rows 5–6) than the no-impact group at both time points, with moderate to large effect sizes. Both groups showed an increase for the digit span sub-test score (with large effect sizes; rows 11–12), but this difference was marginally significant in the impact group only. Lastly, the impact athletes completed the TMTb faster than the non-impact athletes at both time points (marginally significant with large effect sizes, rows 13–14), and there were no statistically significant changes over time on the TMTb in either impact group.

When the cognitive scores of the boxers were examined by concussion history, no significant differences were found. Non-parametric tests (to compensate for unequal group sizes) found no significant between-group or within-group differences for boxers with and without previous concussion history. No-impact combat athletes were not included in these analyses because of no reported concussion history. Cognitive scores were also not significantly different after sparring within the two groups (Table 9.6). Finally, Mann–Whitney tests were used to examine the cognitive results of the non-athlete control participants at a single time point, but none of the cognitive domains showed difference by history of concussion.

## 5.4 Conclusion

### 5.4.1 Summary

The proportion of participants who reported a previous concussions was just below two-thirds for most groups, including 65.3% for the rugby athletes and 58.8% for the non-athletes. None of the no-impact combat athletes (BJJ athletes and one cardio-only participant) reported a history of concussion, while 63.6% of the boxers did. Female participants represented one-third of the overall population in this study, as almost 29.8% rugby of the rugby athletes, 36.8% of the combat athletes, and 35.3% of the non-athlete participants. In terms of average ages, the rugby athletes (23) were younger than the combat athletes (32) and the non-athlete control participants (31; Table 3.1–Table 3.3). The SNR was non-significantly higher at baseline in 2021 (marginally significant for male athletes and a large effect size for female athletes; Table 5.19, rows 1–2), likely because testing quality improved since the 2020 baselines were the first data collected.

#### 5.4.1.1 Concussion history

When the SNR of all participants was compared at baseline, there was no statistically significant difference between those with versus without a history of concussion. When the end-of-season rugby and non-athlete participants were examined together, those with and those without a history of concussion showed significantly different patterns of SNR activity by impact exposure (Table 5.8). Those with a history of concussion also showed faster King-Devick times from baseline to end-of-season (with a moderate effect size), as well as a statistically significant change in orientation scores over time (with a small effect size; Table 5.7). The trajectory of the SNR over a season of rugby was analysed, and while those with a history of concussion showed a trend of change over time, the difference was not statistically significant for either group (Table 5.6). The SNRs of the rugby athletes were not significantly different by concussion history at any of the three time points, and concussion history did not interact with sex over time. Overall, concussion history may affect the electrophysiological response to repetitive impacts, as well as performance on some cognitive measures over time. Differences in boxers by concussion history may become more apparent with larger sample sizes.

#### 5.4.1.2 Sex

The SNR was lower in the female athletes at all three time points. Despite no statistically significant difference in SNR across sex in the non-athlete control group (Table 5.4, row 2), a main effect of higher SNR in male participants was seen (Table 5.9, row 1). In the rugby athletes, female SNRs were significantly lower than male SNRs at all three time points (Table 5.1; Table 5.13, rows 1–3), and a lower distribution was also observed in the female athletes at these time points. SNR quality was also lower in the female participants, as evidenced by the high proportion of harmonic artefacts seen in these readings (over 50%; Table 5.10) and the correlation between harmonic presence and lower SNR (Table 5.11), since the harmonic magnitude increases the noise and reduces the ratio. The increased SNR in female participants over the two trials (Table 5.12) could represent an improvement in adjusting the fit of the headset to female participants, such as moving more hair out of the way or using more saline on the hair/scalp; most likely, the cumulative saline saturation in the hair from both trials improved the conductivity through the electrodes. One comparison for time of day was statistically significant (higher SNR on the second trial for female participants before noon), but this is likely a type I (false positive) error since the effect size was small.

Female and male athletes showed different patterns of SNR change by degree of impact exposure. A lower SNR at baseline that increased over time was seen in both the female rugby (Table 5.13) and combat athletes (Table 5.20). The female athletes demonstrated an increase of SNR from mid-season to the end of the season (marginally significant with a large effect size; Table 5.13 and Figure 5.1–Figure 5.3), while no change was seen over time in the male athletes. In the rugby athletes that participated both years, the scores of the female athletes (Figure 5.6) were lower overall when compared to those of the male athletes (Figure 5.7) over two seasons. A pattern of increase was also seen in the female combat athletes after acute impact exposure (Table 5.20 and Figure 5.9), while the SNR of the male combat athletes showed no significant change.

The male rugby athletes showed no overall changes in the SNR over time, but when examined further by impact exposure, different patterns emerged. The male athletes with regular repetitive impact exposure demonstrated higher SNRs than the male participants with limited or no impact exposure at baseline and end-of-season (Table 5.14–Table 5.16). The male athletes with regular impact exposure also demonstrated higher SNRs at the end-of-season than the male athletes who sustained a concussion (Table 5.16). Further, the SNRs of the female athletes were only lower than that of the male athletes in the regular impact group, and not in the limited impact group. Sample

sizes were too small to explore the relationship between sex and repetitive impact exposure and its effects on the magnitude and trajectory of the SNR, but these findings indicate a potential interaction.

Cognitive differences between the female and male rugby athletes were seen in symptoms, concentration, and the King-Devick, while differences over time were seen in the male athletes in the domains of orientation and concentration (Table 5.21): the female athletes completed the King-Devick test faster than the male athletes, and the male athletes showed improvements in the concentration domains after acute impact exposure and after a season of rugby impacts. No other cognitive differences by sex were statistically significant in the combat athletes, or at the sole time point for the non-athlete control participants.

#### 5.4.1.3 Repetitive impact exposure

The participants with regular impact exposure demonstrated significantly higher SNRs than the participants with limited or no impact exposure overall. The SNRs of the boxers were also significantly higher than that of the no-impact combat (BJJ) athletes. This main effect for impact exposure was seen in the combat athletes at both time points and in the male rugby athletes at the end-of-season (Table 5.16), where the SNR of the repetitive impact exposure rugby athletes was significantly higher than the limited-impact athletes at baseline and the recently-concussed athletes. This pattern could indicate that repetitive impacts adaptively upregulate dynamic processes associated with the SNR activity unless a concussion is sustained, which may cause SNR downregulation to that of an athlete who has not been experiencing the same level of impact exposure.

No impact exposure groups showed statistically significant changes over time, including the concussed athletes (also reported in Table 4.1) and the group who sustained big hits during the season (Table 5.16, row 5). A third of the “big hits” group were suspected to have sustained a concussion that they did not report; of these three athletes, two demonstrated similar SNRs to their baselines at the next follow-up, but the third athlete’s SNR increased to a higher magnitude than the maximal end-of-season SNR in the confirmed concussion group. It is unclear what effect the visual disturbances that some athletes reported may have on the SNR, especially during the acute post-injury period (Table 5.18). Another potential source of variance is the significant between-group difference seen at baseline, specifically the lower SNRs in the athletes who would go on to miss playing time compared to the athletes who would sustain regular impact exposure (Table 5.16, row 2); this may indicate a pre-existing difference between these groups.

Impact exposure was also partially associated with concussion history (Section 5.3.2.3) and sex (Section 5.3.3.3), which further complicates its effect on the SNR.

Lastly, differences were seen in the cognitive measures after a sparring session. The impact combat athletes completed the TMTb faster than the no-impact combat athletes at both time points, but the effect was more distinct after a sparring session (likely due to the practice effect). Both athlete groups showed improvements on the digit span, also likely because of the practice effect, though this effect was marginally higher in the impact athletes. Additionally, the impact athletes reported more symptoms and higher severity than the no-impact athletes at both time points.

**Research Question 1:** In non-concussed athletes and participants, is the SNR different across history of concussion?

The SNR was not different by concussion history, but differences by concussion history were seen in combination with degree of self-reported impact exposure.

**Research Question 2:** In non-concussed athletes and participants, is the SNR different across sex?

Male participants demonstrated a higher average SNR than the female participants. The data quality for the female participants was also poorer, due to the presence of a harmonic artefact and more difficulty fitting the headset on longer hair.

**Research Question 3:** Is the SNR affected by acute repetitive impacts?

The SNR was not affected by acute repetitive impacts, but it was significantly affected by degree of self-reported impact exposure over time.

**Research Question 4:** Is the SNR affected by repetitive impacts over time?

The SNR of male rugby athletes who reported sustaining regular repetitive impacts was significantly higher than the recently-concussed rugby athletes at the end-of-season, as well as the limited-impact male rugby athletes at baseline. However, the SNR of the male athletes showed no significant change over time in all impact exposure groups (including concussion), while the female rugby athletes demonstrated a trend of increase in SNR from mid-season to the end-of-season. The SNR also showed no significant differences across the three time points of both seasons.

### 5.4.2 Limitations

The primary limitation of this study is the lack of biomechanical data, which makes objective comparisons between the SNR and impact exposure impossible. This study also had small sample sizes, both for the female participants and for all the relevant subgroups of impact exposure. Not all subgroups could be analysed statistically, and some subgroups (e.g., concussed female athletes) were not represented at all.

The design of the control group was also not ideal. The initial design of the study with the combat athletes used a non-contact exercise group as the control for the boxers, but recruitment proved too difficult with that group, as they met early in the mornings and often did not have time to participate because they were due at work. Consequently, the potential for impacts or choke holds in the BJJ group is another limitation of this design. The athlete who reported an impact was not removed from analyses because of low sample size, and considering the SNR's stability in the acute repetitive impacts group, the head knock likely did not affect her post-round SNR. With a larger sample size, this study would ideally have a comparison group of people performing no physical exertion and tested roughly 30–60 minutes apart. A further limitation of this study is the single time point of the non-athlete control group, which precluded me from examining natural change over time in a non-athlete population. Using another ERP-derived method, Eckner and colleagues (2016) saw high variability the Brain Network Activation (BNA) scores of a non-concussed athlete population at one time point, and similarly determined that a single assessment is not very useful without a baseline. More data points in control groups over time will provide a more meaningful comparison to the athlete groups.

Another limitation is the inconsistency between cognitive measures used in this study. Because of the shift by the NuroChek research team to replace the K-D with the SCAT-5 in 2021, cognitive data for rugby athletes were not able to be compared between years. The sample sizes of the combat and non-athletes who completed other cognitive measures like the TMTb are also small. A wider range of cognitive measures may help to find domains associated with SNR changes.

The verbal learning subtest was not included in the protocol for the combat athletes because of the time it takes to administer, though it may have revealed cognitive differences after repetitive impacts. Verbal learning and memory deficits are common after repetitive impacts and sport-related concussion (Collins et al., 1999; McAllister et al., 2012; McCrea et al., 2003; Stephen et al., 2022; Talavage et al., 2014). McAllister and colleagues (2012) compared the effects of repetitive impacts in contact and non-contact athletes and found poorer post-season performance by the contact athletes on a similar measure of verbal learning and memory, while the non-contact athletes demonstrated a practice effect. Using fMRI, Talavage and colleagues (2014) studied functional (not clinical) impairment on verbal and visual memory tasks after repetitive impacts and estimated that at least 17% of contact athletes who have not been diagnosed with concussion still experience functional impairments (mainly in visual and verbal

working memory) with no accompanying neurocognitive deficits. Identifying this type of damage would help athletes to manage their brain health over time.

Verbal deficits are also persistent after long-term impact exposure. Moore and colleagues (2017) studied the brain's attention networks and found that athletes who were concussed at least a year before testing remembered significantly fewer words on the delayed recall trial than the athletes with repetitive impact exposure, who in turn remembered significantly fewer words than the non-contact athletes. Some athletes suffer cognitive deficits even after they retire. Verbal memory deficits and mood dysfunction were seen by Lepage and colleagues (2019), who were investigating the long-term effects of repetitive impacts on limbic structure volume in retired professional football players and controls, though the concussion history of the players was not specified. The cognitive results in the acute portion of this study might have been more sensitive if the verbal memory subtest of the SCAT-5 had been used instead of the digit span, though the protocol would have taken longer to administer, further decreasing my sample size. Unfortunately, verbal memory data were also unavailable for the rugby athletes.

### 5.4.3 Strengths

This study presents comprehensive normative SNR data for the included participant groups, separated by sex and concussion history. Despite the issues with COVID-19, I was still able to gather usable data from 121 athletes, which met the a priori sample size of at least 70 athletes in one season. This gave my study ample power to analyse the ranges present across demographic factors in the non-concussed athletes.

Another strength is the inclusion of unreported injuries in rugby athletes (by verbal self-report at mid-season and post-season). However, screening for unreported or subconcussive injuries in rugby athletes could be improved with a standardised questionnaire, as information on when these injuries occurred is missing for many athletes.

Ultimately, this study contributes original data to this field, as analyses of the SNR that focus on exposure to repetitive impacts over a season have not yet been reported for the NuroChek system.

## 5.5 Take-home message

- Concussion history had no main effect on the SNR, but it may have interacted with sex or impact exposure.
- SNRs were significantly higher in male than in female participants.
- Long-term exposure to repetitive impacts may be associated with higher SNR.

# Chapter 6
# Discussion: SNR, Concussion, and Repetitive Impact Exposure in Male Athletes

To test its sensitivity, the NuroChek system was tested in several head injury conditions: post-concussion in rugby; acute impact exposure in boxers; and impacts over a season of rugby). The SNR behaviour in each of these athlete groups and contexts will be discussed in this chapter, which addresses Aim 1 (acute SNR changes) and Aim 2 (SNR changes over time) by comparing the results of Studies A and B to each other and to existing literature. This chapter also addresses Aim 3 by discussing the effects of concussion history on the SNR. Because all concussions were sustained by male athletes, the comparisons discussed in this chapter only include male athletes, while the effects of repetitive impacts in female athletes is discussed in the next chapter.

## 6.1 Electrophysiological changes after concussion

### 6.1.1 Inconsistent subacute SNR behaviour after concussion

There was no consistency in the direction of the SNR change acutely after concussion (Sections 4.3.3 and 4.3.7). Additionally, several concussed participants demonstrated their highest SNR at the first post-injury time point (Figure 4.1 and Table 4.2). No common patterns were observed between the timelines of return-to-baseline SNR, return-to-baseline on cognitive measures, and RTP. Moreover, some athletes sustained their concussion early in the season and provided post-recovery data at the mid-season time point; of these, only one demonstrated a "recovered" SNR (equal to or higher than their baseline). The SNRs of the athletes with concussion showed a decrease in range during recovery, and their average SNRs were lower than the non-concussed athletes at the end-of-season (Section 4.3.3).

The behaviour of the SNR at post-injury and RTP time points is not consistent with the trajectory seen in previous NuroChek studies (Fong et al., 2020; Fong et al., 2021). In the present study, the average SNR baseline for male athletes was 12.8, and the average SNR within 3–5 days post-injury was 10.4. These do not match the SNRs reported by Fong and colleagues (2020); using a previous version of the variable calculation (not equivalent to the calculation used in the present study), they reported an average non-concussed baseline SNR of 4.80 in the male athletes and an average post-

concussion SNR of 2.00. Salazar and colleagues (2021) reported their data in bar graphs as square roots of the SNR, and averages for their non-concussed athletes ranged from 2.5–4.0, or from 6.3–16.0; this range is lower and partially consistent with the averages and ranges reported in Chapters 4 and 5. Without comparable SNR values, the results of these studies cannot be equivalently compared to my findings.

Our results are also not fully consistent with studies using similar flashing light methods that have reported amplitude increases during recovery (X.-P. Chen et al., 2006; Papathanasopoulos et al., 1994), though neither of these examined athletes. Chen and colleagues (2006) found significantly lower N70 and P100 amplitudes in those with mild head injury after 48 hours when compared to controls, but amplitudes had increased in most patients by three months post-injury, whereas we found lower SNRs at the end-of-season, but not during the acute post-injury period. Papathanasopoulos and colleagues (1994) found a within-group increase of P100 amplitude from days 1 to 30 in those with head injuries, though they did not find any differences between the concussion and control groups at day 1. When comparing the SSVEP results of the present study to those using ERP components, differences could be due to translational or methodological differences between ERPs recording in real-time during a cognitive task and a time-locked SSVEP designed to concentrate the signal during a passive task. Flashing lights may not be a reliable way to examine acute concussive damage or estimate recovery, but it may provide evidence of a post-concussive inhibitory process or reduced activation during recovery.

In the present study, it is unclear why the SNR increased after a concussion in some athletes and decreased in others. Rather than an indicator of healthier brain activity than at baseline, a post-injury increase in amplitude likely represents a dysregulated response due to increased sensitivity, a disproportionate amount of mental resources occupied by a disruptive stimulus, or disrupted excitatory/inhibitory networks (Clayton et al., 2020; Fickling et al., 2019). Relative increases in amplitude have been interpreted as the recruitment of additional resources needed to perform tasks equivalently (Fickling et al., 2019; Hudac et al., 2018), while relative decreases in amplitude have been associated with symptom severity (Dupuis et al., 2000; Lavoie et al., 2004), decreased availability of resources (Hudac et al., 2018), or evidence of a previous concussion (Brush et al., 2018; Moore, Broglio, et al., 2014). No commonalities were observed between the athletes whose SNR increased after their concussion when compared to those whose SNR decreased post-injury, so the determinant of the direction of change could be either an unmeasured individual factor (e.g., genetic) or an injury-related factor (e.g., point of impact or amount of force).

The athletes who sustained two concussions during the present study showed no consistency in SNR activity during either injury. Clayton and colleagues (2020) saw more similarities within their twice-concussed athletes, but they reported data from six athletes who sustained a concussion the following season, instead of within the same season. Beyond these two athletes, the present study did not have a large enough sample size to analyse the concussed athletes differently based on their previous concussion history or examine the effects of multiple concussions. When compared to controls, Thériault and colleagues (2009) found reduced amplitudes of P3a and P3b in athletes with a history of multiple concussions who did not report attention or memory problems or any other symptoms. Thus, some of the inconsistencies in the post-injury SNRs could be explained by degrees of concussion history (none, previous, or multiple).

#### 6.1.1.1 Speculation on the nature of the SNR

The SNR likely represents an activation of the pre-attention circuit that attempts to classify visual stimuli, comparable to P50 to N100/P200. These early components represent alerting, sensory filtering and processing, and stimulus classification to prime the brain to process stimuli and prepare to respond (Broglio et al., 2011; Hudac et al., 2018; Kozak, 2018; Reches et al., 2017). In ERP research, it is most similar to studies that used the P100 component because of the occipital localisation and common use of flashing light stimuli.

Changes to the SNR could also represent dynamic injury or healing processes, which maximally occur in the first few days after a concussion. The default mode network (DMN) describes the set of brain processes active during a no-task or resting state, not unlike the exposure period of the SSVEP. DMN activity can be observably disrupted in the weeks and months after concussion (Bigler, 2018; Dunkley et al., 2018; B. Johnson et al., 2012; Zhu et al., 2015). Additionally, McCuddy and colleagues (2018) reported that attention deficits and depressive symptoms were still correlated with functional connectivity changes to emotional regions and brain activity in untasked states at a month post-concussion. A loss or overload of this no-task state functionality (Kozak, 2018) could contribute to the sub-acute instability of the SNR seen at three to five days post-concussion in the present study. Further, the SNR may not necessarily behave consistently in concussed brains at the post-injury time points examined in this study.

Given these global changes in brain activity following concussion, a similar disruption in electrical activity may be measured by the SNR, regardless of the cause of concussion or site of impact (i.e., a frontal vs parietal impact, or a concussion caused by

whiplash or impact to another part of the body). However, a direct impact at one of the occipital target sites could affect local electrical activity directly beneath the EEG sensors and alter SNR values, which would complicate analysis. Occipital impacts are ostensibly less common than frontal or parietal impacts in sport; however, via the contre-coup effect, an impact to the frontal and temporal lobes could also affect the occipital lobe as the momentum travels through the head. The relationship between changes to the SNR (or EEG overall) and cause of injury or impact site is certainly an area deserving of further study.

Another ERP method has shown inconsistencies similar to the present study. Using another method of ERP analysis called Brain Network Activation (BNA), Kiefer and colleagues (2015) described the single case of a 15-year-old hockey player who was tested before and after his concussion during a game; the BNA decreased at the first post-injury visit, then returned to its baseline range by three weeks post-injury. Despite this case, Broglio and colleagues (2017) did not find a consistent electrophysiological post-injury decrease in the BNA from baseline, and saw decreases in the control athletes at the mid-season time point as well. Our results echo the BNA findings of a lack of post-injury decrease and inconsistency in the control athletes, likely because these are common challenges for EEG/ERP-based assessment methods.

Other evidence of non-linear recovery after concussion can be seen by acute imaging. Churchill and colleagues (2019) reported alterations to cerebral blood flow (as seen by arterial spin labelling) in athletes at one week and one year post-injury, but not at RTP; they surmised that competing post-injury processes may account for differential recovery times. Using DTI, Brett and colleagues (2020) found evidence of non-linear recovery in athletes experiencing their second concussion within a year: athletes recovering from their first concussion showed high mean diffusivity after injury, which declined through and after RTP in a linear fashion. However, the athletes recovering from their second concussion showed an increase in mean diffusivity at one week after RTP, which Brett and colleagues (2020) described as a "perturbation in white matter integrity." Though most athletes injured in the present study did not report sustaining a concussion in the previous year, a high percentage did report a history of concussion. Neural adaptations to previous injuries could explain inconsistencies during the recovery process.

Lastly, the clinical utility of the SNR is severely limited without a baseline. In an attempt to validate the use of the BNA in a non-concussed athlete population, Eckner and colleagues (2016) found wide variability of BNA scores between the athletes, and they concluded that this electrophysiological measure had limited utility without knowledge

of the athlete's baseline. Yet even the athletes who had baseline SNRs showed great variability, which limits the utility of the baseline itself. The inconsistencies seen in SNR activity could also be due to another factor untargeted by this study (i.e., time after a meal, medications, or an aspect of internal monitoring). This encapsulates several reasons why the development of an accessible and objective measure of concussion remains difficult.

### 6.1.2 Concussion history may affect SNR trajectory over time

No overall difference in SNR was seen between those with and without a history of concussion, but statistically significant differences with moderate effect sizes were seen when examining the interactive effects of impact exposure by concussion history. These results may indicate some subtle but persistent electrophysiological changes from a previous concussion, which is partially consistent with the findings of other ERP studies that have reported persistent alterations in participants with a remote (2+ years) history of concussion (Broglio et al., 2009; Brush et al., 2018; Carrier-Toutant et al., 2018; De Beaumont et al., 2007; Gaetz & Weinberg, 2000; Hudac et al., 2018; Ledwidge & Molfese, 2016; Moore, Broglio, et al., 2014; Moore, Hillman, et al., 2014; Olson et al., 2018; Ozen et al., 2013; Thériault et al., 2009; Yadav & Ciuffreda, 2015). Since we did not collect detailed data on number of previous concussions or time since last concussion, we cannot speculate on how long these effects may last or how cumulative they are.

#### 6.1.2.1 Speculation on the duration of complete recovery

The concussed athletes in the present study demonstrated a significantly lower SNR by the end-of-season when compared with the non-concussed male rugby athletes. Recovery timelines were highly variable in the concussed athletes, as some athletes returned to play after a week, and others did not return for the remainder of the season, though this was not solely due to the concussion in all cases. The athletes who sustained concussions initially reported symptoms post-injury, but they resolved during recovery; by the end-of-season, all athletes reported zero symptoms, though this could also represent their desire to play more than their actual experience of symptoms.

Many studies have reported variability in the duration of ERP impairment after concussion; however, these studies differed by reported symptoms and follow-up intervals, and most used auditory stimuli with cognitive measures (e.g., an oddball paradigm) to elicit the P300 component. Our results are inconsistent with reports of decreased or down-regulated acute electrophysiological activity post-concussion (Clayton et al., 2020; Fickling et al., 2019), though neither of these studies included a

symptom inventory. Fickling and colleagues (2019) found that P300 amplitude had not returned to its baseline amplitude in concussed hockey athletes who were cleared for RTP by medical staff, and Clayton and colleagues (2020) similarly found that 38% of athletes who demonstrated cognitive recovery (measured by reaction time) still showed P300 alterations upon beginning their RTP protocol. These P300 alterations that persisted beyond RTP are consistent with our findings. Other studies have reported persistently lower P300 amplitudes in symptomatic and asymptomatic concussed athletes at five to seven weeks post-concussion, with more severe ERP deficits in the symptomatic groups (Gosselin et al., 2006; Sicard et al., 2021). Lower N100 amplitudes have been reported in asymptomatic concussed athletes 5 weeks post-concussion, and lower P200 amplitudes in symptomatic athletes at 15 weeks post-concussion (Gosselin et al., 2006). Further, when compared to the asymptomatic and non-concussed control groups, lower P300 amplitude was observed in concussed-and-symptomatic participants (at 28 of the 30 electrodes used) within six months of their injury (Lavoie et al., 2004). These time ranges are similar to the duration of the seasons included in the present study, and may approximate the post-injury intervals seen in our concussed athletes.

