Institute of Sports Medicine
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Neurophysiological Response to Moderate Aerobic Exercise after Sport-Related Concussion

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Declaration of authorship

I hereby declare that the presented work is, to the best of my knowledge and belief, the result of my own research. Support during the research process or co-author contributions are presented for each publication. The work has not been submitted, either partly or completely, for another degree at this or another university. Content and ideas from other sources have been cited throughout the work.

I have read, understood, and accepted the PhD regulations ("Promotionsordnung der Fakultät für Naturwissenschaften an der Universität Paderborn") from the 31. March (AM.UNI.PB 10.21).

Date Signature

Zusammenfassung (DE)

Sportassoziierte Concussion (SaC) ist eine leichte Form des Schädel-Hirn-Traumas. Die diffuse axonale Verletzung der SRC führt zu veränderter Neurotransmission, metabolischen Veränderungen und Ionenverschiebungen. Es wird davon ausgegangen, dass sich diese Veränderungen in den offensichtlichen Anzeichen und Symptomen widerspiegeln. Es besteht jedoch der Wunsch, objektive Marker zu finden, die die Pathologie widerspiegeln.

Zunächst sollte man besser verstehen, wie die derzeitigen Rehabilitationsstrategien die physiologische Regeneration fördern. Es gibt immer mehr Belege für die positiven Auswirkungen von aerobem Training auf die Regeneration, aber es fehlt an Untersuchungen, die die zugrunde liegenden physiologischen Mechanismen untersuchen. Diese experimentelle Labor-Studie, zielte auf diese Forschungslücke ab, indem neurophysiologische Datensätze vor und nach dem Training gesammelt wurden. Funktionelle Konnektivitätsmaße und Small-World-Eigenschaften wurden extrahiert, und bei allen Variablen gab es Hinweise darauf, dass sich die physiologischen Reaktionen von SaC-Sportlern von denen gesunder Kontrollpersonen unterscheiden. Diese veränderte Reaktion könnte auf einen adaptiven, kompensatorischen Mechanismus hindeuten, aber es ist noch weitere Forschung nötig, bevor eindeutige Schlussfolgerungen gezogen werden können.

Abstract (ENG)

Sport-related concussion (SRC) is a mild form of traumatic brain injury. The diffuse axonal injury of SRC leads to altered neurotransmission, metabolic changes, and ionic shifts. These alterations are presumed to be reflected in the overt signs and symptoms. However, there is a desire to establish objective markers that reflect the pathology.

First, what may