Changes to P300 (analogous to those we saw at the end-of-season after concussion) have also been seen months later in concussed non-athlete populations. When compared to a healthy control group, Zhao and colleagues (2018) saw lower P3b and N200 amplitudes in non-athlete participants up to a month after their concussion during a cognitive task. Nandrajog and colleagues (2017) tested participants within a week and at 2–3 months post-concussion, and they found frontal amplitude differences between the concussed and control groups at the first time point, but not the second, though some cognitive deficits did persist at the second time point. Because these studies included different methods, time points, and sex ratios, they cannot be directly compared; however, this wide range of recovery times shows a lack of general consensus, even in the component most closely associated with concussive injury.

It is possible that the SNR is dysregulated beyond 1–2 standard deviations in either direction after injury (Clayton et al., 2020), but a larger sample size of athletes with baseline and acute post-injury data is needed to examine this possibility. If the SNR is a measure of a dynamic healing process, perhaps the maximal activity occurs in the first few days or weeks after a concussion (Brett et al., 2020; Churchill et al., 2019). The RTP policy for club and academy athletes during this study required a mandatory 23-day stand-down period following a diagnosed concussion, while a minimum 7-day stand-down

period was required for the semi-professional athletes. If the SNR decrease over time does represent a persistent concussive deficit, these stand-down times may not be long enough.

Studies using different neurophysiological methodologies have also reported alterations months after concussion, providing support to the growing consensus that physiological recovery of concussion may take longer than current RTP timelines (Kamins et al., 2017). One such method is DTI, which visualises the movement of water through axons; changes in different measures of diffusivity can indicate axonal damage or inflammation (Bigler, 2018; Dimou & Lagopoulos, 2014; Hellewell et al., 2021). Changes in mean diffusivity have been reported within 48 hours (Brett et al., 2020) and within 6 days (Churchill et al., 2019) of a concussion; these alterations can persist beyond RTP (Brett et al., 2020; Churchill et al., 2019) and may still be detectable at one to two months post-injury (R. King et al., 2019; Lancaster et al., 2018; Smits et al., 2011), up to six months post-injury (Brett et al., 2020; Lancaster et al., 2018), or beyond one year post-injury (Chamard et al., 2013; Churchill et al., 2019). These changes can become more severe in patients with multiple concussions (Brett et al., 2020), and diffuse white matter changes can still be seen in retired athletes (Tremblay et al., 2014). Acute increases of fractional anisotropy have also been seen immediately post-injury, at one week, at RTP, and at one month post-injury, but not at one year post-injury (Churchill et al., 2019; Hellewell et al., 2021; Meier et al., 2016). Such variation in the duration of persistent alterations may contribute to the electrophysiological changes seen, or may simply be another example of why physiological recovery from concussion is so difficult to determine.

The effect of repetitive impacts might further interact with unresolved electrophysiological alterations from a previous concussion (Moore et al., 2017). Those with previous concussions also demonstrated significantly faster times on the King-Devick by the end-of-season from baseline, as well as demonstrating a statistically significant change in the domain of orientation over time (Table 5.7), indicating a weaker sensitivity in these methods of acute concussion assessment. However, this evidence is not compelling because of the wide variability seen in the K-D scores as well.

## 6.2 Differences in SNR by degree of impact exposure

The finding of a statistically significant overall main effect for repetitive impact exposure is most consistent with the results of Manning and colleagues (2020); when examining female athletes (contact and non-contact) with resting-state fMRI at two time points (in-season and off-season), they found higher DMN connectivity between the

lateral visual networks and the occipital regions in the contact athletes (when compared to the non-contact athletes) at both time points. While increased ERP amplitude has been reported after concussion (Hudac et al., 2018; Ledwidge & Molfese, 2016; Moore, Hillman, et al., 2014; Moore et al., 2015; Olson et al., 2018), few other studies have reported higher amplitudes in those with repetitive impact exposure; an exception is an observed decrease of amplitude in healthy controls in response to a stimulus, but no corresponding change in the participants with repetitive impact exposure (Fratantoni et al., 2017). This finding of higher electrophysiological magnitude in rugby and combat athletes who experience regular repetitive impacts may have implications for our understanding of concussion, as well as the utility of the NuroChek system.

Our finding of increased SNR in the female combat athletes across a session of sparring is partially inconsistent with the findings of Salazar and colleagues (2021), though our studies differed in a few notable ways: their analyses primarily examined the effect of exercise and fatigue on the SNR (not the effect of the impacts), the boxers in their study wore headgear (while most athletes in this study did not), and they were participating in an official match (while athletes in this study were only training). The present finding of SNR differences between groups of combat athletes is similar to other ERP studies of combat athletes. Di Russo and Spinelli (2010) examined several ERP components in boxers and fencers during a cognitive inhibition task, and found smaller N100, N200, and P300 amplitudes (but not P100 or P200) in the boxers than the fencing group. Bianco and colleagues (2017) studied the same components in boxers and fencers during the same inhibition task and found "enhanced" amplitudes of N100, a P200 subcomponent, N200, and P300 (but not P100) in the fencers. No studies examining P100 before and after a boxing match were found, but the present findings are also consistent with reports of unchanged N100, P200, and N2a/MMN amplitudes in male boxers after a match (Breton et al., 1990; Pincemaille et al., 1989). Lesiakowski and colleagues (2018) reported changes to P100 and N75 associated with visual dysfunction in amateur boxers up to 45 days after impact exposure, and Freed and Hellerstein (1997) determined that P100 deficits and the corresponding visual dysfunction can be improved by an optometric rehabilitation program. This study did not examine long-term changes in combat athletes, but such data would be comparable to that of the rugby athletes, and could help to clarify the behaviour of the SNR across different types of impact exposure.

Inconsistency across type of impact exposure may account for differences with the present results. Acutely decreased amplitude was seen in contact athletes after heading a soccer ball, when compared to non-contact athletes (Moore et al., 2017) or their own

results 24 hours later (Di Virgilio et al., 2016). Altered connectivity was also seen in military personnel with and without a history of concussion, suggesting that non-concussive impact or blast exposure can still cause functional changes when compared to control civilians (Champagne et al., 2021). Some acute changes following repetitive head impacts occur at the cellular level and can persist days later (Bailes et al., 2013), so half an hour after the boxing training may not have been enough time for SNR changes to develop. The difference of half an hour in session times between combat athlete groups is notable as a potential confound, though it is unclear what effect this might have on the SNR. With better consistency in target populations and degrees of recent impact exposure, a common pattern of neuro- or electrophysiological changes may emerge.

The present study found no statistically significant changes to the SNR over time within the rugby impact exposure groups, which is consistent with other relatively stable physiological or cognitive findings over a season of impact exposure (Belanger et al., 2016; Miller et al., 2007; Talavage et al., 2014), though this could indicate that the measures used are not sensitive enough to detect subtle changes. The finding is inconsistent with reports of increases in P3a (Richards, 2017) and decreases in P3b, N100, and N400 (Clayton et al., 2020; Fickling, Poel, et al., 2021; Fickling et al., 2019; Fickling, Smith, et al., 2021; Richards, 2017; Wilson et al., 2015) after a season of repetitive impacts; while decreases are more commonly reported, it is often more complicated (Abbas et al., 2015; Clayton et al., 2020; Richards, 2017). Another source of variance is that many rugby athletes finished one season shortly before beginning another, which may mean that their first SNR was not a true pre-impact baseline. Manning and colleagues (2020) also noted that athletes in their study often did not have lower impact exposure at the baseline time point because many of them had just finished a different rugby season. Since this study's original intent was not to study non-concussive injury, the SNR's association with repetitive impact should be examined using more objective measurements, such as impact sensors and more frequent SNR assessments, as well as more detailed information on recent playing history.

While the SNR was not statistically different over the season in all exposure and demographic groups, the individual trajectories were highly variable over time, making it an unreliable baseline measure for most athletes (Figure 5.4 and Figure 5.8). One athlete sustained a big hit that was ultimately not diagnosed as a concussion, but he was still assessed at the post-injury time points. His SNR trajectory (Figure 4.4) resembles the expected recovery trajectory of a concussion athlete (sudden decrease, followed by gradual increase back towards baseline), and may be evidence of confounded sensitivity

of the SNR to actual concussions. Additionally, several concussed participants demonstrated the highest SNR at their first post-injury time point, which is inconsistent with the predicted post-injury decrease. Thus, while repetitive impacts may affect the SNR magnitude more than concussion, the sample sizes of the different impact exposure sub-groups in the present study were not large enough to make robust comparisons between all impact exposure groups.

### 6.2.1 Big hits and unreported concussions

Of the 31 athletes who reported non-concussive impacts during this study, 15 of these were assessed by the team medical staff, and cleared for concussion (including the athlete in Figure 4.4). Clayton and colleagues (2020) also analysed differences between diagnosed and cleared concussions: they were blinded to the concussion status of the athletes until the end-of-season, and found that 11 of the 56 athletes tested after an injury had not ultimately been diagnosed with concussion, but were still removed from play because of symptoms *"not attributed to a single event, but rather to a series of subacute events such as those experienced by the offensive line in football"* (p. 88), or the front row in rugby. These non-concussed athletes comprised half of the 38% of those whose ERP activity did not normalise by RTP, but activity in these athletes did return to baseline by the end-of-season (Clayton et al., 2020). Yet in the present study, no difference was seen in the non-concussed athletes by self-reported impact exposure (big hits vs regular impact exposure), possibly because of the small sample size of the athletes who reported sustaining a big hit followed by concussion-related events (loss of consciousness, visual dysfunction, or concussion symptoms such as headache, dizziness, or light sensitivity).

The present grouping of rugby athletes by impact exposure is slightly different than that reported by Talavage and colleagues (2014), who found four different trajectories in their athlete groups after a season of American football: athletes with concussion, non-athletes, control athletes who sustained regular repetitive impacts with no functional changes seen by fMRI (n = 4), and a distinctive subset of the control athlete group (n = 4) who showed neurophysiological impairment after a season of repetitive impacts; these functionally-impaired athletes also experienced more total collision events than the other three groups. These groups are not directly comparable because the groups in the present study were based on self-reported impact exposure, but it raises the question of how many athletes have hidden functional impairments.

The last point of note concerns the small number of participants in the "big hits" group who sustained a concussion and did not report it or seek treatment. Three athletes

were thought to have sustained an unreported concussion (representing up to 12.5% of total concussions in this study), based on 1) the athlete's belief that he had sustained a concussion despite reporting minimal symptoms, 2) a reported loss of consciousness, and 3) a reported partial loss of vision after an impact (Table 5.17). The prevalence of unreported concussions is by nature an estimate, but other studies have reported rates that range between 27–64% (LaRoche et al., 2016; Leahy et al., 2020; Meehan et al., 2013). Athletes in this study were not asked why they did not report their injury, but common reasons include not realizing how serious a concussion is, and not wanting to affect their place on the team, miss playing time, or disappoint the team (Escolas et al., 2020; LaRoche et al., 2016; Meier et al., 2015; Treacy & Heflin, 2021). The cultural impact of rugby and masculinity on New Zealand male athletes also cannot be ignored, especially in the ways it has become interwoven with *mana* and physical prowess venerated by Māori culture (Hokowhitu et al., 2008). Nevertheless, unidentified concussions are an important concern, as a second impact while an individual is still symptomatic could cause severe brain damage or death (Bey & Ostick, 2009; Ellis et al., 2015; Grady et al., 2012; Wetjen et al., 2010).

### 6.2.2 Speculation on adaptation of the SNR to repetitive impacts

Most repetitive impacts sustained by athletes will not break the threshold for a diagnosable concussion, but might still cause short-term or cumulative alterations. The higher SNR seen in the repetitive impact athletes could represent a compensatory upregulation or neuroprotective response to these impacts (Manning et al., 2020), despite no observable SNR increase in the combat athletes after acute impact exposure. The SNR of the no-impact combat athletes was lower than that of the impact combat athletes at both time points, which may support the idea that the no-impact athletes have less detectable neural "tolerance" to repetitive impacts (Stemper et al., 2019). Bari and colleagues (2019) also found evidence of increased neurochemical activity in response to repetitive impact exposure that decreased a few months after the exposure ended, though the degree of activity did not correspond with the degree of impact exposure. This is consistent with our finding of higher SNRs in the male rugby athletes with repetitive impact exposure at the end-of-season; it may indicate an adaptation to repetitive impact exposure (or another mechanism of habituation/neuroprotection) is affecting this difference over time.

If so, it is conversely possible that a reduction in this tolerance could indicate a susceptibility to concussion or other neural injury; in other words, an acute increase in

repetitive impact exposure could lower the threshold for subsequent force needed to cause a concussion. Stemper and colleagues (2019) found an increase in repetitive impacts on the days leading up to concussion in 72% of participants, and those with more cumulative impacts then sustained their concussion from impacts with much lower force (measured by accelerometer). They theorised that the acute increase of repetitive impacts may have affected the athletes' neural vulnerability or tolerance to the typical impact load (Stemper et al., 2019). If the SNR does represent an increasing adaptation or preconditioning to repetitive impacts, then those with weakening adaptive responses (i.e., those at risk of sustaining concussion) might be identifiable from decreases in their SNR during the season. For example, of the two concussed athletes who provided mid-season data before their injury, both had a lower SNRs at mid-season than their baselines (Table 4.2); one of these athletes was cleared for a concussion directly before the mid-season assessment, then went on to sustain a concussion four days later. Regular testing of all athletes would be needed to test this idea.

This adaptation to repetitive impacts may develop gradually, making it difficult to see acutely. When Moore and colleagues (2017) asked participating athletes to estimate how many times they may have headed a soccer ball in a game, no correlation was found in the subconcussed group between ERP impairment and estimated number of impacts. A weakened P3b amplitude may not present until a second or third sequential season of contact sport (Clayton et al., 2020; Wilson et al., 2015). Olson and colleagues (2018) did not find any correlation between ERP amplitude and number of years playing a contact sport, but they acknowledge that years of sport are not the most sensitive measures of subconcussive effects. I did not collect data on how long athletes had been playing, and my results do not clearly show if the SNR activity is correlated with higher impact exposure; in addition to the stability of the SNR after a boxing session, the "big hits" group did not show any statistically significant between-group differences from the other impact exposure groups. Ultimately, these subjective or inferential estimates of impact exposure are inadequate, and a physiologic measure used more consistently in combination with accelerometers or impact sensors could reveal a pattern of adaptation.

The in-season variability of the SNR is partially consistent with the findings of Abbas and colleagues (2015) and could represent a delayed habituation to exposure. Using resting state fMRI, Abbas and colleagues (2015) reported a distinct pattern of alteration to the DMN activity in non-concussed football players. They reported an initial decrease of network connections from baseline to the first time point after the season began, followed by a substantial increase at the second mid-season time point, when the

number of network connections had exceeded that of the baseline; this suggests a delayed upregulation to compensate for the impacts. After the end-of-season they finally saw less connectivity than at baseline; they posited that, to support the long-term repair process, the DMN activity might be downregulated after impact exposure ends. They further attributed these changes to compensatory mechanisms that prevent symptoms and help the athletes maintain normal function during regular impact exposure (Abbas et al., 2015). Manning and colleagues (2020) found higher activity between the DMN and the posterior cingulate cortex in contact athletes than non-contact athletes (during both the season and the off-season), and they also theorised that this hyperconnectivity was a compensatory response to repetitive impact exposure. Even if the SNR is not related to the DMN, the brain processes involved in generating the SNR may undergo adaptations that are similarly responsible for the increase in non-concussed athletes over time.

How the repetitive impact load may vary between these combat and rugby athletes is not clear, as Study B also does not report any data on the frequency or intensity of impacts to the head or body. Matser and colleagues (2000) found that two-thirds of boxers in their study received up to 10 punches to the head during a bout, while the other third received more than 10 head punches, with a maximum of 31. Zazryn and colleagues (2003) reported that 89.8% of injuries that boxers sustain are to the head or face, but only 15.9% of those injuries are assessed as concussions; non-concussive injuries to the eye area are the most common (45.9%), followed by injuries to the face (15.0%), cheek (8.4%), and head (2.7%). The boxers in this study likely received a lesser degree of these injuries because they were only training, and not in an official bout or match. Lesiakowski and colleagues (2018) studied sequential components (N75, P100, and N135) using a flashing stimulus and found differences in amplitudes and latencies for each eye; years of boxing experience only correlated with the N75 alterations. These could be related to the visual symptoms seen after impacts in the rugby athletes (Table 5.18). Perhaps with more electrodes and a way to calculate SNR by region or single electrode, the NuroChek system would be able to see differential damage in a more specific region (left, right, or centre occipital).

## 6.3 Cognitive differences by impact exposure group

As well as higher SNRs, the boxers demonstrated faster performance on the TMTb than the BJJ athletes. The finding of faster scores by the boxers on the TMTb is consistent with that of Porter and colleagues (1996), but inconsistent with literature that reports switching deficits to be common after repetitive impacts (Collins et al., 1999;

McAllister et al., 2012; McCrea et al., 2003). Much research on repetitive head impacts has been done over a season of repetitive impacts in American football players, and the rugby athletes in the present study did not complete this measure. Our findings are also inconsistent with those of previous studies in boxers and fencers (Bianco et al., 2017; Di Russo & Spinelli, 2010): in addition to the larger amplitudes ERP seen in the fencing groups, they reported faster and more accurate performances during a cognitive task of inhibition compared to the boxers, as well as stronger attention and motor control. However, rather than repetitive effects, they posited that this could be due to the different cognitive skills needed for fencing versus boxing. By that reasoning, it is possible that the cognitive skill sets used by fencers and BJJ athletes are different as well. Lastly, the faster completion times (with large effect sizes) seen in the boxers and BJJ athletes are most likely due to a practice/learning effect or increasing familiarity with the task.

## 6.4 Other ways to detect repetitive impact damage

As with concussion, damage from repetitive impacts is not observable by standard imaging (Bailes et al., 2013; Bari et al., 2019). Repetitive impacts to the head can be measured by accelerometers placed in helmets (Breton et al., 1990; Di Virgilio et al., 2016; Pincemaille et al., 1989), and the corresponding damage can be observed as neurometabolic changes (Bailes et al., 2013; Bari et al., 2019; Hunter et al., 2019; Owens et al., 2021), white matter damage (Bazarian et al., 2014; Gu et al., 2017; McAllister et al., 2014; Moore et al., 2017), alterations to electrophysiological activity or communication networks (Abbas et al., 2015; Moore et al., 2017; Pearce, 2016), or as subtle neurocognitive deficits in asymptomatic athletes after a season (Bazarian et al., 2014; E. L. Breedlove et al., 2012; McAllister et al., 2012; Talavage et al., 2014).

Neurometabolic changes can be observed using imaging of neurotransmitter activity (via magnetic resonance spectroscopy), and may not return to baseline until 2–5 months after the athlete ends their exposure to repetitive impacts (Bari et al., 2019). Because the injury is subtle, metabolic changes may not present immediately after exposure begins (Bari et al., 2019; Hunter et al., 2019). Long-term exposure to repetitive impacts can damage the blood-brain barrier (Hunter et al., 2019), reduce cerebrovascular function (Owens et al., 2021), cause a chronic metabolic mismatch (Bari et al., 2019), or influence neuroimmunity (Hunter et al., 2019). The electrophysiological change could be linked to a hormonal change over time, similar to the relationship seen by Tanriverdi and colleagues (2013) between the P300 and the growth hormone/insulin-like growth factor-I (GH-IGF-I) axis. When examining a population of boxers, they reported a relationship

between the P300 component and deficiencies in GH and IGF-I that affected 21.9% of their boxers; the P300 deficits were not seen in athletes or controls with no hormonal deficiencies. The relationship between electrophysiological and hormonal changes is likely because P300, GH, and IGF-I are all active across similar regions (Tanriverdi et al., 2013). Other neurological biomarkers linked to repetitive impacts include S100β, tau, neurofilament light, glial fibrillary acidic protein, brain-derived neurotrophic factor, ubiquitin C-terminal hydrolase L1, and neuron-specific enolase (Bazarian et al., 2014; Hirad et al., 2019; Lember et al., 2024; Zetterberg et al., 2016).

White matter can also be damaged without a concussion diagnosis or any accompanying visible or behavioural symptoms (Voss et al., 2015), blurring the physiological line between a concussion and damage from repetitive impacts (Bazarian et al., 2014; Clayton et al., 2020; Gosselin et al., 2006; Moore et al., 2017). Although only female rugby athletes were included in their study, Manning and colleagues (2020) found significant diffusion changes in the corpus callosum, cingulum, and brainstem when they were compared to non-contact athletes (swimmers and rowers); they posited that these changes were the result of repetitive impacts over a season. Axial diffusivity (a measurement of DTI) within the corpus callosum was also significantly lower in the contact athletes with a history of concussion than in those without (Manning et al., 2020). Alterations to fractional anisotropy can be seen after a season of repetitive impacts in college American football players (Hirad et al., 2019; McAllister et al., 2014), in which white matter damage in the right hemisphere was linked to rotational (but not linear) acceleration (Hirad et al., 2019). Further, persistent white matter damage was seen after six months of rest in athletes who were never diagnosed with concussion during the playing season (Bazarian et al., 2014). The higher SNR seen in the repetitive impact athletes may be related to the impact exposure, but it is unclear how long these potential effects may last.

## 6.5 Summary/Key findings

The SNR did not show consistent change after concussion or upon recovery, and the present study did not find any evidence to support its use in concussion assessment or management. The main effect of higher SNR in athletes with repetitive impact exposure may be evidence of a long-term adaptation to repeated impacts, and it complicates the relationship between the SNR and concussion.

**Aim 1 summary:** Not supported. The SNR did not show clinically meaningful change (consistently in one direction) in the days after concussion or in the 30 minutes after a boxing match.

**Aim 2 summary:** Not supported. The SNR did not show clinically meaningful change in the 20 days after concussion.

**Aim 3 partial summary:** Mostly unsupported. There was no main effect for previous/no concussion history and SNR, but concussion history may affect the SNR differentially by impact exposure.

**Aim 4 summary:** Supported. Athletes who sustain regular repetitive impacts demonstrated higher SNRs than no-impact combat athletes and athletes who sustained a recent concussion.

# Chapter 7
# Discussion: SNR and Sex

This chapter discusses the sex differences seen in the present study and places them in context of the wider literature on sex differences in electrophysiology. Specific discussion is given to the differences in magnitude and quality of SNR, and how the sex differences found here (including the statistically non-significant results) compare with previously reported sex or gender differences in electrophysiology and neurophysiology. Many findings of the present study were comparisons that were not significant, and they provide important context to the significant differences we did find. The most notable of these are that no female athletes sustained concussions during this study. Moreover, no significant differences in SNR were found between sex groups of the control participants or different impact exposure groups of female participants, and no interaction was found between sex and concussion history.

## 7.1 No female athletes sustained concussions

All concussions reported during this study were sustained by male participants, which is consistent with research that finds male athletes to sustain more concussions than female athletes, in athlete and general populations (Gardner, Iverson, Williams, et al., 2014; Pieter & Zemper, 1998; Ponsford et al., 2000; Theadom et al., 2020) and with a higher overall prevalence of concussion in men (Accident Compensation Corporation, 2022; Gardner, Iverson, Williams, et al., 2014). However, the finding of zero concussions in the participating female teams across two years is certainly notable, and is inconsistent with reports of more female concussions in sex-matched sports, including rugby (Broshek et al., 2005; Castellanos et al., 2021; Covassin et al., 2012; Harmon et al., 2013; Heming et al., 2023; Merritt et al., 2019). Similar to this study, King and colleagues (2021) followed 69 female amateur rugby union athletes across two seasons in New Zealand, and found only one athlete to sustain a concussion, which kept her out for 30 days. King and colleagues (2018) studied another group of 21 female rugby league athletes over nine games in one season (similar to the length of season for the female rugby athletes in this study), and reported three concussions sustained by these athletes. The lack of concussions in female athletes at any level of play in the present study could be due to a less aggressive playing style than male athletes (Broshek et al., 2005). It might also represent either excellent coaching and injury prevention education of the female teams,

better game-playing technique (particularly tackling), or sex differences in risk-taking behaviour.

Kontos and colleagues (2020) found that female athletes were more likely to delay reporting a concussion. While some female athletes in the present study reported big hits, none met the description of an unreported or undiagnosed concussion. It is unlikely that the female athletes would be less likely to report concussions or symptoms to their athletic or medical staff since their average symptom and symptom severity count was marginally higher than that of the male athletes with a moderate effect size (Table 5.21). Female and male non-concussed athletes have shown different symptom reporting patterns on the SCAT-5 inventory (Kieffer et al., 2021; Robinson, 2019), and may have different attitudes towards injury reporting. In a study examining concussion reporting behaviour in adolescent hockey players, female and male athletes cited different reasons for deciding to report or not report concussions (Hunt et al., 2019). Women are more likely to seek care for concussions than men (Stergiou-Kita et al., 2016), and female athletes are more likely to report more symptoms in general, not just after concussion (D. A. Brown et al., 2015; Kieffer et al., 2021). The relatively higher reporting of concussion and symptoms among women in the literature means it is unlikely that female athletes sustained unreported concussions during this study.

There was also no detectable relationship over time between concussion history and sex in the rugby athletes in this study (Table 9.4), likely because of small sample size. This is inconsistent with the findings of two studies that reported an interaction (Baker, 2008; Carrier-Toutant et al., 2018). DTI axial diffusivity within the corpus callosum was significantly lower in the female contact athletes with a history of concussion than in those without (Manning et al., 2020), which is not consistent with our findings of no significant changes associated with concussion history in female athletes over time. The non-contact athletes in that study also reported no history of concussion (Manning et al., 2020). Larger sample sizes are needed to examine this interaction with more structure.

## 7.2 Electrophysiological differences by sex in the present study

A unique contribution of this study is the SNR data from non-concussed female athletes, which has not been previously reported in studies using the NuroChek system (Fong et al., 2020; Fong et al., 2021; Salazar et al., 2021). Sex differences were seen between the female and male participants, in the trajectories of the female athletes over a season, and by impact exposure (regular versus limited) within the male participants. A common pattern across the female rugby and combat athletes was a lower SNR than the

male athletes at baseline, followed by an increase over time (after acute impact exposure in the combat athletes, and long-term repetitive impact exposure in the rugby athletes). Despite outliers, the SNR distribution was also generally lower in the female (than in male) athletes, and the EEG data from the female participants was more prone to an interference effect (observed as a harmonic artefact in the reading). This artefact, when present, was associated with marginally significant reductions to the quality of data from female participants and statistically significant reductions to the quality of data from male participants. Most of this chapter focuses on the lower SNRs in the female athletes and the quality of SNRs across sex, since not much literature was found to explain the acute increase in SNR in female combat athletes or the longitudinal increase in female rugby athletes. However, other potential causes for these electrophysiological sex differences (e.g., anatomical, hormonal, biomechanical, hairstyle, or another physiological or functional difference in how components are generated or how visual stimuli are processed) are discussed further in section 7.2.1.1.

Finally, differential effects of impact exposure group were found in the SNRs of male participants. Male rugby athletes with regular impact exposure demonstrated higher SNRs than male participants with limited impact exposure at baseline and end-of-season, as well as higher SNRs than the concussed athletes at the end-of-season. Without data from female athletes with concussions or sufficient sample sizes across impact exposure groups, we cannot speculate on the interaction of brain injury with sex and its effects on the SNR. The finding of lower SNR in female rugby athletes was only statistically significant in the group of athletes with regular impact exposure, and not in the participants with limited impact exposure (rugby athletes + non-athletes), but the sample sizes of female athletes were too small to analyse further. These different patterns of SNR change across sex may be evidence of a differential response in female and male brains to repetitive impacts.

### 7.2.1 Lower SNR in female athletes that increases over time

The female rugby athletes showed lower SNRs at all three time points. The SNR of the female athletes showed trajectories of increase in the rugby and combat athlete groups; they also demonstrated higher SNRs from mid-season to the end-of-season. After the increase, the difference between female and male rugby athletes at the end-of-season was still statistically significant, albeit closer in range. The difference seen in the baseline SNRs from 2020 to 2021 is likely due to improved fitting of the headset.

The other pattern of increase was marginally significant (with a large effect size), seen in female (but not in male) combat athletes after a round of sparring. The present increase in female athletes is partially inconsistent with the stable findings of Salazar and colleagues (2021) in boxers and no-impact exercise controls before and after a session, though in their study, sex groups were not analysed separately or compared to each other. The SNR was also relatively stable in the male rugby athletes, with some between-group differences for impact exposure, but no within-group changes over time.

The only participant group that did not show a significant difference in SNR between sexes was that of the non-athlete controls, likely because of the small sample size (six female and eleven male participants). The SNR could also represent a dynamic measure more closely associated with the effects of exercise in the female athletes. It is theoretically possible (though unlikely) that these electrophysiological differences are not detectable in participants without exposure to exercise (the way the Buffalo Treadmill Test is used to elicit persistent deficits during exercise) or that they represent an upregulation of neural activity in response to repetitive impacts. However, a much larger sample size of non-athlete control participants would be needed to examine these associations.

#### 7.2.1.1 Sex differences in electrophysiology

Almost fifty years ago, Buchsbaum and colleagues (1973) were among researchers who reported electrophysiological differences in sex groups of patients when using photic stimuli (Gölgeli et al., 1999), and visual paradigms are still often used to elicit ERP responses across sexes. Using a visuospatial-attention oddball paradigm, Vaquero and colleagues (2004) studied several ERP components and found different patterns of activity across sex groups; in general, men demonstrated higher P100 and P300 amplitudes while women demonstrated higher N100 amplitudes. They attributed this to sex differences in neural generators of these potentials (Vaquero et al., 2004). The closest ERP analogue component to this study is the P100; thus, this is consistent with the present findings. Other studies using a visual oddball paradigm (Bourisly & Pothen, 2016; Bourisly & Shuaib, 2018) found healthy male participants to have higher P200 and P300 amplitudes than the female participants. In a study examining migraineurs with a visual oddball paradigm, Guo and colleagues (2019) found lower amplitudes in the female migraine patients than the male patients; this difference was not explained by age, education, or other clinical characteristics. The female patients showed more difference in amplitude from female controls than the male patient did from male controls, which

may reflect more severe migraines or symptoms in the women (Guo et al., 2019). This finding of lower amplitude in symptomatic female participants is consistent with our findings, as is the finding of no sex differences in the healthy controls. It is unclear what this may mean in the context of the present uninjured population, since effects from repetitive impacts would likely not be comparable with migraines.

Studies using auditory oddball paradigms in healthy participants have also found higher amplitude in men than in women, consistent with the results of the present study. Gölgeli and colleagues (1999) found higher amplitudes of N100–P200 and N200–P300 components in the men compared to women; they theorised that this functional difference was related to neuroanatomical differences between sexes, and they noted that this effect was present at the Oz site specifically. Nagy and colleagues (2003) found the N200 to be more negative in male participants when compared to female participants, but they also found a higher amplitude for the P300 component in the female participants. It is unclear why the pattern of higher amplitudes across sexes varies by type of stimuli used, but it is an interesting avenue of future research into electrophysiological sex differences.

Despite these inconsistencies, there are also studies reported in the literature that differ from the present study. Higher amplitudes of SSVEP responses have been reported in female participants than male participants within several populations, including healthy participants (Kaneda et al., 1996; Nagy et al., 2003; Wada et al., 1994), cannabis users (Skosnik et al., 2006), and patients with schizophrenia (Krishnan et al., 2005; Wada et al., 1995). Kaneda and colleagues (1996) used a flashing stimulus to examine the VEPs of healthy female and male participants; they found higher amplitudes in the female participants, and amplitude was not affected by age, height, or weight. Also inconsistent with the present finding, some research using EEG (Prause et al., 2014; Pravitha et al., 2005) found higher amplitudes for female participants. However, none of the above studies reported an amplitude increase in female athletes over a short or season-long interval.

Some SSVEP studies found main effects for sex at the Oz site (Krishnan et al., 2005; Skosnik et al., 2006; Wada et al., 1995). Sex may have an effect on electrophysiological patterns of visual processing (Guo et al., 2019; Hausinger & Pletzer, 2021) that partially accounts for these differences, since schizophrenia and cannabis use are associated with visual alterations. Hausinger and Pletzer (2021) studied how different visual information processing strategies may be affected by sex hormones, and they discovered men have faster reaction times and higher accuracy during a task of top-down processing; while women had faster reaction times in the bottom-up condition, they were

less accurate. However, this difference was only found in the divided attention task, and they found no sex differences in the selective attention task or in hemispheric asymmetries (Hausinger & Pletzer, 2021). In the context of the present study, it is unclear how occipital or visual processing differences may affect the SNR.

There is no particular consensus concerning the sex differences reported in electrophysiology literature. While some studies include both female and male participants, differences between them were not always reported (Clayton et al., 2020; Salazar et al., 2021) or were not significant (Daltrozzo et al., 2007; Kasai et al., 2002; Mitchell et al., 1987; Sivák et al., 2008). In one case (Baker, 2008), the differences were significant, but the direction was not reported. Other studies have reported inverted behaviours of the ERP components between female and male participants, where the amplitude of a component increased in one group and decreased in the other (Oliver et al., 2016; Vaquero et al., 2004). The inconsistencies and mixed findings of sex may be due to differences in data quality, which highlights the need for further consideration of (and research into) these differences (Gasbarri et al., 2006), including the need to understand the effects of sex on the quality and interpretation of electrophysiological data.

### 7.2.2 Lower-quality SNR in female participants

Despite similar ranges, the distribution of SNR data in the present study differed slightly between the male and female athletes. Male participants demonstrated a more even distribution over this range (Figure 5.1 and Figure 5.2), whereas the distribution of the female participants was smaller and more concentrated (though this effect could be due to inadequate sample size). Other electrophysiological studies have reported high variability (Eckner et al., 2016) in both sex groups (Mitchell et al., 1987), but none of these reported more variability in one particular sex. Similar to what we saw in the female participants, Skosnik and colleagues (2006) described a “floor effect” for male participants in their study, meaning that the overall low EEG response magnitudes in the men made any group differences undetectable. The lowest magnitudes of SNR data represented in this study (i.e., below 3.0 as the highest SNR of two or three trials) could similarly contribute to a “floor effect” in some of the female participants of this study, thus impacting sensitivity and the ability of the SNR to detect subtle changes in these women. However, it is more important to note that all data were included in analyses (regardless of magnitude) because of the importance of *bona fide* data for the evaluation of the NuroChek system, and to avoid introducing bias into the data distribution.

In some instances, low SNRs in female participants could be improved during the second trial. Beyond more saline saturation and fitting improvements around longer or thicker hair, a possible explanation for the increase of SNR seen in the second trial is that of a delayed habituation to the flashing light stimulus; this effect may not be seen in the male participants because perhaps they habituated more quickly to the light after the priming trial. Consistent with this finding, Fong and colleagues (2021) noted that athletes in their study demonstrated higher SNRs during the second trial, due to a "familiarity with the task." Though the sample size was small, one finding of a statistically significant increase during the second trial in female participants indicated that it may specifically occur during morning testing sessions. Perhaps this delayed habituation is only been present in the female participants in the first half of the day, which could be due to many factors associated with the morning routine of these participants, including caffeine intake. Alternately, it may indicate a type I error (false positive).

In addition to lower SNR in female participants, a higher proportion of their trials showed harmonic artefacts, making it difficult to obtain a clean, high-quality SNR from these participants. The harmonic artefact was identifiable in over 51.8% of trials from female participants, and only in 15.1% of trials from the male participants. The presence of this artefact was significantly associated with lower SNR magnitude, which means that the quality of more than half of the trials from female participants were somewhat compromised, while only 15% of data from the male athletes were similarly compromised (though the effect on male trials may be more significant; Table 5.11). Despite the following the instructions to add extra saline and expose the scalp in the event of participants with long hair (Fong et al., 2021), these artefacts persisted, suggesting that they may be more naturally present in female SSVEP readings of this type. Additionally, many male athletes had long or thick hair; thus, reduced impedance of the electrodes because of hair does not fully explain this sex difference in the presence of harmonic artefacts. Algorithms are available to identify and remove artefacts such as the harmonic reflection from EEG/ERP signals (Gonçalves et al., 2007; Klug & Kloosterman, 2022), but it is possible that the calculation of the SNR may not include such an algorithm because it was developed using the EEG signals of male athletes, who (according to this study) only demonstrate the harmonic artefact 15% of the time.

These harmonic waveforms are mathematically related to the stimulus frequency. Norcia and colleagues (2015) described the harmonic response to a single frequency and its potential cause (p. 4, emphasis added): *"The presence of frequencies in the response (the output) that were not present in the stimulus (the input) indicates that the response*

*of the visual system is due to the* ***activity of nonlinear neural mechanisms****."* A harmonic artefact was reported by Appelbaum and colleagues (2006) in response to different visual stimuli patterns in an attention task. Wada and colleagues (1994) also reported that in response to photic stimulation, female participants demonstrated a higher amplitude than the male participants at the target frequency or at one harmonically related to it. It could represent an internal aspect of electrophysiology such as neural network organisation, or an external source of interference such as contaminants in the hair.

Sex differences may be present at the occipital (target) electrode sites. Gölgeli and colleagues (1999) reported that female participants demonstrated lower amplitudes at the Oz site than the male participants; female participants instead demonstrated higher amplitudes at the Fz site than the Oz site. In contrast, Wada and colleagues (1994) found significantly higher amplitudes at parieto-occipital sites (including the Oz) in the female participants than the males, and Krishnan and colleagues (2005) found larger signal power from the female participants at the Fz and Oz sites than the male participants. Moreover, because of differences in head size across sex, it is possible that the electrodes on the back panel do not align with the true anatomical sites.

It is also possible that, in addition to the target electrode sites, there are electrophysiological differences at the reference sites. In one study measuring P300 amplitude during a distressing narrative task (Gasbarri et al., 2006), women and men both demonstrated increased P300, but in significantly different locations; women demonstrated the increase in the left hemisphere (P3 site), while men demonstrated the increase in the right hemisphere (P4 site). Since the NuroChek headset uses P1 and P2 sites as the reference and ground sites (Figure 3.4), perhaps the differences seen are a result of sex differences at these sites. As the NuroChek system has primarily been tested in male athletes, sex differences like lower magnitude and higher harmonic presence are important factors when considering the widespread utility (and future development) of this system for concussion assessment.

### 7.2.3 Relationship between impact exposure and sex

The differences between each participant group (rugby, combat, and non-athlete) were not statistically significant within each sex group at the baseline, but the athlete groups did show statistically significant differences over time. When repetitive impacts were analysed by sex, significant differences were only present in the male athletes (reported in Section 5.3.3.3.1), and the difference between the impact and no-impact groups of female athletes was not statistically significant (Table 5.14, row 3). Because of

the “floor effect,” the lower SNR in female participants may be too low to demonstrate these subtle changes. Without larger sample sizes of female athletes for all four impact exposure groups, it is unclear how the SNR of female athletes may be affected across impact conditions.

Other studies have found functional differences by impact exposure and sex. Using magnetic resonance spectroscopy and accelerometers, Bari and colleagues (2019) found that male collision athletes showed more neurometabolic changes, as well as higher impact exposure, than female collision athletes. This is likely consistent with our findings; the seasons for the female rugby athletes were shorter than for the male athletes, which limits the number of impacts they would have experienced. An accelerometer study by King and colleagues (2018) also found that the average acceleration of 15 *g* experienced by the female rugby league athletes in their study was comparable to impacts experienced by junior athletes, but lower than those experienced by other male rugby or soccer athletes. If female athletes already have lower SNR magnitudes, then less impact exposure might explain why no difference was seen between the female impact exposure groups.

Bari and colleagues (2019) offered a nuanced explanation for the sex differences: in their study, male athletes showed neurochemical alterations in the dorsolateral prefrontal cortex, an area with more vulnerability when exposed to repetitive impacts, while female athletes only showed alterations in the primary motor cortex, likely as a response to the injury alone. In other words, the male athletes showed more vulnerability to cumulative damage from repetitive impacts than the female athletes, though these effects were alleviated 2–5 months after the exposure to collision sport ended (Bari et al., 2019). While this may not be directly comparable to the present results, it is an example of how differential alterations can manifest between sex groups.

The present non-significant finding of the SNR difference between female impact exposure groups is also inconsistent with several studies that report neurophysiological differences in female athletes after a season of repetitive impacts (Manning et al., 2020; Myer et al., 2019; Sollmann et al., 2018), though there is little commonality across imaging modalities or target populations. Using fMRI and DTI, Manning and colleagues (2020) found neurophysiological differences between rugby and non-contact athletes during both the season and the off-season. In an interventional study using DTI, Myer and colleagues (2019) reported three types of diffusivity differences from pre-season to post-season in adolescent female soccer control athletes who did not receive the intervention. When studying ice hockey players after a season of contact, Sollmann and colleagues (2018) reported decreases of diffusion measures (via diffusion MRI) in the

female athletes, and no significant changes in the male athletes; this is inconsistent with our finding of significantly increased SNR in female athletes and the smaller but still significant SNR increase in male athletes. While the lack of change over time could be interpreted as stable over time, it is more likely that since NuroChek demonstrated lower sensitivity to the SNR in female athletes, it is not clinically adequate to detect subtle changes in female athletes.

## 7.3 Cognitive and symptom differences by sex groups

Differences between the female and male rugby athletes were seen in the concentration and King-Devick tests (as well as symptoms reported), while changes over time were seen in the domains of orientation and concentration for the male athletes only (Table 5.21). No differences were seen in the cognitive scores of the female athletes over time. Further, no cognitive differences by sex were found for the combat athletes or at the single time point for the non-athlete control participants.

Female athletes reported marginally more symptoms (with moderate effect sizes) at baseline and end-of-season than male athletes, which is consistent with other studies that found higher symptom numbers and severity reported by female athletes at these time points (D. A. Brown et al., 2015; Kieffer et al., 2021). Kieffer and colleagues (2021) reported statistically similar symptom numbers between female and male athletes at baseline, as well as stable symptom numbers in male athletes from baseline to mid-season, which is consistent with the present results. However, Kieffer and colleagues (2021) also found symptom trajectories that this study did not, specifically an increase of symptoms in female athletes from baseline to mid-season and higher symptoms in female athletes at mid-season when compared to male athletes. In female athletes only, Manning and colleagues (2020) found that non-contact athletes in the off-season reported more symptoms and higher severity than during the season or than by the contact athletes at either time point. This seems to indicate a difference in symptom reporting by type of sport. Symptoms experienced after physical exertion can also differ by sex: after participants exercised briefly, Miutz and colleagues (2023) found that whereas many reported symptoms were similar, male participants were more likely to report a feeling of pressure in the head, while female participants were more likely to report a headache. Though we did not find significantly different patterns of symptoms by impact exposure in the female athletes, a larger sample size is needed to examine symptom and cognitive differences over time between female athletes of different impact exposures.

The male athletes showed improvements in concentration (reciting digits and months backwards) after acute impact exposure and after a season of rugby. This could reflect increased familiarity with the task (practice effect) or intentionally poor performance at baseline, though it is unclear why this effect was not seen in the female athletes as well. Different attentional and information processing strategies in women and men may be indicated by different localisations of ERP amplitudes during visual attention tasks (Bourisly & Shuaib, 2018; Vaquero et al., 2004). Female participants have also shown more EEG activity at prefrontal, frontal-temporal, and centro-parietal sites than male participants during the no-task, eyes-closed condition, which may imply more independent and parallel processing strategies in female brains in no-task conditions (Pravitha et al., 2005). Concentration efforts may also change differentially over time. Manning and colleagues (2020) found concentration scores to increase from in-season to the off-season in the female contact athletes, but they found no corresponding change in the non-contact athletes. Alternately, the digit span is a very limited test for concentration deficits, and may not be ideal for measurement of this domain.

In the present study, the female athletes had faster King-Devick scores than the male athletes at both baseline and end-of-season. When testing children and adolescents with the K-D, Moran and colleagues (2017) also found the female athletes (m = 50.54 seconds, SD = 11.1) completed the K-D faster than the male athletes (m = 56.13 seconds, SD = 11.3). In contrast, Heick and colleagues (2016) found that female participants between ages 14–24 had slower completion times than male participants in the same age range. Clugston and colleagues (2019) found the K-D performances at baseline to be similar between sex groups of university athletes, whose average age was three years lower than that of the present study. Other studies using the K-D did not differentiate performances between sex groups (Galetta, Brandes, et al., 2011; Marinides et al., 2014; Rizzo et al., 2016; Sherry et al., 2021), found mixed results (Gallagher et al., 2021), or included very few female participants at all (Harris et al., 2021; Moody et al., 2019). Also inconsistent with our results, Sollmann and colleagues (2018) found improvements in a similar domain of visuomotor speed (measured by the ImPACT) in the male athletes from pre-season to post-season, but they found no statistically different changes in the female athletes. However, the K-D and the ImPACT were designed to detect reading disorders and changes after concussion, respectively, and may not be appropriate or sensitive enough to detect subtle neurocognitive alterations after a season of repetitive impacts (Sollmann et al., 2018). It is also possible that female and male brains experience different

visual processing changes after repetitive impacts or by age, which may also contribute to the differences in SNR by sex.

## 7.4 Neurophysiological differences by sex

The electrophysiological differences by sex in the present study may be due to anatomical (i.e., head size, thickness of skull, or biological layers within) or functional (i.e., hormonal or metabolic) differences between female and male physiology (Gregori et al., 2006; Hausinger & Pletzer, 2021; Hu et al., 2013; Skosnik et al., 2006; Wada et al., 1994). "Sexual dimorphism" describes aspects of anatomy or function that differ measurably across sexes, like the size or placement of different regions or neuronal components (Bourisly & Shuaib, 2018; Dollé et al., 2018; Späni et al., 2018; VanRyzin et al., 2020). Since neural activity has shown regional or lateralised differences across sexes (Gasbarri et al., 2006; Hausinger & Pletzer, 2021; Hu et al., 2013; McGlone, 1980; Prause et al., 2014; Vaquero et al., 2004), the SNR (and corresponding brain activity) is likely not intrinsically weaker in female brains, but it is somehow blocked, missed, or obscured because the SSVEP is limited by the fixed placement and surface-level nature of the headset's non-invasive scalp electrodes. Due to female physiology, the activity may take place elsewhere, such as in a different (possibly subcortical) region, across the corpus callosum, or an otherwise differential lateralisation in female brains. The disproportionate presence of the harmonic artefact pattern in SNRs in female participants also supports the reasoning that lower signal strength in female athletes represents a different distribution of neural networks than in male athletes.

Sex differences as seen by imaging techniques may provide some insight into these different organisations. In studies using microscopy, spectroscopy, and more standard imaging methods like fMRI and DTI, differences have been reported in healthy men and women, as well as across sex groups of participants with different conditions, including repetitive impact exposure and traumatic brain injury. Because of the absence of female athletes with concussion in the present study, sex differences in concussion are outside the scope of this research. Sex-related differences in concussion and TBI have been discussed in a number of studies and reviews (Mondello et al., 2020; Solomito et al., 2019; Späni et al., 2018; Sufrinko et al., 2017; Thibeault et al., 2019), including anatomical differences between healthy participants (like axonal structure or reliance on the corpus callosum) and functional differences after repetitive impact exposure (like changes to neurochemical levels or cerebral blood flow). These are explored further below.

### 7.4.1 Structural

Structural differences in axons may contribute to the electrophysiological differences across sex. One study examining sex differences in axonal strength in rats by transmission electron microscopy (Dollé et al., 2018) posits that female axons may have one-third fewer microtubules than male axons, which may contribute to increased vulnerability to mechanical damage or physiological dysfunction in female brains. The male brain is slightly larger than the female brain (McGlone, 1980; Solomito et al., 2019), so axon size could be somewhat proportional to brain size (Dollé et al., 2018). Axons in female brains may also have reduced fibre and myelin integrity in some regions, as measured by DTI (which can trace how water diffuses through myelin); some studies have reported sex differences in the myelination (measured by axial and radial diffusivity) of many regions, including occipital sites and the corpus callosum (Kumar et al., 2013; Menzler et al., 2011). If a smaller diameter of axons in female brains is combined with sex differences in other factors like myelination, the electrical signal transmitted within may require less amplitude and be less detectable than a signal transmitted through the larger male axons.

A higher volume of communication between hemispheres in women may also be contribute to these differences. While communication in male brains is generally more lateralised and single hemisphere-dependent, female brains utilise greater bi-hemisphere communication networks across the corpus callosum (Solomito et al., 2019). Sex-related differences regarding the size, shape, thickness, and density of the corpus callosa are mixed; as discussed in a review by Solomito and colleagues (2019, p. 107), *"Men have more gray matter than white matter which indicates more active neurons, while women have more white matter suggesting a greater communication between different areas of the brain."* Additionally, size of the axons and size of the corpus callosum do not necessarily correlate, as the male corpus callosum may be thicker because it has more myelinated axons, but the female corpus callosum is composed of more (unmyelinated) axons overall (Solomito et al., 2019). Though the evolutionary reason for these different arrangements is not known,[21] greater bi-hemispheric activity may be a way that female brains compensate for their dimorphically smaller size (Dollé et al., 2018). In theory, activity that occurs occipitally in male brains may instead travel across the corpus callosum in female brains, and a lower SNR in female athletes may be representative of

[21] Dollé and colleagues posit that male neurons developed more resilience as a response to a historically higher risk of head trauma in men.

this sex difference in "load-bearing" areas of the brain. These differences are also relevant when considering the effects of repetitive impacts over a season; many studies (Beckwith et al., 2018; Hellewell et al., 2021; R. King et al., 2019; Manning et al., 2020; McAllister et al., 2014; Smits et al., 2011) have reported the corpus callosum to be affected by repetitive impacts.

Taken together, a higher number of smaller axons in the female corpus callosum (Dollé et al., 2018; Solomito et al., 2019) could be an indication of more interhemispheric activity, and may partially explain the lower SNR in female athletes. If female brains use more diffuse/diversified networks to perform tasks than male brains (Solomito et al., 2019), then a wider distribution of electrical activity may make their 15 Hz signal less concentrated and less distinguishable from the noise in the occipital region of interest. Perhaps the electrophysiological activity associated with the SNR is localised cortically in the male athletes, and cortically/sub-cortically or across the corpus callosum in the female athletes. Other anatomical explanations include a differential head-neck stabilisation responses to acceleration and impacts seen in soccer players (Tierney et al., 2008; Tierney et al., 2005). In a controversial review of brain asymmetries by sex, McGlone (1980) reported many anatomical and functional differences, and emphasised that the functional differences are likely a result of anatomical differences between sex groups. McGlone (1980) further argued for neutrality when studying these differences to avoid the bias toward implications of cognitive superiority by sex.

### 7.4.2 Functional

Neurophysiological sex differences can be due to functional causes, like changes in hormones (Hausinger & Pletzer, 2021), neurometabolic patterns or rates (Hu et al., 2013), cerebral blood flow (Thibeault et al., 2019), or myelination (Solomito et al., 2019). During a passive, eyes-closed scan using FDG-PET, Hu and colleagues (2013) reported evidence of functional sex differences as different patterns of glucose metabolism between sex groups, including more posterior activity in the female participants. Differences in posterior metabolism could make it a poor reference site. Sex differences can also be seen as the use of different electrophysiological networks used to perform the same function (Hausinger & Pletzer, 2021; Oliver et al., 2016). Hausinger and Pletzer (2021) found evidence of different strategies during a visual processing task, which was correlated with differences in testosterone, oestradiol, and progesterone levels across sexes. This could partially explain the lower SNRs seen in the female participants (despite the occasional magnitude of 20.0+ in female athletes).

Sex hormones are another often-suggested cause for functional sex differences (Bari et al., 2019; Bourisly & Pothen, 2016; Gölgeli et al., 1999; Wada et al., 1994). Most studies that have included a hormonal component have focused on the menstrual cycle, but these results are not robust. Some studies have only included participants in their luteal phase (Hausinger & Pletzer, 2021; Pravitha et al., 2005), or have found no effect for phase of menstrual cycle (Dumais et al., 2018). Only one study was found that used both electrophysiological and endocrinological methods (Kaneda et al., 1996); they found no notable association between ERP behaviour and menstrual phase (follicular/luteal). Thus, while it is possible that a hormonal component could play a role in sex differences, this was not directly examined by the present study or other SSVEP studies, and remains a limitation (Skosnik et al., 2006).

Sex differences may be present in the no-task state (Guo et al., 2019; Pravitha et al., 2005) or the related DMN[22] (Manning et al., 2020). Using a standard EEG paradigm with trials of "eyes open," "eyes closed," and "eyes closed and counting numbers," Pravitha and colleagues (2005) found sex differences during the passive eyes-closed trials, but no sex differences in the active eyes-closed + number-counting trials; they concluded that the sex differences that exist in a no-task state may become obscured by the cognitive processes needed to perform a mental task. This may explain the present findings of sex differences during a no-task state, though the findings of Pravitha and colleagues (2005) were during the eyes-closed condition and our participants' eyes were open, with their entire visual field exposed to photic stimulation. In contrast, Wada and colleagues (1994) found sex differences in healthy young adults during the resting EEG, which were more pronounced in the photic stimulation conditions, and Krishnan and colleagues (2005) found sex differences during the photic stimulation and not during the resting EEG. Generally, ERP amplitudes during a passive state are smaller than those during active tasks (Polich, 2007) or photic stimulation (Krishnan et al., 2005), so these differences may have been obscured by several factors.

Using DTI and resting-state fMRI to study the DMN in female non-concussed contact (rugby) and non-contact (swimmers or rowers) athletes, Manning and colleagues (2020) found diffusion changes and greater connectivity between the DMN and the posterior cingulate cortex in the contact athletes than the non-contact athletes, in both the in-season and off-season. This is consistent with the present finding of higher SNRs in contact athletes compared to non-contact athletes, but it is inconsistent with the increase

[22] The default mode network was first discussed in Sections 6.1.1.1 and 6.2.1.

found in female athletes, possibly because they only used two time points for each group (during competition season and off-season). Another study using fMRI (Dumais et al., 2018) reported sex differences in DMN suppression in favour of the activation of attention and reward networks. Electrophysiological differences in attentional processes were also reported (Nagy et al., 2003; Sumich et al., 2014), with a bias for novelty in the male participants. Shifts between the DMN and attention network (or any reward networks involved) during the 30-second exposure to the photic stimulus might also account for the SNR differences seen in the present study.

## 7.5 Conclusion

This chapter addressed the Aim 3 finding of a main effect for higher average SNR in male participants. Two possibilities could explain the lower SNRs seen in female participants: the headset is either measuring an incorrect source of the SNR, or the SNR is being improperly translated from the correct source. Functional and anatomical differences have been reported across sex, which means that the activity represented by the SNR could occur elsewhere in the female brain. Sex differences have been reported at occipital and parietal electrode sites (Gasbarri et al., 2006; Krishnan et al., 2005; Skosnik et al., 2006; Wada et al., 1994), including the Oz used by the present study, which supports the latter theory. Higher SNR in male brains could also indicate a relatively higher amount of cortical activity for the 15 Hz frequency, and posit that this activity occurs elsewhere in the female brain, potentially too deep to be detected by surface EEG or more diffusely because of greater network recruitment (across the corpus callosum, for example). The high presence of harmonic artifacts in the readings from the female athletes supports the idea that the induced brain activity is originating in a location that is hard to monitor in the female brains. Together, this results in reduced sensitivity of the SNR in female athletes.

Despite many reports of sex differences in electrophysiology, sex is often not considered as a factor in this research for various reasons, including sample size (Clayton et al., 2020; Riel et al., 2019). If male and female brains experience (or respond to) concussion differently, then assessment methods must consider sex-specific factors (Pravitha et al., 2005). This headset was developed and tested on male athletes, which could explain the poor sensitivity to the 15 Hz activity in female brains. It is possible that the quality of the SNR signal from female participants could be improved if the harmonic artefacts could be algorithmically removed from the noise, therefore increasing the ratio

of signal to noise. Alternately, a smaller electrode panel may help to measure the true target sites more accurately in female participants with smaller heads.

### 7.5.1 Limitations

Sex parity is a recurring limitation in the included studies, most notably in the absence of any concussions in female athletes. Despite deliberate intentions to collect equal sample sizes of female and male participants, I encountered more difficulties collecting data from the female teams than the male for reasons at every level, from organisational to individual. The need to take their practices more seriously was commonly cited, possibly a consequence of the way they feel female rugby to be perceived in New Zealand. Overall, I tested more than twice as many male rugby athletes than female athletes. However, of those that did participate, the female participants were more specific in describing their own concussion history than the male participants, and tended to report more symptoms overall. Perhaps there is a difference in how concussions are perceived between female and male athletes; maybe female athletes perceive them to be more or less severe than the male athletes who are not so reluctant to participate.

The duration of the rugby seasons could have affected trajectory differences. The seasons for the female club and semi-professional athletes were half as long than the seasons for the male club and semi-professional athletes. It is possible that the increase seen in female rugby athletes over two months was not seen in the male rugby athletes because their mid-season tests were often more than two months after their baselines. Other common limitations for research in sex differences include age and hormonal factors (Pravitha et al., 2005; Skosnik et al., 2006). Although menstrual cycle data were collected from the female participants, these data were not complete enough to be included in analyses. Another significant limitation is the lack of control data in the same participants over time, which could have helped to account for other potential confounds (including time of day, diet, medical and psychological history, prescriptions, and body type).

To close, the present research largely discusses sex in binary terms[23] because of the widespread conflation of sex with gender in the referenced literature, and because of lack of available research in this field that includes non-binary people or approaches sex as a spectrum (Giordano et al., 2020). Discussion of electrophysiology by binary sex is

[23] Although I have taken care to use inclusive phrasing like “across sexes” or “between sex groups” instead of “between sexes.” The demographic questionnaire was also amended in 2021 to include an option to self-describe or select “non-binary/gender-diverse,” but no participants identified with this category.

not necessarily a fully descriptive categorisation, as it does not address the variation of characteristics within sexes; for instance, current research that discusses monthly menstrual cycles often does not address the corresponding daily testosterone cycle and its effects on aspects of concussion recovery (Giordano et al., 2020). Sex and gender are not fully distinct from each other (Henne, 2020), and these related differences in the brain have been a sensitive and often politically-charged issue (McGlone, 1980). The paradigm shift within scientific literature from upholding a sex binary to acknowledging the spectrum of physiological traits and characteristics is also often viewed politically instead of as a nuanced approach to individual differences (Orthia et al., 2023). Nonetheless, addressing sex as a non-binary variable allows for better personalisation of treatment and is a vital step for including this population in healthcare literature (Giordano et al., 2020).

### 7.5.2 Strengths

The sex difference reported in Study B caused me to separate many of the analyses by sex, and to improve the accuracy of Study A by only comparing the concussed male athletes to other male athletes. As a result, the present study also adds to the few studies that report sex differences in electrophysiology and in athletes.

# Chapter 8
# General discussion: Evaluation of NuroChek System

The NuroChek system exposes the participant to a flashing light stimulus, measures the steady-state visual evoked response in the occipital cortex over 30 seconds, and determines the strength of the response signal by comparing it to the background noise (Section 3.2.2). Athletes were tested with the headset at several time points (including multiple post-injury intervals when possible) to determine the utility of the headset as a tool to assess sport-related concussions (SRCs) and manage recovery; details of the timelines can be found in Section 3.3 for each group. To determine its overall accuracy, the NuroChek system was evaluated by its validity and reliability (Legarreta et al., 2019; Robinson, 2019). Validity determines if the SNR is an accurate way to study electrophysiological changes after acute concussion, and includes elements of precision and sensitivity. Reliability determines if the SNR values are acutely stable over two trials and if they are seasonally stable over the three time points. NuroChek was also evaluated for its accessibility, which describes factors of participant comfort and how difficult the system is to use.

Many previous analyses that were reported in Chapters 4 and 5 are revisited for how they apply to these criteria, and new analyses were conducted when required (reported in Supplemental Section 9.3.3). Each criteria section ends with a summary of the findings. A combined discussion of the overall accuracy of the NuroChek system and the SNR variable follows, which places these findings in the context of the neuroethics regarding these devices, similar concussion assessment methods that are being developed, and a closing discussion of the limitations, strengths, and implications for future research.

## 8.1 Validity

Several types of validity are examined for the SNR. Construct/internal validity determines how the SNR compares to the actual presence of concussion, and concurrent/external validity determines how the SNR compares to other measures of concussion assessment. Discriminant validity is a subset of this criterion that describes if the SNR is affected by non-target factors like sex, impact exposure, concussion history, or age. Data from the concussed (n = 21) and non-concussed (n = 85) male rugby athletes

were used for the determinations of construct and concurrent validity, and data from all participants were used for the determination of discriminant validity.

### 8.1.1 Construct validity

The assessment of construct validity explores if the SNR was sensitive to changes after acute concussion. There was no clear relationship between baseline, post-injury, and recovery SNRs in athletes who sustained concussions, and no evidence was found to support the usefulness of the NuroChek system in concussion assessment or management (Chapter 4). The present findings are not directly comparable with those of Fong and colleagues (2020) because they used different equipment and a different SNR calculation; further, each participant was tested at baseline and after every game (including the game during which they sustained their concussion), then once more at the recovery time point, at least 12 days later. In contrast, participants in the present study were tested at multiple post-injury time points, and at one mid-season time point. Our SNR data also cannot be directly compared to that of Salazar and colleagues (2021) because they only reported the square root of the average SNR for each participant group. Our results are similar to those of Broglio and colleagues (2017), who also found inconsistent post-injury changes in the BNA, as well as instability in the non-concussed athletes over time.

Biomechanical damage from concussion and repetitive impact exposure may manifest in deeper regions such as the brainstem and corpus callosum (Bigler, 2018); without corresponding surface (cortical) damage, SSVEP/EEG may not be sensitive enough to detect the structural damage. Fong and colleagues (2021) noted that it was unclear if post-injury alterations to the SNR seen in their study were a reflection of primary (white matter) or secondary (neuroinflammation) damage. It is possible that the SNR is associated with an aspect of concussion that is too variable between individuals to be used diagnostically or prognostically.

The NuroChek headset received FDA approval for use as an EEG (not diagnostic) device in April 2020. According to Fong and colleagues (2021), this *"improved portable SSVEP system was also validated against an established EEG amplifier to ensure the investigative design is capable of obtaining research quality EEG measurements"* (p. 1). Since we did not have access to an EEG amplifier for comparison, we cannot confirm or refute the accuracy/validity/precision of the measurements. We requested the full dataset of the impedance data (from each trial and individual target electrode site) from the NuroChek team; however, we could not confirm the identifying information of SNR and

time/date for the individual data points in the impedance data received with our own data, and we consequently could not undertake these analyses.

Construct validity also determines if the SNR is correctly measuring the 15 Hz signal. In addition to Fong and colleagues (2020), several other SSVEP researchers have found the 15 Hz frequency to be maximal at the occipital electrodes (Kritzman et al., 2022; Pastor et al., 2003; Radtke et al., 2021; Skosnik et al., 2006), including Salazar and colleagues (2021), who used the same headset device as the one in this study. Tobimatsu and colleagues (1994) also used "LED goggle stimulation" with an SSVEP stimulus to elicit the 15 Hz frequency, and Pastor and colleagues (2003) found the occipital 15 Hz frequency to be one of the most reactive when used with the strobing light stimulus. Metabolic alterations were seen (by PET imaging) in the following areas of the visual cortex in response to the repetitive light stimulation at 15 Hz (Pastor et al., 2003; p. 11623 and 11625; emphasis added):

> *Stimulation at 5, 10, 15, and 25 Hz activated both primary and association visual cortex in a wide region with the base at the occipital pole and the vertex at the anterior extent of the calcarine sulcus, at its junction with the parieto-occipital sulcus. ... It encompasses the cortical representation of both the peripheral retina and the macular region.* ***Thus, there is indeed an area of the visual cortex in which the resting cerebral blood flow follows the same pattern of activation as the EEG SSVER[24] with regard to the repetitive stimulation frequencies*** *studied in this report.*

In the earliest SSVEP experiments, Adrian and Matthews (1934) established that the "potential waves" they found were indeed generated by the occipital cortex, and were not correlated with muscle movement of the eye orbits, facial muscles, or hair follicles in the scalp. The Oz, O1, or O2 electrode sites used in the present study have been used in ERP research in concussion (X.-P. Chen et al., 2006; Freed & Hellerstein, 1997; Thériault et al., 2011; Vaquero et al., 2004; Yadav & Ciuffreda, 2015) or SSVEP research in other populations (Adrian & Matthews, 1934; Krishnan et al., 2005; Skosnik et al., 2006). The signal from the P100 component is also generated from the occipital region by flashing lights (X.-P. Chen et al., 2006; Freed & Hellerstein, 1997; Gaetz & Weinberg, 2000; Papathanasopoulos et al., 1994; Wirth et al., 2006; Yadav & Ciuffreda, 2015), and it has shown similar sex differences with auditory stimuli (Vaquero et al., 2004). Its behaviour has previously been described (in Sections 2.1.1, 2.3.2.1, and 7.2.1.1); based on this

[24] Pastor and colleagues (2003) used the term "steady-state visual-evoked response."

previous research, using a flashing light stimulus is a valid method to study electrophysiological changes in the occipital region and at the target sites used in the present study.

While the target electrodes may be accurately selected, the reference points used may not be appropriate. Sex differences at the parietal reference and ground electrodes (Gasbarri et al., 2006; Pravitha et al., 2005) may cause inconsistencies in the "noise" readings, decreasing the overall accuracy of the ratio in female participants. Many ERP studies used one or both mastoids used as reference (Bianco et al., 2017; Carrier-Toutant et al., 2018; Chang et al., 2018; Gardener et al., 2013; Guo et al., 2019; D. King et al., 2018; Melynyte et al., 2017; Moore, Hillman, et al., 2014; Parks et al., 2015; Ruiter et al., 2019; Vaquero et al., 2004), so perhaps a future iteration of this headset could design a panel with a flexible lower band to utilise the mastoid sites as references. Another option is the Cz site (Mitchell et al., 1987; Moore et al., 2017; Olson et al., 2018; Sicard et al., 2021; Teel et al., 2014; Wirth et al., 2006; Zhao et al., 2018), which is also often used as a reference and which could be assessed by an additional electrode site on the top strap that connects the visor to the back panel. According to the most recent guidelines by the International Society for Clinical Electrophysiology and Vision (Odom et al., 2016): *"The active electrode is placed on the occipital scalp over the visual cortex at Oz with the reference electrode at Fz. A separate electrode should be attached and connected to the ground. Commonly used ground electrode positions include the forehead, vertex (Cz), mastoid, earlobe (A1 or A2) or linked earlobes."*

### 8.1.2 Concurrent validity

To determine the concurrent validity of the SNR, changes in SNR were compared to changes in scores of two cognitive measures commonly used in concussion assessment, the SCAT-5 and the King-Devick assessments. The SNR was correlated with the K-D time and the SCAT-5 symptoms at baseline in all athletes overall, but not at any other time point (Section 4.3.7). When the SNR was compared to the SCAT-5 or the King-Devick, no domain showed statistically significant change between baseline and post-injury for the concussed athletes. Churchill and colleagues (2019) also found no significant effect for concussion on the SCAT-5 cognitive domains at acute injury or at RTP. As the SCAT was designed as a post-injury screen for gross cognitive alterations, many elements lose their sensitivity quickly, and are not sensitive to concussion recovery (McCrea et al., 2003; McCrory et al., 2017; Pontifex et al., 2009; Richards, 2017). For instance, the modified balance task loses sensitivity as one recovers (Iverson & Koehle,

2013), and can show no difference from baseline as early as three days post-injury (Riemann & Guskiewicz, 2000), despite evidence of EEG alterations during a balance/posture task at seven days post-injury (Slobounov et al., 2012). Other domains like verbal memory may show different patterns of impairment in concussion and after repeated impacts, weakening their sensitivity in concussion assessment (Moore et al., 2017). Changes to the domains of orientation and concentration were also seen over time in the non-concussed athletes, which indicates less stability and weaker sensitivity in these subtests during the sub-acute/recovery phase.

No statistically significant correlations were found between concussion status and performance on the K-D, likely because the K-D is not a good measure of concussion assessment in rugby athletes (Fuller et al., 2019) and has limited utility in tracking recovery. The K-D also shows changes after repetitive impacts when measured by accelerometer (Moody et al., 2019), which weakens its utility in detecting concussion. A review examining the K-D's use in SRC (Harris et al., 2021) recommended using it with another screening tool, despite finding "low credibility of evidence" for the studies included because of small sample sizes and risk of bias (e.g., most studies reported fewer concussions than average, and most only included male participants younger than 25).

The K-D may not even be a stable measure for healthy athletes across time. The present study found a statistically significant between-groups effect for sex at all time points, and statistically significant within-group changes in athletes with and without a history of concussion. Gunasekaran and colleagues (2020) found that the difference between an athlete's baseline and optimal time (usually within the first 8 times taking the test) was 4.2 seconds on average, but may be as much as 14.9 seconds; they recommended re-testing any athletes whose best baseline score is more than 60 seconds, but this was not always possible in the present study. When the K-D is used as a pass-fail (i.e., any faster time becomes the new baseline, and any slower time fails), researchers have found it to have a 23% rate of false negatives and up to a 33% rate of false positives (K. M. Breedlove et al., 2019; Harris et al., 2021; Molloy et al., 2017). In the two athletes who provided a baseline before their concussion, the post-injury (three days) K-D time was slower by 7.4 seconds in one and faster by 0.3 seconds in the other. Additionally, 29 of 60 non-concussed athletes had slower K-D times at the end-of-season when compared with their baseline; this indicates that the K-D time was not stable across a season for 48.3% of athletes.

Neither a cognitive return to baseline nor the SNR coincided with the physiotherapist's decision to allow the athlete to RTP. Many studies acknowledge that

neuropsychological and electrophysiological recovery do not always correlate (Broglio et al., 2009; Clayton et al., 2020; Fratantoni et al., 2017; Gosselin et al., 2012; Hudac et al., 2018; Kozak, 2018; Ledwidge & Molfese, 2016; Olson et al., 2018; Ozen et al., 2013; Thériault et al., 2011), yet without an objective construct of concussive damage or a standard for comparison, it is difficult to determine construct validity. Our results also support the finding that different aspects of concussion damage may recover at different rates (Table 4.3), and that concussion recovery routinely takes longer than the expected timeline of 1–2 weeks (Kamins et al., 2017). The nuanced determination of a trained physiotherapist remains the best method for managing recovery and RTP.

Analyses between symptomatic and asymptomatic athletes with concussion were not conducted in the present study because of small sample size of post-injury symptom data, but only one concussed athlete reported symptoms at 12 days post-injury, and no athletes reported symptoms at 20 days post-injury. When concussed-and-symptomatic athletes and control athletes were compared to concussed-but-asymptomatic athletes (Gosselin et al., 2006; Kontos et al., 2016; Lavoie et al., 2004; Sicard et al., 2021) or subconcussed athletes (Moore et al., 2017), the asymptomatic or subconcussed athletes' electrophysiological profiles shows more overlap with that of the concussed athlete than the healthy athlete. The present finding of significantly higher SNR and higher symptoms in the impact group of combat athletes (than the non-impact group) may be partially consistent with other studies that have found associations between symptom severity and electrophysiological change, though this was after concussion (Dupuis et al., 2000; Lavoie et al., 2004; Sicard et al., 2021; Thériault et al., 2009). As the present post-injury sample sizes with baseline symptom inventory data were too small to draw conclusions, further research is necessary to determine if the variability of SNR after injury may be explained by symptom severity.

### 8.1.3 Discriminant validity

Discriminant validity examines if the SNR reflects electrophysiological alterations after concussion, or if it is confounded by other factors. This section will discuss other factors that may have caused significant SNR differences in the non-concussed athletes (by group or over time) beyond sex and concussion history. The effects of repetitive impacts are revisited in this context, and factors of age, exercise, and attention/focus were also examined for differential effects.

The main effect of higher SNR in athletes with regular impact exposure complicates the sensitivity of the SNR to concussion beyond the post-injury

inconsistencies reported above. If the SNR is higher in athletes who regularly experience non-concussive injury, then differences in an athlete's SNR from their baseline are difficult to interpret in the context of concussion. Because many rugby athletes participated in sequential seasons throughout the year, it cannot be assumed that an athlete's baseline accurately represents their SNR before impact exposure. Additionally, one athlete was tested multiple times after a big hit that was determined not to be a concussion (Figure 4.4), and the trajectory of his SNR during recovery represents a false positive by the headset. By definition, an objective measure of concussion would not be affected by repetitive but non-concussive impacts. Though we cannot conclude that repetitive impacts are directly responsible for the higher magnitudes seen in this group, it does at least demonstrate that the SNR is not stable in non-concussed athletes over a season, and that the effects of repetitive impacts may interact with sex (Section 5.3.3.3) or concussion history (Section 5.3.2.3).

Repetitive impacts have been associated with alterations to electrophysiological activity or communication networks (Abbas et al., 2015; Moore et al., 2017; Pearce, 2016), though they have mainly been studied with more sophisticated imaging equipment that assesses white matter damage (Bazarian et al., 2014; Gu et al., 2017; McAllister et al., 2014; Moore et al., 2017) and neurometabolic changes (Bailes et al., 2013; Bari et al., 2019; Hunter et al., 2019). Some researchers have found neurocognitive deficits in non-concussed athletes after a season of repetitive impacts (Bazarian et al., 2014; E. L. Breedlove et al., 2012; McAllister et al., 2012; Talavage et al., 2014), while others have found subconcussion to be too subtle to cause neurocognitive effects after one season (McAllister & McCrea, 2017; Miller et al., 2007). Results of cumulative damage to white matter over multiple seasons of repetitive impacts in non-concussed athletes are mixed (Bari et al., 2019; Bazarian et al., 2014; McAllister et al., 2012). The complete effects of repetitive impacts are still not fully understood, largely because so much about concussion is still unknown.

Some SCAT-5 domains improved after repetitive impacts, most likely due to the practice effect or an increased familiarity with the task. The concentration subtest of digit span showed a large effect size for an increase after a round of sparring in both the impact and no-impact groups of combat athletes. The non-concussed male rugby athletes also demonstrate a statistically significant increase of the concentration domain over the season, but sample sizes were not large enough to compare impact exposure for these data. However, similar increases in concentration have been seen over a season in non-concussed athletes (Miller et al., 2007). In contrast, a season-long study using the SCAT-

3 (Richards, 2017) found the football players who experienced the most impact exposure demonstrate concentration deficits. Further research into changes in concentration should be studied using a more sensitive measure than the digit span, as it is only intended to act as a screen for gross post-injury deficits. Orientation was also marginally affected in the rugby athletes (Table 5.7) and was not examined in the boxers in this study; however, studies have reported an asymmetry related to the orienting reaction when stimuli was delivered to the right ear (Breton et al., 1990). The other domains of the SCAT-5 did not show statistical differences over time.

The SNR was also affected if the participant spoke, if someone spoke to the participant, if the participant's phone alerted during the trial, or if the background noise was very loud. In most cases, these brief interruptions did not result in low SNRs (as seen on the app immediately after the trial), but if the EEG pattern had high background noise, these participants were often asked (and consented) to sit for a third SNR trial to get the cleanest result possible. Because of the nature of baseline testing and the layouts of the rugby clubs or fields, it was not always possible to test the athletes in a completely silent area; in these cases, participants were instructed to focus on the lights and not the noise, but this still presents a confound and potential source of variance. If so, a link between the SNR magnitude and these distractions could mean that the SNR is related to the domain of attention or concentration, and future NuroChek studies may control for this by asking the participants to wear noise cancelling headphones or other ear protection during the trials, especially in a sideline scenario.

The combat athletes and concussed and non-concussed rugby athletes showed alterations (statistically significant or with a large effect size) in the SCAT-5 domain of concentration over time. While Salazar and colleagues (2021) found no change before and after physical fatigue, the SNR showed a trend of increase after the Stroop mental fatigue task ($p = .059$), which could indicate that the SNR is altered or becomes less stable during the mental effort condition. Previous studies have shown the SSVEP or EEG signal to be affected during a mental task like arithmetic, counting heartbeats, or other distractors (Adrian & Matthews, 1934; Kritzman et al., 2022; Pravitha et al., 2005). Alterations to SSVEP have also been shown to precede attentional lapses by up to 20 seconds (Dockree & Robertson, 2011; R. G. O'Connell et al., 2009). If concentration on the stimulus is essential to produce the SSVEP (Mora-Cortes et al., 2018), it is possible that gross changes to concentration over time may contribute to some of the variations in SNR.

Attentional differences may also affect the localisation of the SSVEP in the occipital region (Norcia et al., 2015). Using a visual segregation task (Appelbaum et al.,

2006), the occipital localisation of the SSVEP was medial when the participant focused on a background, but became bilateral if the participant focused on a figure in the foreground. Similarly, Andersen and colleagues (2012) manipulated the contrast of a light or dark flickering dot pattern against its background and measured the SSVEP of participants; they found changes in occipital and parietal sites, which may indicate competing visual processing strategies. Participants in the present study were instructed to look as closely to the lights as they could without giving themselves a headache, but it is possible that focusing on the flashing lights in the foreground versus focusing slightly away from them into the background of the visor may have altered the localisation of the SNR between electrode sites. However, because the SNR is calculated from all three sites, it is unclear what effect these asymmetries may have had on the final SNR.

The present finding of increased SNR in female combat athletes after a round of sparring (marginally significant with a large effect size but a small sample size; Section 5.3.3.4) is partially inconsistent with findings of no statistically significant differences in exercise groups of amateur boxers and treadmill runners (Salazar et al., 2021); though, as previously mentioned, they did not analyse female and male participants separately. The present finding is consistent with that of Devilbiss and colleagues (2019), who reported that the effects of exercise on EEG may be stronger in female athletes. Exertion and strenuous tasks can also affect ERPs (Teel et al., 2014), and our findings support that the SSVEP may be more resistant to these limitations in male athletes (Salazar et al., 2021). The immediate effects of exercise are also thought to affect performance on the SCAT and the K-D (Devilbiss et al., 2019; Molloy et al., 2017). Since many baseline and sideline tests may be performed directly after the athlete has been exercising, it is important to understand how exercise may (or may not) affect electrophysiological readings.

Age is thought to affect ERP (Baillargeon et al., 2012; Gaetz & Weinberg, 2000; Mitchell et al., 1987), so analyses were performed to explore any relationship between age and SNR (Supplemental Table 9.7). Age was not significantly different between the female and male athletes, $U = 2304.000$, $p = .225$, $r = -.097$, $N = 151$, and non-parametric Spearman's correlations were not statistically significant between age and SNR, overall or in either sex group (rows 1–3). An effect for age may still exist, but without preliminary findings and a population with a wider age range, this possibility was not explored.

### 8.1.4 Summary

Ultimately, there is little evidence to support the construct validity of the SNR to detect post-concussive damage because the SNR did not show a consistent pattern in post-

injury changes, and because the cognitive measures used did not prove themselves to be sensitive to concussive assessment or recovery. Additionally, no concurrent validity was found between the SNR and cognitive measures. The lack of usable impedance data also limits the interpretability of the internal validity of the SNR to concussive damage.

Several factors affected SNR magnitude, most notably sex and repetitive impact exposure. By anecdotal observation, focus or concentration on the stimulus also affected the SNR magnitude; though the visual stimulus is isolated quite effectively, it is still vulnerable to interference from other sensory (particularly auditory) distractions. Increases of the SNR were seen after a season of rugby in those with a history of concussion, but no other effects for history of concussion were seen. No effects were seen for age or exercise.

Since this study could not control for other factors (e.g., amount of sleep, medications or stimulants like caffeine taken, mood, alertness, stress, etc.) it is possible that the SNR fluctuates for many reasons, though that would also make the NuroChek headset impractical for use in assessment. The headset may be best utilised with more frequent testing to establish averages and ranges for regular fluctuations, since single testing sessions in this study (even with 3 trials) are inconsistent and their interpretability is limited.

Other anatomical or functional factors may affect specificity of the SNR as well, including skull thickness and functional neural organisation (discussed as sex differences in Section 7.4). Though Kaneda and colleagues (1996) found VEP amplitude not to be affected by age, height, or weight, they did find that latency was affected by body height. An and colleagues (2015) found EEG signals from 4–10 Hz to be affected by blood glucose levels. Eckner and colleagues (2016) also found wide variability between non-concussed participants, and concluded their electrophysiological measure had limited utility without knowledge of the athlete's baseline. It is important to consider any and all potential confounds when evaluating the interpretability of a measure like the SNR.

## 8.2 Reliability

Reliability describes if the SNR is stable over time, and if the results are repeatable. Since two trials of the headset were performed at each time point, these SNR values were compared to each other to evaluate test-retest and internal reliability. Comparisons were made between SNRs taken before and after 12 pm to determine if there was an effect for time of day. Within-group stability over one season was also evaluated, and data collected from three separate headset units were compared to each other to examine the inter-rater

reliability. Finally, the averages and ranges of SNRs for each participant population and demographic found in the present study are presented as normative data.

As reported in Section 5.3.3.1.2, the SNR did not change significantly over two trials in male participants, and increased by the second trial in female participants during the morning testing sessions, likely due to an improvement in fitting or an adequate saturation of saline solution in the hair. No other effects were found for time of day.

Despite the variability of the SNR over a season in non-concussed athletes (Section 5.3.3.3.2), the SNR of the athletes who participated both years was not significantly different between years. Wilson and colleagues (2015) found weaker P3b amplitudes in the third- and fourth-year athletes and concluded that the cumulative effects of repetitive impacts did not become apparent until the third year. Without knowing how many rugby seasons each of the participating athletes had played, it is difficult to speculate on how the SNR might change over four seasons. Number of seasons is also not a specific measure of impact exposure (Olson et al., 2018).

The SNR values in the datasets from the 2020 and 2021 seasons were not significantly different from each other at any time point. The NuroChek headsets were estimated to last for up to 1500 individual testing trials, but the first headset (A) was the only unit to approach this theoretical threshold. Headset A failed during the 2021 baselines after ~1200 tests (approximately 14 months of use). The second headset (B) was used for the remainder of the rugby season (including the remaining baselines), the boxers, and half the non-athlete controls in 2022; this headset failed after being charged overnight. Headset B was replaced by a third headset (C) after 914 total tests (and after 14 months[25] of use). Headset C was used for the remaining tests in no-impact combat athletes and non-athlete controls (approximately 6 weeks) for a total test count of 554 (but it arrived with a higher existing test count than headsets A and B, which each had been used for less than 150 previous tests).

Correlations were not used to examine inter-rater reliability between headset units because of the variety between participant groups and sex; instead, Mann-Whitney tests were used to compare the average SNRs before and after switching the headsets (reported in Supplemental Table 9.8). To examine the switch from headsets A to B (on 22 March 2021), baseline data collected with headset A was compared to baseline and mid-season data collected with headset B (row 1). Because only three female athletes were tested with

[25] Both of these 14-month spans included a period of 3–8 weeks of inactivity due to Covid-19 lockdowns.

headset A in 2021, the headsets are only compared in the male athletes for this year. The switch from headset B to C compared baseline data from the combat athletes and non-athlete controls collected before and after 19 May 2022 (rows 2–3). Although the SNRs tended to be higher with headset A before it was retired, there were no statistically significant differences between the headsets before and after the switch.

### 8.2.1 Normative data

The overall SNR averages and ages are reported in Table 8.1, and are broken down by study group and sex. The ranges and standard deviation for each group describe the amount of variation of SNR. The signal strength thresholds for interpretability are: 0.0–4.9 = weak signal; 5.0–10.9 = moderate signal strength; 11.0–19.9 = strong signal; 20.0–28.0 = very strong signal. The "weak" SNR data below 5.0 was not removed because it constitutes *bona fide* data and is critical for the evaluation of the NuroChek system.

Table 8.1: Overall average SNRs by sex and participant group at baseline.

| | **N=** | **age M (SD)** | **SNR M** | **SD** | **min** | **max** | **range** |
|---|---|---|---|---|---|---|---|
| **All** | **152** | 25.51 (6.99) | **10.362** | 5.9729 | 1.9 | 30.1 | 28.2 |
| Female | 50 | 26.48 (7.46) | **6.684** | 3.9245 | 1.9 | 21.6 | 19.7 |
| Male | 102 | 25.05 (6.74) | **12.165** | 5.9905 | 2.4 | 30.1 | 17.7 |
| **Concussed rugby** | **14** | 23.84 (3.75) | **12.843** | 7.800 | 3.6 | 30.1 | 26.5 |
| **Non-concussed rugby** | **100** | 23.55 (5.64) | **10.255** | 5.331 | 2.4 | 23.8 | 21.4 |
| Non-concussed female | 36 | 23.64 (5.37) | **6.708** | 3.2378 | 2.8 | 17.3 | 14.5 |
| Non-concussed male | 64 | 23.50 (5.82) | **12.25** | 5.2554 | 2.4 | 23.8 | 21.4 |
| **Impact combat (boxers)** | **11** | 28.82 (8.29) | **13.064** | 7.9736 | 2.4 | 27.9 | 25.5 |
| Impact female | 3 | 39.51 (10.12) | **10.033** | 10.186 4 | 2.4 | 21.6 | 19.2 |
| Impact male | 8 | 25.30 (4.73) | **14.200** | 7.4678 | 3.5 | 27.9 | 24.4 |
| **No-impact combat (BJJ)** | **9** | 33.49 (9.13) | **6.000** | 2.569 | 1.9 | 10.3 | 8.4 |
| No-impact female | 5 | 33.32 (6.26) | **4.380** | 1.6829 | 1.9 | 6.3 | 4.4 |
| No-impact male | 4 | 35.57 (12.18) | **8.025** | 1.996 | 6.3 | 10.3 | 4.0 |
| **Control** | **17** | 30.87 (6.44) | **8.782** | 5.913 | 2.2 | 28.4 | 26.2 |
| Control female | 6 | 31.16 (7.60) | **6.783** | 4.6611 | 2.2 | 13.9 | 11.7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Control male | 11 | 30.70 (6.08) | **9.873** | 6.4326 | 5.1 | 28.4 | 23.3 |

*BJJ- Brazilian Jiu Jitsu.*

Similarities were seen between all the impact athlete groups, whose average SNRs ranged roughly from 10.0–15.0. The highest averages (>13.0) were seen in the non-concussed rugby athletes at the end-of-season, especially those who reported previous concussions and in the male athletes (who had high SNRs at mid-season as well). Lower averages (<10.0) were seen at baseline for the female athletes overall, the non-athlete control participants and the limited-impact rugby athletes, and in the non-impact combat athletes at both time points. The least amount of SNR variability (by range/standard deviation) was found in the no-impact combat athletes, possibly due to the relatively small sample size.

Additionally, the regular repetitive impact group had the lowest prevalence of concussion history, and those who sustained concussions during the season had the highest prevalence of historical concussions at baseline. Of the non-athlete control participants, the highest average SNR was seen in those who reported a previous concussion.

### 8.2.2 Summary

The NuroChek system and SNR showed adequate test-retest reliability. The headset fit improved for female participants on the second trial, especially during morning testing times, but the averages of the two trials were not different in any other condition. Despite the reported variability within a season of rugby, the SNR showed adequate internal reliability over two years. The average SNRs of athletes who participated both years were statistically similar at each time point in 2020 and 2021. I also found adequate inter-rater reliability across the three headsets used (though this is not a true measure of inter-rater reliability since I was the sole investigator). There was no statistically significant difference the performance of headsets before and after the headsets were switched in male or female participants. Finally, the normative data presented in Section 5.2.1 shows the average SNR distributions across participant and demographic groups.

## 8.3 Accessibility

The accessibility of the headset is measured by how easy it was to learn to use, and how well the participants tolerated the flashing light stimulus. In terms of functional accessibility, the inion became simple to find on participants after some practice. The optimal impedance threshold was below 15,000 ohms and was indicated by a green dot

on the app during fitting, though (according to the NuroChek development team) impedance was considered adequate if it was under 30,000 ohms. The headset can be used with most hair types and styles, though thicker hair requires extra saline applied directly to the target area. It is also quick to clean and reset the headset between uses; time between recorded trials was not more than five minutes, and participants can easily be tested in succession if the participant profiles are created before the testing session.

In terms of logistical accessibility, headsets A and B lasted for about a year of use each (excluding the Covid-19 lockdown periods). During periods of heavy testing, the headset was charged every 2–3 days; during periods of light testing the battery held a charge for less than a week, even if it was not used. The iPad required a wi-fi connection to access the NuroChek app, and this was done with a SIM card or mobile hotspot when testing outdoors. The test results not designated as the baseline were accessible on the app for six months and through the online portal at any time.

### 8.3.1 Data quality improved after two months of use/experience

To examine ease of use, data from both trials of each assessment were divided into a learning period (before September 2020[26]) and an experienced period (after September 2020, when the data quality had been verified by the NuroChek team). These data were also compared to each other (using the Mann–Whitney test) separately by sex, and the results of these analyses are reported in Supplemental Table 9.9. The learning data had a significantly lower SNR1 and SNR2 than the experienced data at the same time points (row 1), a relationship that was more significant in the male athletes (rows 7–8). The trend seen in female participants across experience groups (row 5) was the opposite, in that the learning SNR2 was marginally higher than the experienced SNR2. Overall, the SNRs taken during the experienced period were significantly higher, especially in the male athletes and for the first trial. Further analyses concerning the harmonic artefact during the learning trials can be found in Supplemental Section 9.3.3.2; surprisingly, the proportional presence of the harmonic artefact was much lower during the learning period, and the SNRs with the presence of the harmonic artefact were significantly lower than those without.

Of the 791 SNR readings, 124 were below 3.0 (15.7%), which could be considered unusable (given the upper ranges and nature of the ratio), but these data were not excluded

[26] Baselines were done in one month from January–February, and mid-season tests were done in August, giving two total months of experience on either end of a long stoppage for Covid-19 lockdown and then beginning the season.

to avoid bias and to preserve the *bona fide* distributions. Overall, the SNR magnitudes increased with more experience using the headset, especially in the male participants. The proportion of data with harmonic artefacts taken during the experienced period, combined with the prevalence across sexes, seems to indicate that despite proper fitting, a harmonic artefact is present in a statistically significant portion of the female participants.

### 8.3.2 Comfort of participants

Most participants reported no discomfort during or after the flashing light stimulus, but some participants reported some degree of discomfort. At least three participants reported that the light hurt their eyes, and two participants said the lights made them feel sleepy. Two participants withdrew after the first time point because of discomfort during the trials, and several participants declined a third trial, though most participants consented when asked.

Skosnik and colleagues (2006) found the SSVEP to be *"well suited for psychiatric and drug-using populations, as the SSVEP can be acquired with minimal task demands"* (p. 145). It stands to reason that the advantages would also benefit those with a recent concussion and/or fatigue from exercise. Fong and colleagues (2021) found best results with a priming trial and an optimum stimulus exposure time of 30 seconds, and other SSVEP researchers have also used a 30-second exposure to flickering light into open or closed eyes (Wada et al., 1995; Wada et al., 1994). A longer exposure period might yield a higher magnitude, but direct photic stimulation for longer than 30 seconds may be too burdensome to recently injured participants, or it may conversely lead to attenuation of the signal. This is important because to obtain optimal SSVEP results, participants must pay constant attention to the stimulus (Kritzman et al., 2022; Mora-Cortes et al., 2018; R. G. O'Connell et al., 2009).

### 8.3.3 No increased risk of seizure in concussed participants

After performing nearly 2,500 trials on over 200 individuals throughout the 3-year course of this study, no epileptic events were recorded. The NuroChek headset does not put non-epileptic participants at risk of having a seizure. Though there is the risk that the headset could trigger an epileptic seizure in a participant if they have never been diagnosed with epilepsy, this risk is mitigated as much as possible through careful screening for episodes of unexplained fainting. To avoid any risk of seizure induced by the flashing lights, any participant who reported a history of epilepsy, seizures, or unexplained fainting was excluded. Participants with a history of light-induced migraines were also excluded to avoid triggering one during a training session. Participants were

monitored with verbal check-ins during the trials to ensure that they were responsive and comfortable.

There is no established link between concussion and increased susceptibility to seizures. Some individuals experience concussive convulsions immediately after a concussive impact, lasting up to 150 seconds. These have been examined in longitudinal studies, and are not associated with the long-term development of epilepsy that cannot be otherwise explained by late-onset epilepsy with family history (Kuhl et al., 2018). While some persistent concussive damage is associated with seizures, concussion is not thought to be epileptogenic (McGinty & Costello, 2016). It may trigger a latent epilepsy in some individuals, but this is rare (Wennberg et al., 2018): a longitudinal study of 330 mTBI patients over 7.6 years found no higher rates of epilepsy in an mTBI population than in the general population.

### 8.3.4 Summary

No accessibility issues affected the use of the NuroChek headset. The quality of SNR data improved after two months of field experience, and was supplemented by close consultation with the NuroChek team for quality reports and fitting advice. While the harmonic artefact could sometimes be eliminated through improved fitting of the headset, the SNR was not significantly higher for the second headset trial, except in one condition (female participants who were tested before noon). This shows that the SNR is relatively stable after minor adjustments to improve the signal quality.

The NuroChek headset was generally well-tolerated by participants in the present study. No epileptic events occurred during this study, and only a few participants experienced discomfort from the flashing lights that necessitated their withdrawal. Several participants experienced discomfort of the eyes, but the headset was not responsible for any reported side effects after testing.

## 8.4 Summary of overall accuracy

A tool like the NuroChek headset could enable athletes to make more informed decisions about their health. Continuous monitoring of impact exposure in real time could also help athletes to manage their own risk. Unfortunately, the present study finds no evidence that NuroChek can be used to guide a sports physician's decision regarding the assessment or management of sport-related concussion. The SNR did not show a consistent pattern after concussion, and the SNR also changed over time in the non-concussed athletes. The present study has identified additional factors that may affect the SNR, specifically sex, repetitive impacts, and auditory distractions. Despite adequate

reliability and accessibility of the headset, construct and discriminant validity could not be established for post-injury changes in the SNR.

The flashing light stimulus and occipital targets are reportedly valid ways to study the 15 Hz frequency, and the NuroChek headset has been reported to be as accurate as a standard EEG amplifier (Fong et al., 2021). Therefore, the NuroChek headset should be a valid approach to study the 15 Hz frequency. However, our results provide less support for the link between the 15 Hz frequency and post-concussive changes; we found no evidence that the NuroChek headset could provide meaningful information for the acute management of an athlete's concussion. The SNR most likely represents a post-injury construct or domain with considerable variation between individuals, which was not measured by the other tests used. A requirement of an objective concussion assessment method is that it should show consistent change after injury. However, concussed brains often do not behave consistently, and it cannot be assumed that all concussions manifest and recover similarly. The non-specific nature of concussive damage and symptoms (Dikmen et al., 2004; Gunstad & Suhr, 2002; Stafford et al., 2020; Voormolen et al., 2019) also makes it difficult to develop a standard assessment method, even when using the baseline paradigm.

The SNR was also affected by other factors, particularly sex and repetitive impact exposure. The mechanism of increase of the SNR is still not understood, but the SNR shows variation between athletes of the same impact exposure and demographic groups. The higher SNR in non-concussed male rugby athletes may represent a gradual adaptation to repetitive impacts, which could also explain the relatively lower SNRs seen in the no-impact combat athletes. The SNR remained stable after an acute impact exposure, possibly because the adaptive response is also being trained during the combat session. The SNR quality was lower in female participants in several ways: the magnitude was lower, the harmonic artefact was more frequent, and while the SNRs of the male athletes increased after a learning period of using the headset, the SNRs of the female athletes did not show equal improvements. More research is needed to understand the interactive effects of repetitive impacts and sex on neurophysiology.

The SNR showed adequate reliability over the short-term (across two trials) and the long-term (over two years), but the increase in non-concussed athletes after a season remains unexplained. There was no statistically significant effect for time of day or headset unit used. The headset also proved to be accessible and easy to use for this purpose. Readings from the headset improved in quality after a short learning period, and the stimulus and protocol were well-tolerated by most participants.

The most recent publication from the NuroChek development team (Hoang et al., 2023) explores using machine learning (ML) in combination with characteristics of the raw EEG signal (collected by the headset) to identify concussion in athletes with no baseline (n = 299 male athletes; n = 137 female athletes). One machine-learning model they explored may be 62% accurate in its assessment of a single time point. Once again, neither their data or proposed ML models are separated by sex. Female athletes make up a smaller but growing proportion of athletes, yet they are often under-represented in research on concussion and repetitive impacts (Covassin et al., 2018; Henne, 2020; Le Flao et al., 2022; Stephen et al., 2022). Given the anatomical and functional differences seen in the present study and many others, a ML model that considers sex differences may improve diagnostic accuracy for this device.

## 8.5 Scope and context of interpretation

### 8.5.1 Similar assessment methods or concussion-related headsets

The NuroChek headset is designed to compare post-injury and recovery time points to a baseline; it also provides evidence of a persistent SNR decrease that does not correspond with any observed functional alterations. Two goals currently being explored in other SRC assessment research are 1) a reliable physiological measure of concussive damage that can track recovery and inform injury management strategies, and 2) early identification of those who will have a slower recovery (McCrea et al., 2015). Developing a meaningful way to evaluate all types of concussive damage, including quality-of-life symptoms like mental health and sleep quality, is also important for individuals in the short- and long-term (Broglio, Guskiewicz, et al., 2017).

In the same vein as Hoang and colleagues (2023), the sensitivity of electrophysiological methods may be improved when combined with artificial intelligence. A different machine-learning model using a single ERP assessment (Boshra et al., 2019) was able to distinguish between a combination of ERP and EEG readings from post-acutely concussed individuals (m = 20 days post-injury) and healthy controls with an 85% success rate. In another study, Shim and colleagues (2020) used ML to create a model of biomechanical forces associated with concussive injury. This model was able to predict if the specific conditions of an impact resulted in a concussion within 10 seconds. Bazarian and colleagues (2021) also found ML of qEEG signals to be useful in concussion diagnosis by creating the Concussion Index to aid in classification. ML can be further useful in predicting risk by identifying which athletes may sustain concussion based on their cognitive baseline data (Castellanos et al., 2021), as well as predicting

protracted recovery by comparing performance on the K-D, Vestibular Ocular Motor Screening measure, and C3 Logix Trails test (Chu et al., 2022). The use of ML can increase the number of alterations in the ERP or raw EEG signals that are associated with concussion diagnosis, and it may improve the interpretability of such variations, but use of ML in concussion is still preliminary.

Another electrophysiological measure developed for concussion assessment was the Brain Network Activation variable, or the BNA. This method examines the activation of different regional networks, and while it initially showed some promise in concussion assessment and prognosis, it was ultimately too variable in non-concussed athletes and not sensitive to acute concussion within 72 hours (Broglio, Williams, et al., 2017; Eckner et al., 2016; Kiefer et al., 2015; Kontos et al., 2016; Reches et al., 2017). Though the search to find a single variable or index of post-concussive functioning is a high priority in concussion research, the nuances of post-injury electrophysiological alterations across individuals have proven to be confounding to this goal.

A common approach to increase the multidimensionality of neurocognitive measures is to use them in combination (McCrea et al., 2015; Resch et al., 2016). A handheld device called DETECT presents neurocognitive tests and assesses attention and reaction time, and it can also be used to measure functional impairment from repetitive impacts (Espinoza et al., 2021). Another platform called the Evidence-Based Clinical Outcome Assessment Platform (EB-COP) aims to recommend the best available concussion assessment measures based on defined parameters of use such as intended population, purpose of use, concept of interest, psychometrics, and relevance (Christoforou et al., 2020). The more domains that are analysed, the greater chance that at least one will be affected by concussive damage; however, this also lengthens the amount of time needed to perform the test. Though computerised testing is not new, the ability to use algorithms to determine optimal measures could decrease testing time in these participants.

Eye-tracking technology is also used to estimate oculomotor damage and monitor recovery from concussion. In a review and meta-analysis regarding technology that monitored eye movements after SRC (including saccades and changes in pupil size), Snegireva and colleagues (2018) found that concussed participants showed impairment in the movement (saccades and smooth pursuit), position, and direction of their eyes, but that these tests were only sensitive to concussive changes for the first month post-injury. Carrick and colleagues (2021) have studied the use of a pupillary light reflex as a biomarker of a historical concussion, but this work is also preliminary. Other headsets

marketed towards concussion are being studied, and some of these use virtual reality to improve rehabilitation; for example, NeuroDotVR is a training program to rehabilitate visual dysfunction (Versek et al., 2019), and HeadRehab VR can help improve performance on balance testing (Teel et al., 2014). Ophthalmic biomarkers may also be a viable approach in conjunction with electrophysiological measures of optical structures and functions.

### 8.5.2 Limitations

Although limitations for each chapter have already been addressed (Sections 4.4.1, 5.4.1, and 7.5.1), this section discusses limitations specific to the design, data collection, and interpretability of the present study. These limitations help to demarcate the scope of this study, as well as to describe more overarching difficulties.

#### 8.5.2.1 Design limitations

While most athletes were tested during the same time slot as their baseline (trainings in the evenings or gym sessions in the early mornings), scheduling for the follow-up assessments prioritised when would be most convenient for the participant when scheduling the follow-up assessments. Though the analyses for time of day did not show an effect, it is likely more complex than the binary before or after noon.

In efforts to obtain the highest SNR for each participant (and because I was usually blinded to the previous results at the time of testing), the number of trials per assessment was not consistent, leading to bias in number of times a participant was tested per session. The initial NuroChek guidelines advised me to aim for an SNR of 5.0 or higher as a baseline, so if a participant presented with two low trials, and if I felt that the placement or impedance could be improved, they were tested a third time. However, if the participant's SNR was over 5.0 on one or both initial trials, they were rarely tested a third time. As an example, one athlete demonstrated a baseline of 21.2 and his two trials at the end of the season were 14.4 and 16.9. If he had been tested a third time at the end-of-season, it is possible he could have demonstrated a higher result, closer to the baseline. Similarly for athletes whose post-season signal strength exceeded that of their baseline: if they were tested for a third trial at baseline it might have been equivalent to (or higher than) their post-season results. In this way, the preconception of range for a "healthy" person introduced bias, and disproportionately more low than high SNRs were collected. Each data point is also vulnerable to type II errors (false negative) due to incorrect placement of the headset. Additionally, not all tests were able to be performed in silent

environments, so some SNRs may be biased as lower values because of the environmental noise.

The cognitive measures used were (in part) selected by the development team of the NuroChek system, who changed their protocols between the first and second seasons of the study to use the SCAT-5 instead of the King-Devick. Each cognitive test had its own limitations or weaknesses. Use of the King-Devick data was not continued for the present study after 2020 because the preliminary results did not show any correlations between K-D times and concussion or SNR, and because administration of the SCAT-5 already lengthened my testing time by more than 10 minutes. The King-Devick is not considered sensitive to concussion in rugby players (Fuller et al., 2019), and without specific recovery information from the physiotherapist for the first year, it was not possible to assess recovery or correlate the electrophysiological behaviour to concussion sequelae. Additionally, some of the baseline SCAT-5 assessments were provided by the team physiotherapists, and these were done on previous or adapted versions. Because of this, some domains (including immediate and delayed memory) were incomplete or administered incorrectly and could not be analysed in all groups.

#### 8.5.2.2 Data collection limitations

Inconsistent post-injury follow-up is a weak point of this study (some of which is attributable to the various Covid-19 lockdowns). It was difficult to schedule athletes for all post-injury assessments after their concussion, as well as scheduling all athletes for end-of-season assessments; as a result, the variation in final testing times in relation to when the season ended may be a confound of these analyses. The time between rounds in groups of combat athletes was also longer in the BJJ athletes by half an hour, to avoid interrupting these athletes' training sessions.

Another major limitation of this study is the lack of data on female athletes, especially those with concussions. It is unclear why no female athletes on the participating teams sustained concussions. Despite emailing every week during the season to ask about injuries, it is possible that injuries were sustained by female athletes that did not wish to participate, and so I was not informed. It is also possible that the female athletes use more effective injury-prevention strategies than the male athletes. Very few local gyms allowed sparring with head contact, and fewer had training sessions for female boxers. Unfortunately, headset B failed during an out-of-town testing session with female boxers, when the backup headset was not available. Despite all efforts to reach parity between sex groups, recruiting from female participants was more challenging overall.

The Impedance data from each electrode could have helped determine the validity of the SNR and the headset itself, but it was unavailable. Multiple attempts were made to obtain the impedance data from NuroChek, but unfortunately, none of the exported data were able to be matched to the dates or SNR values in my datasets. Because of this discrepancy, analyses on impedance or error rate calculations were not able to be run. From data collection notes, lower impedance did not always correspond with the highest SNR obtained across trials, and the visual magnitude of the EEG signal (displayed with the SNR) was sometimes higher in the trial with the lower SNR. More extensive note-taking on impedance data during the data collection could improve this limitation, and future analyses could examine the relationship between SNR and the magnitude of the represented signal.

The analyses of the headset changes are also confounded by the different groups or shift in time points being collected at that time. Headset A began to fail during the 2021 rugby baselines,[27] so it is possible that, despite the trend of higher SNRs in Headset A than B, some of the 2021 baselines may be biased toward lower SNRs because the O1 electrode was not engaging. Headset B failed suddenly at the end of collection from the boxer group, and the next data collected with Headset C were for the BJJ group, so this comparison was confounded as well. This factor may be unimportant since the SNRs were not significantly different by headset, but it would be ideal in future studies to rotate between multiple headsets during data collection for each time point; this would reduce the chance of introducing a confound when changing the headset.

#### 8.5.2.3 Interpretability limitations

The interpretation of these results is complicated by the small sample size. All statistically significant results, even those with large effect sizes, are only based on a small sample size, and often unequal group sizes as well. Coupled with the inconsistencies during follow-up assessments, it is quite possible that many other variables account for the results reported in this study. Even the effect for sex, arguably the clearest and strongest finding of this study, was not seen in the small non-athlete control group. Thus, the generalisability of these findings into the wider field of electrophysiology is unclear.

A common limitation of commercial EEG devices is a reduced amount of electrode sites, which can affect the validity or quality of signal obtained (Fontanillo Lopez et al., 2020). In the pilot and validation studies (Fong et al., 2020; Fong et al.,

[27] After I reported a persistent lack of impedance on the O1 electrode, the NuroChek team advised me to switch to the second headset.

2021), the EEG signal was collected from the O1 and O2 sites, while the P3 and P4 sites served as reference and "common-mode" sites, respectively. While the current generation of NuroChek features five electrodes (with different reference sites), it is unclear how this shift may contribute to the differences between their findings and the present results.

### 8.5.3 Strengths

A main strength of this study is the substantial proportion of female athletes at approximately 30%. Though the number of concussed participants was relatively small, the large pool of non-concussed athletes demonstrated the natural variation of the SNR across many populations. The rugby athletes who participated during both seasons also contributed novel longitudinal data of the SNR over a period of almost two years, in some cases. Further, the present study compared the SNR of participants across different levels of impact exposure to examine this crucial potential confound in the assessment of concussive injury. The number of data points allowed me to test the effects of demographic factors in many conditions with suitable sample sizes.

### 8.5.4 Future research

Future studies using the NuroChek headset should aim to test the concussed athletes at much more acute intervals, ideally at least three times during the first 72 hours post-injury. Variance may also decrease if athletes are assessed for a baseline before each game. Since localisation of activity is important in the literature reviewed, future research may benefit from having the ability to analyse data separately from the three electrodes of the NuroChek headset. Accurate, time-locked impedance data may be able to identify asymmetries in occipital activity.

Many of the present findings could be explored further using the SNR or the raw EEG data from the NuroChek headset in conjunction with another physiological measure. The use of artificial intelligence, combined with a true objective measure of concussion, could be used to examine subtle changes in other types of imaging (fMRI, DTI, etc.) and may be a promising avenue of early detection. Additionally, this approach could identify what regional damage is specifically associated with concussion and could observe how these regions change during recovery. The link between concentration and SNR could also be further explored to see if the SNR is useful in monitoring post-concussive concentration deficits. Additionally, the athletes who reported visual disturbances after a big hit may have had different SNRs than the other athletes, and though it may not benefit research into objective assessment, this may be an interesting avenue of future research regarding post-concussive visual functioning in an acute setting. Future NuroChek system

research could seek to clarify the relationship between SNR and impact exposure in combination with accelerometer data. Finally, SSVEP testing with the NuroChek headset could also be used in conjunction with PET imaging (Section 2.2) (da Silva et al., 1999; Pastor et al., 2003) and machine learning (Section 8.5.1) (Bazarian et al., 2021; Hoang et al., 2023) to investigate other avenues of concussive and subconcussive injury.

Compliance may improve if athletes had access to their own data. Continuous monitoring of one's impact exposure in real time could help athletes to manage their concussion risk and overall brain health (Stemper et al., 2019). The rise of the "quantified self" (especially in sport) and interest in self-regulation offers a potentially new way to educate athlete about their level of risk and allow them to track their "brain health" (Fontanillo Lopez et al., 2020; George & Bhila, 2020).

Further research is needed to understand why the female athletes' SNRs were lower, especially since the outliers suggest that female SNRs can equal or exceed male SNRs, even when the female participants have thick hair. Future NuroChek system research could ask all participants about any product or other potential contaminants in their hair, and future research into similar assessment devices should specifically consider female physiology during the design phase. Future electrophysiology research should also consider sex differences in electrode placement and signal quality, as well as controlling for factors of repetitive impact exposure, age, exercise, and focus.

Overall, future research into objective concussion assessment should consider the nature and definition of concussive damage. When examining recovery, the difference is subtle between persistent damage and a benign but permanent rerouting of networks or activity. Future research must determine what this means for how these type of alterations are discussed, what this means for recovery, and what it means for the definition of concussion itself (Kozak, 2018).

#### 8.5.4.1 Ethical considerations of electrophysiology in health technology

Electroencephalography has emerged as a widely viable method for assessment and rehabilitation for traumatic brain injury, sleep disorders, seizure prediction, and motor disorders (Fontanillo Lopez et al., 2020). Yet there are many ethical issues to consider when using technology to gather an individual's private data, and these considerations are particularly important when designing a device intended to be used by novices or people with little training in scientific equipment. Safety is of course the largest concern when considering the utility of any novel technology. Since the NuroChek headset uses flashing lights to evoke the target brain activity, athletes were carefully screened for

epilepsy or any unexplained fainting before being tested, and if they expressed any discomfort, they were given the option to discontinue. In addition to safety, the experience and comfort of the participants is important to consider when developing these devices.

Privacy protocols are crucial when digital data will be shared between different research or client entities. Electrophysiological data is considered particularly sensitive because it is information that the individuals do not even know about themselves (Fontanillo Lopez et al., 2020). All data should be de-identified before they are shared across platforms (as was done in the present study), but for many reasons this is not always the case, and while it is categorically impossible to prevent all security breaches (Bilder & Reise, 2019) it remains essential to maintain the most updated security protections for all data. Furthermore, while the coaches and staff do need a certain amount of medical information to keep their athletes safe and healthy, an athlete should not feel compelled to share this information to an unnecessarily large staff. As in all cases, every effort should be made to protect the identity of any participant who is generously sharing such private data for research purposes.

The principle of informed consent relies on the individual's accurate understanding of their own data and its implications for their health, as well as the assumption that the data is a valid representation of its intended domain (Bilder & Reise, 2019; Fontanillo Lopez et al., 2020; L. S. M. Johnson et al., 2015). If an individual has access to accurate and appropriate technology, then it can provide great benefits and empowerment, like assistive devices for those with disabilities, or those who want to track their health over time (Fontanillo Lopez et al., 2020; George & Bhila, 2020). However, if the measures do not actually represent the specific domains targeted, then the results will be irreconcilably wrong and might be irresponsible to dispense (Bilder & Reise, 2019; Fontanillo Lopez et al., 2020). For example, showing a participant an SNR value that is higher than their baseline may reinforce the athlete's desire to take more physical risks, even if a higher SNR does not indicate a healthier brain. To avoid interpreting data incorrectly, the generalisability of the results seen in these small pilot or validation studies must also be considered across age (beyond the standard model that studies 18–25 year old athletes), sex/gender, and concussion history, as well as race/ethnicity (Houck et al., 2018; Kontos et al., 2010). While the previous study by Fong and colleagues (2020) included only male athletes, the present results show that NuroChek does not perform equivalently between male and female athletes. These factors are important to consider when deciding how to test these devices, as is deliberately reporting results by demographic factors, even if they are non-significant.

Autonomy, or the informed ability of an individual to choose their own actions, can be compromised when such objective yet invisible data becomes the determinant of an athlete's fitness to compete. The use of these data can create a medical conflict of interest between an athlete and a coach (L. S. M. Johnson et al., 2015); for instance, if one is concerned for the athlete's health and the other wants the athlete to return to the game. When an athlete may be cognitively impaired because of the neurotrauma, the motivation of the coach or staff who interprets the results for the athlete must be considered. If, based on favourable data from this type of device, the coach's decision to return the athlete to play results in further neurotrauma (or threats to the athlete's autonomy), then suddenly many people share partial responsibility for this athlete's injury. Additionally, though these devices may have great predictive capabilities (Fontanillo Lopez et al., 2020), technology with undisclosed or proprietary algorithms should never be used as the sole criteria for risk-prediction decisions, in sport or in a legal setting like probation determination (L. S. M. Johnson et al., 2015). Headsets like NuroChek system should be used in athletes privately and in combination with other concussion assessment methods; if an athlete is held out of a game, the reason should be given as "concussion concerns," not "bad brain scan." The chance is also higher that a misunderstanding over novel technology could negatively affect an athlete's reputation, or artificially inflate their sense of safety and estimation of brain health with a false negative. When evaluating the utility of brain-focused technology, it is important to identify if the data generated are creating empowerment or limitation for the individuals using these devices.

Finally, the research must be interpreted through the lens of any financial conflicts of interest that the authors may have. While a review by Fontanillo Lopez and colleagues (2020) found medical devices to be the top application for commercial EEG technology,[28] they note that such data are considered so sensitive that brain scanning for commercial purposes is illegal in France. Despite the occasional overlap, the interests of scientists and the private sector are often very different (Fontanillo Lopez et al., 2020). Improvements in technology and decreases in price mean that more companies can create products that make extraordinary claims to improve brain health, such as the process of assessing concussion. "Neuro-gadgets" are a lucrative field that must be closely monitored as it develops (Fontanillo Lopez et al., 2020; L. S. M. Johnson et al., 2015). EEG technology greatly benefits many people that use it regularly, and these considerations are not reasons

[28] Medical applications were cited in 74 studies, followed by neuro-ergonomics/smart environment applications (41), self-regulation/self-tracking (26), games/entertainment (25), neuromarketing (21), education (20), and security/authentication (20).

to stop using it, but rather, ideas for how to improve this technology. Transparency regarding use of these sensitive data, as well as discussing the issues that accompany them, is necessary to protect such information and the people to whom it belongs.

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# Chapter 9: Appendices

## 9.1 Ethical approvals

### 9.1.1 HREC approval (rugby athletes)

The University of Waikato
Private Bag 3105
Gate 1, Knighton Road
Hamilton, New Zealand

Human Research Ethics Committee
Julie Barbour
Telephone: +64 7 837 9336
Email:humanethics@waikato.ac.nz


22 March 2019

Brett Langley
Nicola Starkey
Nicholas Gill
By email: brett.langley@waikato.ac.nz

Dear Brett

**HREC(Health)2019#10 : Evaluation of an EEG based concussion system**

Thank you for submitting your amended application HREC(Health)2019#17 for ethical approval.

We are now pleased to provide formal approval for your project, including the following activities:

- evaluation of an EEG based concussion detection device on a pool of approximately 200 healthy participants, likely to be involved in rugby.
- evaluation of the same device on a subgroup of the healthy participants who have a diagnosed or suspected concussion. Both healthy and concussed participants will participate in two 30 second tests of the device, worn on the head, and the King Devick rapid number naming test. Healthy participants will be tested twice, 1m apart. Concussed participants will be tested after diagnosis, at 72h, 5d, 10d, 15d, and 20d post injury.

You have indicated that an adverse event directly related to the testing of the device and requiring medical treatment will result in the immediate abandonment of the project.

When you receive locality approvals from the various sites for your project, please send these to us. We will file them with your paperwork. We appreciate that locality approvals may take different forms, such as a signed letter, an email, or a verbal approval given face to face or over the phone. In the case of verbal approvals, please record the date, name of approver and their role within the relevant organisation, the nature of approval given, and the name of the researcher who received the approval. Provide this information in an email to the committee.

Please contact the committee by email (humanethics@waikato.ac.nz) if you wish to make changes to your project as it unfolds, quoting your application number with your future correspondence. Any minor changes or additions to the approved research activities can be handled outside the monthly application cycle.

We wish you all the best with your research.

Regards,

**Julie Barbour PhD**
**Chairperson**
**University of Waikato Human Research Ethics Committee**

## 9.1.2 NZR approval (rugby athletes)

**New Zealand Rugby Medical and Science Advisory Panel**
**Principal Researcher**: Dr Brett Langley
**Study Title**: *Evaluation of an EEG based concussion system*

Dear Brett,

I am pleased to inform you that the Medical and Science Advisory Panel (MSAP) for New Zealand Rugby (NZR) has reviewed your proposal and would like to provide its approval for the proposed study *Evaluation of an EEG based concussion system*.

With regards to participants, MSAP has approved this study being performed at Mitre 10 Cup and community level, but at this stage you will not be able to access Super Rugby players.

You have noted that in addition to testing with the EEG based concussion system, participants will perform a King-Devick test. In relation to the King-Devick test, the Panel wanted to refer you to a study by Fuller et al[1] which you may already be aware of. You may wish to consider this when discussing your results.

At the conclusion of your study please provide MSAP with a brief summary report of your findings. This report will be passed along to relevant parties in NZR to ensure that this research is disseminated across the organization.

If you require anything further or if we can be of assistance, please contact me via email Karen.Rasmussen@nzrugby.co.nz or phone 027 2114051.

Kind regards,

Karen Rasmussen

On behalf of the New Zealand Rugby Medical and Science Advisory Panel



[1] Fuller GW, Cross MJ, Stokes KA, et al. King-Devick concussion test performs poorly as a screening tool in elite rugby union players: a prospective cohort study of two screening tests versus a clinical reference standard. Br J Sports Med 2018;0:1-7

## 9.1.3 HDEC out-of-scope letter (rugby athletes)

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011
0800 4 ETHICS
hdecs@moh.govt.nz

1 March 2019

Dr Brett Langley
University of Waikato
blangley@waikato.ac.nz

Dear Dr Langley,

| Study title: | Evaluation of an EEG based concussion system |
|---|---|

Thank you for emailing HDEC a completed scope of review form on 25 February 2019. The Secretariat has assessed the information provided in your form and supporting documents against the Standard Operating Procedures.

Your study will not require submission to HDEC as, on the basis of the information you have submitted, it does not appear to be within the scope of HDEC review. This scope is described in section three of the Standard Operating Procedures for Health and Disability Ethics Committees.

Specifically, your study contains no features which could be considered of more than minimal risk to participants. An observational study requires HDEC review only if the study involves more than minimal risk (that is, potential participants could reasonably be expected to regard the probability and magnitude of possible harms resulting from their participation in the study to be greater than those encountered in those aspects of their everyday life that relate to the study).

For the avoidance of doubt, an observational study always involves more than minimal risk if it involves one or more of the following:

- one or more participants who will not have given informed consent to participate, or
- one or more participants who are vulnerable (that is, who have restricted capability to make independent decisions about their participation in the study), or
- standard treatment being withheld from one or more participants, or
- the storage, preservation or use of human tissue without consent, or
- the disclosure of health information without authorisation.

If you consider that our advice on your project being out of scope is in incorrect please contact us as soon as possible giving reasons for this.

This letter does not constitute ethical approval or endorsement for the activity described in your application, but may be used as evidence that HDEC review is not required for it.

Please note, your locality may have additional ethical review policies, please check with your locality. If your study involves a DHB, you must contact the DHB's research office before you begin. If your study involves a university or polytechnic, you must contact its institutional ethics committee before you begin.

Please don't hesitate to contact us for further information.

Yours sincerely,

Mark Joyce
Advisor
Health and Disability Ethics Committees
hdecs@moh.govt.nz

## 9.1.4 HREC approval (combat athletes)

The University of Waikato
Private Bag 3105
Gate 1, Knighton Road
Hamilton, New Zealand

Human Research Ethics Committee
Roger Moltzen
Telephone: +64021658119
Email:humanethics@waikato.ac.nz

THE UNIVERSITY OF WAIKATO
*Te Whare Wānanga o Waikato*

8 December 2021

Jen Treacy
Te Huataki Waiora - School of Health
DHECS
By email: jen.treacy4@gmail.com

Dear Jen

**HREC(Health)2021#86 : Evaluation of an EEG based concussion system**

Thank you for your responses to the Committee feedback.

We are now pleased to provide formal approval for your project.

Please contact the Committee by email (humanethics@waikato.ac.nz) if you wish to make changes to your project as it unfolds, quoting your application number with your future correspondence. Any minor changes or additions to the approved research activities can be handled outside the monthly application cycle.

We wish you all the best with your research.

Regards,

**Emeritus Professor Roger Moltzen MNZM**
**Chairperson**
**University of Waikato Human Research Ethics Committee**

## 9.1.5 HREC approval (non-athlete control participants)

The University of Waikato
Private Bag 3105
Gate 1, Knighton Road
Hamilton, New Zealand

Human Research Ethics Committee
Roger Moltzen
Telephone: +64021658119
Email:humanethics@waikato.ac.nz

THE UNIVERSITY OF WAIKATO
*Te Whare Wānanga o Waikato*

4 May 2021

Jen Treacy
Te Huataki Waiora School of Health
DHECS
By email: jen.treacy4@gmail.com

Dear Jen

**HREC(Health)2021#08 : Testing the NuroChek headset in chronic concussion patients**

Thank you for your responses to the Committee feedback.

We are now pleased to provide formal approval for your project.

Please contact the committee by email (humanethics@waikato.ac.nz) if you wish to make changes to your project as it unfolds, quoting your application number with your future correspondence. Any minor changes or additions to the approved research activities can be handled outside the monthly application cycle.

We wish you all the best with your research.

Regards,

**Emeritus Professor Roger Moltzen MNZM**
**Chairperson**
**University of Waikato Human Research Ethics Committee**

## 9.2 Materials

### 9.2.1 Informed consent form

#### 9.2.1.1 Informed consent form for rugby athletes (2020)

**Faculty of Health, Sport, and Human Performance**
The University of Waikato
Private Bag 3105
Hamilton, New Zealand, 3240

0800 WAIKATO (924 528)
www.waikato.ac.nz

THE UNIVERSITY OF WAIKATO
*Te Whare Wānanga o Waikato*

**CONSENT FORM FOR PARTICIPANTS**

**Project Title:** *Evaluation of an EEG based concussion system*

- □ I have read the Participant Information Sheet for this study.
- □ I confirm that the nature, purpose, and risks of the research project and voluntary nature of participation have been fully explained to my satisfaction by _____. Specifically, the details of the tests proposed and the anticipated length of time it will take, and an indication of any discomfort that may be expected have been explained to me.
- □ I confirm that to the best of my knowledge I do not have:
  a. Epilepsy
  b. A seizure disorder
  c. A history of any fit, faint or funny turn
  d. Sensitivity to flashing lights
  e. Legal blindness
- □ I freely agree to participate in this research project according to the conditions in the Participant Information Sheet which I confirm has been provided to me.
- □ I understand that my involvement in this study may not be of any direct benefit to me.
- □ I have been given the opportunity to have a member of my family or another person present while the study is explained to me.
- □ I have been told that no information regarding my medical history will be divulged to unauthorised third parties and the results of any tests involving me will not be published so as to reveal my identity.
- □ I understand that I am free to withdraw from the study at any stage without prejudice or penalty up until 3 weeks following participation. If I decide to withdraw from the study, I do not have to give a reason.
- □ I am 18 years of age or over.

I agree to provide information to the researchers under the conditions of confidentiality set out on the Participant Information Sheet.

Signed: _____

Name: _____

Date: _____

***Contact information:*** If you have any questions or concerns about the project, either now or in the future, please feel free to contact:

**Brett Langley**
The University of Waikato, Faculty of Health, Sport and Human Performance
Ph: 022 426 1292, Email: blangley@waikato.ac.nz

## 9.2.1.2 Informed consent form for rugby athletes (2021)

**Faculty of Health, Sport, and Human Performance**
The University of Waikato
Private Bag 3105
Hamilton, New Zealand, 3240

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THE UNIVERSITY OF WAIKATO
*Te Whare Wānanga o Waikato*

**CONSENT FORM FOR PARTICIPANTS**

**Project Title:** *Evaluation of an EEG based concussion system*

□ I have read the Participant Information Sheet for this study.

□ I confirm that the nature, purpose, and risks of the research project and voluntary nature of participation have been fully explained to my satisfaction by _____. Specifically, the details of the tests proposed and the anticipated length of time it will take, and an indication of any discomfort that may be expected have been explained to me.

□ I confirm that to the best of my knowledge I do not have:
a. Epilepsy
b. A seizure disorder
c. A history of any fit, faint or funny turn
d. Sensitivity to flashing lights
e. Legal blindness

□ I freely agree to participate in this research project according to the conditions in the Participant Information Sheet which I confirm has been provided to me.

□ I understand that my involvement in this study may not be of any direct benefit to me.

□ I authorise the team staff to discuss my medical and injury information with the researchers.

□ I have been given the opportunity to have a member of my family or another person present while the study is explained to me.

□ I have been told that no information regarding my medical history will be divulged to unauthorised third parties and the results of any tests involving me will not be published so as to reveal my identity.

□ I understand that I am free to withdraw from the study at any stage without prejudice or penalty up until 3 weeks following participation. If I decide to withdraw from the study, I do not have to give a reason.

□ I am 18 years of age or over.

I agree to provide information to the researchers under the conditions of confidentiality set out on the Participant Information Sheet.

Signed: _____

Name: _____

Date: _____

***Contact information:*** If you have any questions or concerns about the project, either now or in the future, please feel free to contact: **Brett Langley**
The University of Waikato, Faculty of Health, Sport and Human Performance Ph: 022 426 1292,
Email: blangley@waikato.ac.nz

## 9.2.1.3 Informed consent form for combat athletes

Adams Centre for High Performance
52 Miro St
Mt Maunganui 3116
Tauranga, New Zealand

Jen Treacy
PhD candidate
jt182@students.waikato.ac.nz
020 4188 9270

THE UNIVERSITY OF WAIKATO
*Te Whare Wānanga o Waikato*

**CONSENT FORM FOR PARTICIPANTS**

**Project Title:** *Evaluation of an EEG based concussion system*

□ I have read the Participant Information Sheet for this study.

□ I confirm that the nature, purpose, and risks of the research project and voluntary nature of participation have been fully explained to my satisfaction by _____. Specifically, the details of the tests proposed and the anticipated length of time it will take, and an indication of any discomfort that may be expected have been explained to me.

□ I confirm that to the best of my knowledge I do not have:
a. Epilepsy
b. A seizure disorder
c. A history of any fit, faint or funny turn
d. Sensitivity to flashing lights
e. Legal blindness

□ I freely agree to participate in this research project according to the conditions in the Participant Information Sheet which I confirm has been provided to me.

□ I understand that my involvement in this study may not be of any direct benefit to me.

□ I have been given the opportunity to have a member of my family or another person present while the study is explained to me.

□ I understand that no information regarding my medical history will be divulged to unauthorised third parties and the results of any tests involving me will not be published so as to reveal my identity.

□ I understand that I am free to stop and withdraw from the study at any stage without prejudice or penalty up until 3 weeks following participation. If I decide to withdraw from the study, I do not have to give a reason.

□ I am 18 years of age or over.

I agree to provide information to the researchers under the conditions of confidentiality set out on the Participant Information Sheet.

Signed: _____

Name: _____

Date: _____

***Contact information:*** If you have any questions or concerns about the project, either now or in the future, please feel free to contact: **Brett Langley** at the University of Waikato, School of Health Ph: 022 426 1292,
Email: blangley@waikato.ac.nz

## 9.2.1.4 Informed consent form for non-athlete control participants

**Faculty of Te Huataki Waiora School of Health**
The University of Waikato
Private Bag 3105
Hamilton, New Zealand, 3240

0800 WAIKATO (924 528)
www.waikato.ac.nz

THE UNIVERSITY OF WAIKATO
*Te Whare Wānanga o Waikato*

**CONSENT FORM FOR PARTICIPANTS**

**Project Title:** *Evaluation of an EEG based concussion system*

□ I have read the Participant Information Sheet for this study.

□ I confirm that the nature, purpose, and risks of the research project and voluntary nature of participation have been fully explained to my satisfaction by _____. Specifically, the details of the tests proposed and the anticipated length of time it will take, and an indication of any discomfort that may be expected have been explained to me.

□ I confirm that to the best of my knowledge I do not have:
a. Epilepsy
b. A seizure disorder
c. A history of any fit, faint or funny turn
d. Sensitivity to flashing lights
e. Legal blindness

□ I freely agree to participate in this research project according to the conditions in the Participant Information Sheet which I confirm has been provided to me.

□ I understand that my involvement in this study may not be of any direct benefit to me.

□ I have been given the opportunity to have a member of my family or another person present while the study is explained to me.

□ I understand that no information regarding my medical history will be divulged to unauthorised third parties and the results of any tests involving me will not be published so as to reveal my identity.

□ I understand that I am free to withdraw from the study at any stage up until 3 weeks following participation. If I decide to withdraw from the study, I do not have to give a reason.

□ I am 16 years of age or over.

I agree to provide information to the researchers under the conditions of confidentiality set out on the Participant Information Sheet.

Signed: _____
Name: _____
Date: _____

***Contact information:*** This study was approved by the Human Research Ethics Committee at the University of Waikato. If you have any questions or concerns about the project, either now or in the future, please feel free to contact: **Brett Langley,** University of Waikato, Faculty of Health, Sport and Human Performance Ph: 022 426 1292, Email: blangley@waikato.ac.nz OR the **HREC** directly at humanethics@waikato.ac.nz

## 9.2.2 Demographic questionnaire

### 9.2.2.1 Demographic questionnaire for rugby athletes (2020)

**1. Participant Information**

Name: _____

(First, Middle, Last)

Date of Birth: ___/____/___

(DD, MM, YY)

Centre / Team: _____

Phone #: _____ Gender: ☐ M ☐ F ☐ Other

Email: _____ Subject ID: _____

**2. Investigator Information**

Investigator Name: _____

(First, Middle, Last)

Email: _____

Phone #: _____

**3. Screening Date and Time**

Date: ___/___/___

(DD, MM, YY)

Time (24 hours): ___:___

**4. Screening Information**

4.1. Do you have a history of seizures? ☐ Yes ☐ No

4.2. Do you have a history of epilepsy? ☐ Yes ☐ No

4.3. Do you have a history of fits, faints or 'funny turns'? ☐ Yes ☐ No

4.4. Do you have an existing brain injury and/or condition for at least the past month?

☐ Yes ☐ No

4.5. Do you currently have any headaches, migraines or eyestrain? ☐ Yes ☐ No

4.6. Are you legally blind? ☐ Yes ☐ No

If 'yes' to any question above, you cannot participate in this study.

**5. Medical History**

Concussion for the purposes of these questions, are symptoms (whether on the sporting field, playground, home or elsewhere) AND following an impact where you:

- felt drowsy
- had a severe headache (way worse than any regular headache)
- felt pressure in your head
- experienced nausea
- had blurred or abnormal vision
- couldn't tolerate bright light or noise
- had ringing in your ears
- were disorientated or confused
- were uncoordinated or fell over or had balance problems
- were "dinged" or had you "bell rung"
- felt like you were slowed down, "in a fog" or "didn't quite feel right"
- were unconscious for any period of time

5.1. Have you ever had a concussion or been told by a doctor that you had a concussion?

☐ Yes ☐ No

5.2. (If yes in 5.1.) How many times have you had a concussion?

☐ 1-3 ☐ 4-6 ☐ 7-9 ☐ 10+

5.3. Have you ever had to go or been taken to the Emergency Room for a head injury or concussion? ☐ Yes ☐ No

5.4. Have you ever had a scan (e.g., CT or MRI) for a head injury or concussion?

☐ Yes ☐ No

5.5. Have you ever been hospitalised for a head injury or concussion? ☐ Yes ☐ No

5.6. Has a doctor ever restricted your participation in athletic activities because of a concussion? ☐ Yes ☐ No

### 9.2.2.2 Demographic questionnaire for rugby athletes (2021)

**1. Participant Information**

Name: _____

(First, Middle, Last)

Date of Birth: ___/____/___

(DD, MM, YY)

Centre / Team: _____

Phone #: _____

Email: _____

Gender: ☐ M ☐ F ☐ non-binary/gender-diverse: _____

Ethnicity (can rank if multiple): ☐ Māori ☐ Pasifika ☐ Asian ☐ Middle Eastern

☐ Latin American ☐ African ☐ NZ European/Pākehā ☐ Other European

☐ other: _____

When did your last sport season end?: _____ What sport?: _____

Is English your first language?: ☐ Yes ☐ No

Do you take oral contraceptives?: ☐ Yes ☐ No What type?: _____

Start date of your last menstrual period: _____

**2. Investigator Information**

Investigator Name: _____

(First, Middle, Last)

Email: _____

Phone #: _____

**3. Screening Date and Time**

Date: ___/___/___

(DD, MM, YY)

Time (24 hours): ___:___

**4. Screening Information**

4.1. Do you have a history of seizures?: ☐ Yes ☐ No

4.2. Do you have a history of epilepsy?: ☐ Yes ☐ No

4.3. Do you have a history of fits, faints or 'funny turns'?: ☐ Yes ☐ No

4.4. Do you have an existing brain injury and/or condition for at least the past month?: ☐ Yes ☐ No

4.5. Do you currently have any headaches, migraines or eyestrain?: ☐ Yes ☐ No

4.6. Are you legally blind?: ☐ Yes ☐ No

If 'yes' to any question above, you cannot participate in this study.

**5. Medical History**

Concussion for the purposes of these questions, are symptoms (whether on the sporting field, playground, home or elsewhere) AND following an impact where you:

- felt drowsy
- had a severe headache (way worse than any regular headache)
- felt pressure in your head
- experienced nausea
- had blurred or abnormal vision
- couldn't tolerate bright light or noise
- had ringing in your ears
- were disorientated or confused
- were uncoordinated or fell over or had balance problems
- were "dinged" or had you "bell rung"
- felt like you were slowed down, "in a fog" or "didn't quite feel right"
- were unconscious for any period of time

5.1. Have you ever had a concussion or been told by a doctor that you had a concussion?: ☐ Yes ☐ No

5.2. (If yes in 5.1.) How many times have you had a concussion?:

☐ 1-3 ☐ 4-6 ☐ 7-9 ☐ 10+

Date of your last concussion: _____ Still symptomatic?: ☐ Yes ☐ No

5.3. Have you ever had to go/been taken to the Emergency Room for a head injury or concussion?: ☐ Yes ☐ No

5.4. Have you ever had a scan (e.g., CT or MRI) for a head injury or concussion?: ☐ Yes ☐ No

5.5. Have you ever been hospitalised for a head injury or concussion?: ☐ Yes ☐ No

5.6. Has a doctor ever restricted your participation in sport because of a concussion?: ☐ Yes ☐ No

### 9.2.2.3 Demographic questionnaire for combat athletes

**Participant Information**

Name: _____

Date of Birth (DD, MM, YY): ___/____/___

Phone #: _____

Email: _____

What type(s) of combat sports do you participate in?:

_____

How many times a month do you train?: _____

Gender: ☐ M ☐ F ☐ non-binary/gender-diverse: _____

How would you describe your ethnicity? (check all that apply): ☐ Māori ☐ Pasifika

☐ NZ European ☐ Other European ☐ Asian ☐ Middle Eastern/Latin American/African

☐ Prefer to self-describe: _____

Have you been diagnosed with dyslexia or another learning disorder?: ☐ Yes ☐ No

Which is your dominant hand?: ☐ Right ☐ Left

Do you take oral contraceptives?: ☐ Yes ☐ No

What type?: _____

Start date of your last menstrual period: _____

**Screening Information**

Do you have a history of seizures? ☐ Yes ☐ No

Do you have a history of epilepsy? ☐ Yes ☐ No

Do you have a history of unexplained fainting? ☐ Yes ☐ No

Do you have an existing brain injury and/or condition for at least the past month?

☐ Yes ☐ No

Do you currently have any headaches, migraines or eyestrain? ☐ Yes ☐ No

Are you legally blind? ☐ Yes ☐ No

If ‘yes’ to any question above, you cannot participate in this study.

**Concussion History**

Following an impact, have you ever:

- felt drowsy
- had a severe headache (way worse than any regular headache)
- felt pressure in your head
- experienced nausea
- had blurred or abnormal vision
- couldn't tolerate bright light or noise
- had ringing in your ears
- were disorientated or confused
- were uncoordinated or fell over or had balance problems
- were "dinged" or had your "bell rung"
- felt like you were slowed down, "in a fog" or "didn't quite feel right"
- were unconscious for any period of time

Have you ever had a concussion or been told by a doctor that you had a concussion?

☐ Yes ☐ No

(If yes) How many times have you had a concussion? _____

Did you experience ☐ loss of consciousness? ☐ memory loss before/after injury?

Explain: _____

Have you ever had to go or been taken to the Emergency Room for a head injury or concussion? ☐ Yes ☐ No

Have you ever had a scan (e.g., CT or MRI) for a head injury or concussion?

☐ Yes ☐ No

Have you ever been hospitalised for a head injury or concussion? ☐ Yes ☐ No

Has a doctor ever restricted your participation in athletic activities because of a concussion? ☐ Yes ☐ No

### 9.2.2.4 Demographic questionnaire for non-athlete control participants

**Participant Screening and History Questionnaire**

Name: _____

Date of Birth (DD, MM, YY): ___/____/___

Phone #: _____

Email: _____

Gender: ☐ M ☐ F ☐ non-binary/gender-diverse: _____

How would you describe your ethnicity? (check all that apply): ☐ Māori ☐ Pasifika

☐ NZ European ☐ Other European ☐ Asian ☐ Middle Eastern/Latin American/African

☐ Prefer to self-describe: _____

Have you been diagnosed with dyslexia or another learning disorder?: ☐ Yes ☐ No

Which is your dominant hand?: ☐ Right ☐ Left

Do you take oral contraceptives?: ☐ Yes ☐ No

What type?: _____

Start date of your last menstrual period: _____

**Screening Information**

Do you have a history of seizures? ☐ Yes ☐ No

Do you have a history of epilepsy? ☐ Yes ☐ No

Do you have a history of unexplained fainting? ☐ Yes ☐ No

Do you have an existing brain injury and/or condition for at least the past month?

☐ Yes ☐ No

Do you currently have any headaches, migraines or eyestrain? ☐ Yes ☐ No

Are you legally blind? ☐ Yes ☐ No

If ‘yes’ to any question above, you cannot participate in this study.

**Concussion History**

Following an impact, have you ever:

- felt drowsy
- had a severe headache (way worse than any regular headache)
- felt pressure in your head

- experienced nausea
- had blurred or abnormal vision
- couldn't tolerate bright light or noise
- had ringing in your ears
- were disorientated or confused
- were uncoordinated or fell over or had balance problems
- were "dinged" or had your "bell rung"
- felt like you were slowed down, "in a fog" or "didn't quite feel right"
- were unconscious for any period of time

Have you ever had a concussion or been told by a doctor that you had a concussion?

☐ Yes ☐ No

(If yes) How many times have you had a concussion? _____

Did you experience ☐ loss of consciousness? ☐ memory loss before/after injury?

Explain: _____

Have you ever had to go or been taken to the Emergency Room for a head injury or concussion? ☐ Yes ☐ No

Have you ever had a scan (e.g., CT or MRI) for a head injury or concussion?

☐ Yes ☐ No

Have you ever been hospitalised for a head injury or concussion? ☐ Yes ☐ No

Has a doctor ever restricted your participation in athletic activities because of a concussion? ☐ Yes ☐ No

# 9.2.3 Sport Concussion Assessment Test (SCAT-5)

## OFFICE OR OFF-FIELD ASSESSMENT

**Please note that the neurocognitive assessment should be done in a distraction-free environment with the athlete in a resting state.**

## STEP 1: ATHLETE BACKGROUND

Sport / team / school: _____

Date / time of injury: _____

Years of education completed: _____

Age: _____

Gender: M / F / Other

Dominant hand: left / neither / right

How many diagnosed concussions has the athlete had in the past?: _____

When was the most recent concussion?: _____

How long was the recovery (time to being cleared to play) from the most recent concussion?: _____ (days)

**Has the athlete ever been:**

| | | |
|---|---|---|
| Hospitalized for a head injury? | Yes | No |
| Diagnosed / treated for headache disorder or migraines? | Yes | No |
| Diagnosed with a learning disability / dyslexia? | Yes | No |
| Diagnosed with ADD / ADHD? | Yes | No |
| Diagnosed with depression, anxiety or other psychiatric disorder? | Yes | No |

Current medications? If yes, please list:

_____

_____

_____

_____

_____

_____

Name: _____

DOB: _____

Address: _____

ID number: _____

Examiner: _____

Date: _____

2

## STEP 2: SYMPTOM EVALUATION

*The athlete should be given the symptom form and asked to read this instruction paragraph out loud then complete the symptom scale. For the baseline assessment, the athlete should rate his/her symptoms based on how he/she typically feels and for the post injury assessment the athlete should rate their symptoms at this point in time.*

**Please Check:** ☐ **Baseline** ☐ **Post-Injury**

**Please hand the form to the athlete**

| | none | mild | | moderate | | severe | |
|---|---|---|---|---|---|---|---|
| Headache | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| "Pressure in head" | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Neck Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Nausea or vomiting | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Dizziness | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Blurred vision | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Balance problems | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Sensitivity to light | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Sensitivity to noise | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Feeling slowed down | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Feeling like "in a fog" | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| "Don't feel right" | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Difficulty concentrating | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Difficulty remembering | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Fatigue or low energy | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Confusion | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Drowsiness | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| More emotional | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Irritability | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Sadness | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Nervous or Anxious | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Trouble falling asleep (if applicable) | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Total number of symptoms: | | | | | | | of 22 |
| Symptom severity score: | | | | | | | of 132 |
| Do your symptoms get worse with physical activity? | | | | | | Y | N |
| Do your symptoms get worse with mental activity? | | | | | | Y | N |
| If 100% is feeling perfectly normal, what percent of normal do you feel? | | | | | | | |

If not 100%, why?

_____

_____

_____

**Please hand form back to examiner**

3

## STEP 3: COGNITIVE SCREENING

**Standardised Assessment of Concussion (SAC)[4]**

Name: _____

DOB: _____

Address: _____

ID number: _____

Examiner: _____

Date: _____

### ORIENTATION

| | | |
|---|---|---|
| What month is it? | 0 | 1 |
| What is the date today? | 0 | 1 |
| What is the day of the week? | 0 | 1 |
| What year is it? | 0 | 1 |
| What time is it right now? (within 1 hour) | 0 | 1 |
| **Orientation score** | | of 5 |

### IMMEDIATE MEMORY

The Immediate Memory component can be completed using the traditional 5-word per trial list or optionally using 10-words per trial to minimise any ceiling effect. All 3 trials must be administered irrespective of the number correct on the first trial. Administer at the rate of one word per second.

**Please choose EITHER the 5 or 10 word list groups and circle the specific word list chosen for this test.**

*I am going to test your memory. I will read you a list of words and when I am done, repeat back as many words as you can remember, in any order. For Trials 2 & 3: I am going to repeat the same list again. Repeat back as many words as you can remember in any order, even if you said the word before.*

| List | Alternate 5 word lists | | | | | Score (of 5) Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|---|---|---|---|---|
| A | Finger | Penny | Blanket | Lemon | Insect | | | |
| B | Candle | Paper | Sugar | Sandwich | Wagon | | | |
| C | Baby | Monkey | Perfume | Sunset | Iron | | | |
| D | Elbow | Apple | Carpet | Saddle | Bubble | | | |
| E | Jacket | Arrow | Pepper | Cotton | Movie | | | |
| F | Dollar | Honey | Mirror | Saddle | Anchor | | | |
| | | | | | **Immediate Memory Score** | | | of 15 |
| | | | | | **Time that last trial was completed** | | | |

| List | Alternate 10 word lists | | | | | Score (of 10) Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|---|---|---|---|---|
| G | Finger<br>Candle | Penny<br>Paper | Blanket<br>Sugar | Lemon<br>Sandwich | Insect<br>Wagon | | | |
| H | Baby<br>Elbow | Monkey<br>Apple | Perfume<br>Carpet | Sunset<br>Saddle | Iron<br>Bubble | | | |
| I | Jacket<br>Dollar | Arrow<br>Honey | Pepper<br>Mirror | Cotton<br>Saddle | Movie<br>Anchor | | | |
| | | | | | **Immediate Memory Score** | | | of 30 |
| | | | | | **Time that last trial was completed** | | | |

## CONCENTRATION

### DIGITS BACKWARDS

Please circle the Digit list chosen (A, B, C, D, E, F). Administer at the rate of one digit per second reading DOWN the selected column.

*I am going to read a string of numbers and when I am done, you repeat them back to me in reverse order of how I read them to you. For example, if I say 7-1-9, you would say 9-1-7.*

| Concentration Number Lists (circle one) | | | | | |
|---|---|---|---|---|---|
| List A | List B | List C | | | |
| 4-9-3 | 5-2-6 | 1-4-2 | Y | N | 0 |
| 6-2-9 | 4-1-5 | 6-5-8 | Y | N | 1 |
| 3-8-1-4 | 1-7-9-5 | 6-8-3-1 | Y | N | 0 |
| 3-2-7-9 | 4-9-6-8 | 3-4-8-1 | Y | N | 1 |
| 6-2-9-7-1 | 4-8-5-2-7 | 4-9-1-5-3 | Y | N | 0 |
| 1-5-2-8-6 | 6-1-8-4-3 | 6-8-2-5-1 | Y | N | 1 |
| 7-1-8-4-6-2 | 8-3-1-9-6-4 | 3-7-6-5-1-9 | Y | N | 0 |
| 5-3-9-1-4-8 | 7-2-4-8-5-6 | 9-2-6-5-1-4 | Y | N | 1 |
| List D | List E | List F | | | |
| 7-8-2 | 3-8-2 | 2-7-1 | Y | N | 0 |
| 9-2-6 | 5-1-8 | 4-7-9 | Y | N | 1 |
| 4-1-8-3 | 2-7-9-3 | 1-6-8-3 | Y | N | 0 |
| 9-7-2-3 | 2-1-6-9 | 3-9-2-4 | Y | N | 1 |
| 1-7-9-2-6 | 4-1-8-6-9 | 2-4-7-5-8 | Y | N | 0 |
| 4-1-7-5-2 | 9-4-1-7-5 | 8-3-9-6-4 | Y | N | 1 |
| 2-6-4-8-1-7 | 6-9-7-3-8-2 | 5-8-6-2-4-9 | Y | N | 0 |
| 8-4-1-9-3-5 | 4-2-7-9-3-8 | 3-1-7-8-2-6 | Y | N | 1 |
| | | **Digits Score:** | | | of 4 |

### MONTHS IN REVERSE ORDER

*Now tell me the months of the year in reverse order. Start with the last month and go backward. So you'll say December, November. Go ahead.*

| | |
|---|---|
| Dec - Nov - Oct - Sept - Aug - Jul - Jun - May - Apr - Mar - Feb - Jan | 0 1 |
| **Months Score** | of 1 |
| **Concentration Total Score (Digits + Months)** | of 5 |

4

## STEP 4: NEUROLOGICAL SCREEN

See the instruction sheet (page 7) for details of test administration and scoring of the tests.

| | | |
|---|---|---|
| Can the patient read aloud (e.g. symptom check-list) and follow instructions without difficulty? | Y | N |
| Does the patient have a full range of pain-free PASSIVE cervical spine movement? | Y | N |
| Without moving their head or neck, can the patient look side-to-side and up-and-down without double vision? | Y | N |
| Can the patient perform the finger nose coordination test normally? | Y | N |
| Can the patient perform tandem gait normally? | Y | N |

## BALANCE EXAMINATION

### Modified Balance Error Scoring System (mBESS) testing[5]

Which foot was tested (i.e. which is the non-dominant foot) ☐ Left ☐ Right

Testing surface (hard floor, field, etc.) _____

Footwear (shoes, barefoot, braces, tape, etc.) _____

| Condition | Errors |
|---|---|
| **Double leg stance** | of 10 |
| **Single leg stance (non-dominant foot)** | of 10 |
| **Tandem stance (non-dominant foot at the back)** | of 10 |
| **Total Errors** | of 30 |

Name: _____

DOB: _____

Address: _____

ID number: _____

Examiner: _____

Date: _____

5

## STEP 5: DELAYED RECALL:

The delayed recall should be performed after 5 minutes have elapsed since the end of the Immediate Recall section. Score 1 pt. for each correct response.

*Do you remember that list of words I read a few times earlier? Tell me as many words from the list as you can remember in any order.*

**Time Started**

Please record each word correctly recalled. Total score equals number of words recalled.

_____

_____

_____

**Total number of words recalled accurately:** of 5 or of 10

6

## STEP 6: DECISION

| **Domain** | **Date & time of assessment:** | | |
|---|---|---|---|
| Symptom number (of 22) | | | |
| Symptom severity score (of 132) | | | |
| Orientation (of 5) | | | |
| Immediate memory | of 15<br>of 30 | of 15<br>of 30 | of 15<br>of 30 |
| Concentration (of 5) | | | |
| Neuro exam | Normal<br>Abnormal | Normal<br>Abnormal | Normal<br>Abnormal |
| Balance errors (of 30) | | | |
| Delayed Recall | of 5<br>of 10 | of 5<br>of 10 | of 5<br>of 10 |

Date and time of injury: _____

If the athlete is known to you prior to their injury, are they different from their usual self?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**
(If different, describe why in the clinical notes section)

Concussion Diagnosed?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**

If re-testing, has the athlete improved?
☐ **Yes** ☐ **No** ☐ **Unsure** ☐ **Not Applicable**

**I am a physician or licensed healthcare professional and I have personally administered or supervised the administration of this SCAT5.**

Signature: _____

Name: _____

Title: _____

Registration number (if applicable): _____

Date: _____

## 9.3 Supplemental tables

### 9.3.1 Study A: Changes in concussed male athletes

#### 9.3.1.1 Comparisons of cognitive domains over time in concussed athletes (Wilcoxon)

Table 9.1: Comparison of cognitive domains over time in concussed athletes.

| | T1 | T2 | test | stat | p | effect size | z score | N = | T1 N = | T1 M (SD) | T2 N = | T2 M (SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Symx# BL | Symx# PI | Wilcoxon signed-rank | 16.000 | 0.249 | 0.471 | 1.153 | 6 | 9 | 3.9 (6.64) | 9 | 4.1 (3.66) |
| 2 | Symx# BL | Symx# EOS | Wilcoxon signed-rank | 0.000 | 0.180 | **-0.548** | -1.342 | 6 | 9 | 1.1 (1.62) | 8 | 0 (0) |
| 3 | Sever BL | Sever PI | Wilcoxon signed-rank | 15.500 | 0.293 | 0.429 | 1.051 | 6 | 9 | 7.6 (15.32) | 9 | 6.0 (5.87) |
| 4 | Sever BL | Sever EOS | Wilcoxon signed-rank | 0.000 | 0.180 | **-0.548** | -1.342 | 6 | 9 | 1.7 (2.18) | 8 | 0 (0) |
| 5 | Orient BL | Orient PI | Wilcoxon signed-rank | 0.000 | 0.157 | **-0.577** | -1.414 | 6 | 9 | 5 (0) | 9 | 4.8 (0.44) |
| 6 | Orient BL | Orient EOS | Wilcoxon signed-rank | 0.000 | 1.000 | | | 6 | 9 | 5 (0) | 8 | 5 (0) |
| 7 | Concen BL | Concen PI | Wilcoxon signed-rank | 13.000 | 0.129 | **0.620** | 1.518 | 6 | 9 | 3.1 (0.93) | 9 | 3.8 (1.20) |
| 8 | Concen BL | Concen EOS | Wilcoxon signed-rank | 10.000 | **0.059** | **0.772** | 1.890 | 6 | 9 | 3.1 (0.93) | 8 | 4.1 (0.83) |
| 9 | Balance BL | Balance PI | Wilcoxon signed-rank | 11.000 | 0.916 | 0.043 | 0.105 | 6 | 9 | 3.8 (4.27) | 9 | 3.3 (4.24) |
| 10 | Balance BL | Balance EOS | Wilcoxon signed-rank | 5.000 | 0.498 | -0.276 | -0.677 | 6 | 9 | 4.8 (5.33) | 8 | 2.9 (3.23) |
| 11 | K-D BL | K-D EOS | Wilcoxon signed-rank | 13.000 | 0.484 | -0.247 | -0.700 | 8 | 9 | 48.96 (5.22) | 11 | 45.50 (5.72) |

**- p < .05; BL- baseline; EOS- end-of-season; symx#- symptom number; sever- symptom severity; orient- orientation; concen- concentration; neuro- neurological; K-D- King-Devick.*

### 9.3.1.2 Comparison of SNR by concussion status over time (rm-ANOVA)

Table 9.2: Comparison of SNR by concussion status over time.

| | G1 | G2 | test | stat | df | p | effect size | N = |
|---|---|---|---|---|---|---|---|---|
| 1 | Concussion status | Time | rm-ANOVA interaction | 3.740 | 1 | **0.057** | 0.051 | 85 |
| 2 | **Concussion status** | Time | rm-ANOVA group | 1.174 | 1 | 0.282 | 0.016 | 85 |
| 3 | Concussion status | **Time** | rm-ANOVA time | 0.183 | 1 | 0.670 | 0.003 | 85 |

**- p < .05; **- p < .01; ***- p < .001; G- group; conc- concussed; BL- baseline; EOS- end-of-season; SNR- signal-to-noise ratio.*

Means for the male rugby athletes by impact exposure can be found in Table 5.15.

### 9.3.1.3 Comparison of cognitive performance at baseline and end-of-season by concussion status (Mann-Whitney)

Table 9.3: Comparison of cognitive performance across time, by concussion status.

| | G1 | G2 | test | stat | df | p | effect size | z score | G1 N = | G1 M (SD) / mean rank | G2 N = | G2 M (SD) / mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Conc symx# BL | Non-conc symx# BL | Mann-Whitney | 64.000 | | **0.060** | -0.330 | -1.927 | 9 | 12.11 | 25 | 19.44 |
| 2 | Conc symx# EOS | Non-conc symx# EOS | Mann-Whitney | 44.000 | | **0.053** | -0.428 | -2.303 | 8 | 10.00 | 21 | 16.90 |
| 3 | Conc sever BL | Non-conc sever BL | Mann-Whitney | 65.000 | | **0.066** | -0.323 | -1.881 | 9 | 12.22 | 25 | 19.40 |
| 4 | Conc sever EOS | Non-conc sever EOS | Mann-Whitney | 44.000 | | **0.053** | -0.428 | -2.306 | 8 | 10.00 | 21 | 16.90 |
| 5 | Conc orient BL | Non-conc orient BL | Mann-Whitney | 130.500 | | 0.489 | 0.216 | 1.259 | 9 | 19.50 | 25 | 16.78 |
| 6 | Conc orient EOS | Non-conc orient EOS | Mann-Whitney | 124.000 | | **0.053** | 0.434 | 2.336 | 8 | 20.00 | 21 | 13.10 |
| 7 | Conc concen BL | Non-conc concen BL | Mann-Whitney | 93.000 | | 0.465 | -0.136 | -0.793 | 9 | 15.33 | 25 | 18.28 |
| 8 | Conc concen EOS | Non-conc concen EOS | Mann-Whitney | 87.000 | | 0.905 | 0.029 | 0.155 | 8 | 15.38 | 21 | 14.86 |
| 9 | Conc neuro BL | Non-conc neuro BL | Mann-Whitney | 107.000 | | 0.395 | 0.194 | 1.100 | 7 | 19.29 | 25 | 15.72 |
| 10 | Conc neuro EOS | Non-conc neuro EOS | Mann-Whitney | 89.500 | | 0.793 | 0.076 | 0.410 | 8 | 15.69 | 21 | 14.74 |
| 11 | Conc bal BL | Non-conc bal BL | Mann-Whitney | 114.500 | | 0.939 | 0.014 | 0.079 | 9 | 17.72 | 25 | 17.42 |
| 12 | Conc bal EOS | Non-conc bal EOS | Mann-Whitney | 83.000 | | 0.981 | -0.009 | -0.050 | 8 | 14.88 | 21 | 15.05 |
| 13 | Conc K-D BL | Non-conc K-D BL | t-test | 0.243 | 51 | 0.405 | 0.089 | | 9 | 48.96 (5.22) | 44 | 48.27 (8.18) |
| 14 | Conc K-D EOS | Non-conc K-D EOS | t-test | -1.232 | 52 | 0.112 | -0.416 | | 11 | 45.50 (5.72) | 43 | 48.45 (7.37) |

**- p < .05; **- p < .01; ***- p < .001; G- group; BL- baseline; EOS- end-of-season; conc- concussed; non-conc- non-concussed; symx#- symptom number; sever- symptom severity; orient- orientation; concen- concentration; neuro- neurological; bal- balance; K-D- King-Devick.*

### 9.3.2 Study B: SNR and concussion history, sex, and repetitive impacts

#### 9.3.2.1 Comparisons of SNR by sex and concussion history (Mann-Whitney)

Table 9.4: Analyses of SNR by sex and concussion history.

| | G1 | G2 | test | stat | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 M mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Female CH BL | Female no CH BL | Mann-Whitney | 104.000 | 0.109 | -0.271 | -1.623 | 22 | 16.23 | 14 | 22.07 |
| 2 | Female CH EOS | Female no CH EOS | Mann-Whitney | 109.500 | 0.967 | -0.008 | -0.042 | 17 | 15.44 | 13 | 15.58 |
| 3 | Male CH BL | Male no CH BL | Mann-Whitney | 505.000 | 0.880 | 0.019 | 0.150 | 38 | 32.79 | 26 | 32.08 |
| 4 | Male CH MS | Male no CH MS | Mann-Whitney | 158.500 | 0.628 | -0.078 | -0.491 | 27 | 19.87 | 13 | 21.81 |
| 5 | Male CH EOS | Male no CH EOS | Mann-Whitney | 510.000 | 0.165 | 0.181 | 1.389 | 35 | 32.57 | 24 | 26.25 |

**- $p < .05$; **- $p < .01$; ***- $p < .001$; G- group; BL- baseline; MS- mid-season; EOS- end-of-season; CH & conc hist- concussion history.*

Average SNRs can be found in Table 5.1 for each time point. Sample sizes for the comparison for female athletes at mid-season were too small to be run.

### 9.3.2.2 Analyses by sex and time of day on SNR of all participants (Mann-Whitney and Wilcoxon)

Table 9.5: Analyses by sex and time of day on SNR of all participants.

| | G1 | G2 | test | stat (df) | p | effect size | z score | G1 N = | G1 mean rank / M (SD) | G2 N = | G2 mean rank / M (SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Before noon SNR1 | After noon SNR1 | Mann-Whitney | 3672.000 | 0.154 | 0.167 | 1.426 | 73 | 75.70 | 89 | 86.26 |
| 2 | Before noon SNR2 | After noon SNR2 | Mann-Whitney | 3614.000 | 0.218 | 0.144 | 1.232 | 73 | 76.49 | 89 | 85.61 |
| 3 | Female SNR1 before noon | Female SNR1 after noon | Mann-Whitney | 247.000 | 0.725 | -0.061 | -0.352 | 33 | 25.5 | 16 | 23.97 |
| 4 | Female SNR2 before noon | Female SNR2 after noon | Mann-Whitney | 227.000 | 0.430 | -0.137 | -0.789 | 33 | 26.12 | 16 | 22.69 |
| 5 | Male SNR1 before noon | Male SNR1 after noon | Mann-Whitney | 1419.500 | 0.808 | -0.038 | -0.243 | 40 | 58.01 | 73 | 56.45 |
| 6 | Male SNR2 before noon | Male SNR2 after noon | Mann-Whitney | 1570.500 | 0.507 | 0.105 | 0.664 | 40 | 54.24 | 73 | 58.51 |
| 7 | Female before noon | SNR1 & SNR2 | Wilcoxon signed-rank | 365.000 | **0.022*** | 0.399 | 2.293 | 33 | 5.35 | | 7.21 |
| 8 | Female after noon | SNR1 & SNR2 | Wilcoxon signed-rank | 87.000 | 0.326 | 0.246 | 0.983 | 16 | 4.39 | | 4.74 |
| 9 | Male before noon | SNR1 & SNR2 | Wilcoxon signed-rank | 366.000 | 0.554 | -0.093 | -0.591 | 40 | 10.84 | | 10.40 |
| 10 | Male after noon | SNR1 & SNR2 | Wilcoxon signed-rank | 1528.000 | 0.328 | 0.115 | 0.979 | 73 | 9.85 | | 10.68 |

**- p < .05; **- p < .01; ***- p < .001; SNR- signal-to-noise ratio; G- group; SNR1- first trial; SNR2- second trial.*

### 9.3.2.3 Comparison of cognitive scores of combat athletes (Mann-Whitney and Wilcoxon)

Table 9.6: Comparison of cognitive scores of combat athletes before and after the round, by impact exposure.

| | G1 | G2 | test | stat | p | effect size | z-score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Impact symx# pre | No impact symx# pre | Mann-Whitney | 109.500 | **0.019*** | 0.488 | 2.389 | 14 | 15.32 | 10 | 8.55 |
| 2 | Impact symx# post | No impact symx# post | Mann-Whitney | 108.500 | **0.022*** | 0.469 | 2.298 | 14 | 15.25 | 10 | 8.65 |
| 3 | Impact symx# pre | Impact symx# post | Wilcoxon signed-rank | 34.000 | 0.693 | -0.106 | -0.395 | 14 | 4.4 (3.55) | | 3.9 (3.00) |
| 4 | No impact symx# pre | No impact symx# post | Wilcoxon signed-rank | 7.500 | 0.317 | 0.316 | 1.000 | 10 | 1.2 (1.87) | | 1.4 (2.17) |
| 5 | Impact sever pre | No impact sever pre | Mann-Whitney | 111.000 | **0.016*** | **0.504** | 2.469 | 14 | 15.43 | 10 | 8.40 |
| 6 | Impact sever post | No impact sever post | Mann-Whitney | 111.000 | **0.016*** | 0.497 | 2.435 | 14 | 15.43 | 10 | 8.40 |
| 7 | Impact sever pre | Impact sever post | Wilcoxon signed-rank | 28.000 | 0.220 | -0.328 | -1.227 | 14 | 8.9 (7.84) | | 5.6 (4.27) |
| 8 | No impact sever pre | No impact sever post | Wilcoxon signed-rank | 7.500 | 0.317 | 0.316 | 1.000 | 10 | 1.7 (2.75) | | 1.9 (3.11) |
| 9 | Impact DS pre | No impact DS pre | Mann-Whitney | 68.500 | 0.402 | 0.188 | 0.922 | 14 | 12.39 | 10 | 9.94 |
| 10 | Impact DS post | No impact DS post | Mann-Whitney | 67.000 | 0.482 | 0.167 | 0.781 | 14 | 12.29 | 8 | 10.13 |
| 11 | Impact DS pre | Impact DS post | Wilcoxon signed-rank | 45.000 | **0.052** | **0.519** | 1.941 | 14 | 2.4 (0.85) | | 2.9 (1.14) |
| 12 | No impact DS pre | No impact DS post | Wilcoxon signed-rank | 17.500 | 0.102 | **0.577** | 1.633 | 8 | 2.1 (0.64) | | 2.6 (0.92) |
| | **G1** | **G2** | **test** | **stat** | **p** | **effect size** | **z-score** | **G1 N =** | **G1 M (SD)** | **G2 N =** | **G2 M (SD)** |
| 13 | Impact TMT pre | No impact TMT pre | T-test | -1.490 (7.332) | **0.089** | **-0.830** | | 13 | 47.22 (6.02) | 7 | 55.17 (13.40) |
| 14 | Impact TMT post | No impact TMT post | T-test | -1.582 (18) | **0.066** | **-0.710** | | 13 | 47.57 (8.56) | 7 | 54.52 (10.81) |
| 15 | Impact TMT pre | Impact TMT post | Paired t-test | -0.022 (11) | 0.491 | -0.006 | | 12 | 47.25 (6.29) | $M_{diff}$: -0.06 | 47.31 (8.89) |
| 16 | No impact TMT pre | No impact TMT post | Paired t-test | 0.260 (6) | 0.402 | 0.085 | | 7 | 55.17 (13.40) | $M_{diff}$: 0.65 | 54.52 (10.81) |

**- p < .05; **- p < .01; ***- p < .001; G- group; pre- before the round; post- after the round; symx#- symptom number; sever- symptom severity; DS- digit span; TMT- Trail-Making Test, form B.*

### 9.3.3 Discussion: Headset evaluation

#### 9.3.3.1 Age and SNR (Spearman's)

Table 9.7: Comparisons of SNR by age.

| | V1 | V2 | test | stat | p | N = |
|---|---|---|---|---|---|---|
| 1 | SNR BL | Age | Spearman's correlation | 0.007 | 0.935 | 151 |
| 2 | Female SNR BL | Age | Spearman's correlation | -0.067 | 0.645 | 50 |
| 3 | Male SNR BL | Age | Spearman's correlation | 0.095 | 0.343 | 101 |

**- p < .05; **- p < .01; ***- p < .001; V- variable; SNR- signal-to-noise ratio; BL- baseline.*

#### 9.3.3.2 Headset change (Mann-Whitney)

Table 9.8: Comparison of SNRs from headsets A, B, and C in 2021 and 2022.

| | G1 | G2 | test | stat | p | effect size | z score | N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Male headset A 2021 | Male headset B 2021 | Mann-Whitney | 186.000 | **0.083** | -0.253 | -1.734 | 28 | 26.86 | 19 | 19.79 |
| 2 | Male headset B 2022 | Male headset C 2022 | Mann-Whitney | 46.000 | 0.291 | 0.055 | 0.270 | 16 | 13.63 | 8 | 10.25 |
| 3 | Female headset B 2022 | Female headset C 2022 | Mann-Whitney | 18.500 | 0.593 | -0.143 | -0.534 | 9 | 7.94 | 5 | 6.70 |

**- p < .05; **- p < .01; ***- p < .001; SNR- signal-to-noise ratio; G- group.*

### 9.3.3.3 Learning trials (Mann-Whitney and McNemar's)

Table 9.9: SNR by level of experience with the headset.

| | G1 | G2 | test | stat | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Learning SNR1 | Exper SNR1 | Mann-Whitney | 6085.500 | **0.042*** | 0.142 | 2.032 | 95 | 93.94 | 110 | 110.82 |
| 2 | Learning SNR2 | Exper SNR2 | Mann-Whitney | 5096.000 | 0.720 | 0.025 | 0.359 | 90 | 98.88 | 110 | 101.83 |
| 3 | Learning SNR3 | Exper SNR3 | Mann-Whitney | 194.000 | 0.118 | -0.228 | -1.561 | 28 | 26.57 | 19 | 20.21 |
| 4 | Female learning SNR1 | Female exper SNR1 | Mann-Whitney | 389.000 | 0.417 | -0.104 | -0.812 | 24 | 33.29 | 37 | 29.51 |
| 5 | Female learning SNR2 | Female exper SNR2 | Mann-Whitney | 311.000 | **0.082** | -0.225 | -1.741 | 23 | 35.48 | 37 | 27.41 |
| 6 | Female learning SNR3 | Female exper SNR3 | Mann-Whitney | 32.000 | 0.118 | -0.341 | -1.564 | 9 | 13.44 | 12 | 9.17 |
| 7 | Male learning SNR1 | Male exper SNR1 | Mann-Whitney | 3402.000 | **0.001**** | 0.270 | 3.239 | 71 | 61.08 | 73 | 83.60 |
| 8 | Male learning SNR2 | Male exper SNR2 | Mann-Whitney | 2942.500 | **0.038*** | 0.175 | 2.073 | 67 | 63.08 | 73 | 77.31 |
| 9 | Male learning SNR3 | Male exper SNR3 | Mann-Whitney | 77.500 | 0.534 | 0.125 | 0.637 | 19 | 12.92 | 7 | 15.07 |

**- p < .05; **- p < .01; ***- p < .001; exper- experienced; G- group.*

#### *9.3.3.3.1 Harmonic artefact (Mann-Whitney and McNemar's)*

Despite the confound of being biased towards the baselines, harmonic data for both trials were also coded as "learning" if they were collected within the first 4 months of using the headset. A Chi-square test revealed the prevalence of the harmonic pattern to be significantly lower in the low-experience condition, and higher in the high-experience condition, $\chi^2 = 67.172$, $p < .001$, Cramer's $V = .291$, $N = 791$ (Table 9.10). The proportional presence of the harmonic artefact was much lower during the learning period.

Table 9.10: Group sizes for the Chi-square test comparing harmonic pattern and experience using the headset.

| | learning | experienced |
|---|---|---|
| harmonic | 11 | 199 |
| no harmonic | 200 | 381 |

Analyses regarding the level of experience are reported in Table 9.11. Mann-Whitney tests were used to compare the harmonic presence in the learning and experienced groups (rows 1-2), and McNemar's test was used two compare the two categorical variables (harmonic presence and experience level) across the two trials (rows 3-7). The SNRs with the harmonic pattern were also significantly lower than the SNRs without it (with a moderate effect size, row 2). Paired analyses across the two trials showed a statistically significant decrease of the harmonic pattern across all conditions except the learning condition (rows 3-7), likely because of experience and knowing how to adjust the headset fitting, and because of the low presence of harmonic interference during the learning period.

Table 9.11: Comparison of SNRs with and without harmonic pattern, by data quality level.

| | G1 | G2 | test | stat | df | p | effect size | z score | G1 N = | G1 mean rank | G2 N = | G2 mean rank |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | No harmonic learning | Harmonic learning | Mann-Whitney | 973.000 | | 0.519 | -0.044 | -0.644 | 200 | 106.64 | 11 | 94.45 |
| 2 | No harmonic exper | Harmonic exper | Mann-Whitney | 21181.000 | | **<0.001*** ** | -0.363 | -8.731 | 381 | 334.41 | 199 | 206.44 |
| 3 | Harm1 | Harm2 | McNemar's | 24.453 | 1 | **<0.001*** ** | | | 358 | | | |
| 4 | Female harm1 | Female harm2 | McNemar's | 5.670 | 1 | **0.015*** | | | 110 | | | |
| 5 | Male harm1 | Male harm2 | McNemar's | 18.893 | 1 | **<0.001*** ** | | | 248 | | | |
| 6 | Harm1 learning | Harm2 lower-qual | McNemar's | 0.250 | 1 | 0.625 | | | 85 | | | |
| 7 | Harm1 exper | Harm2 exper | McNemar's | 23.592 | 1 | **<0.001*** ** | | | 273 | | | |

**- p < .05; **- p < .01; ***- p < .001; G- group; exper- experience; harm1- harmonic at time 1; harm2- harmonic at time 2.*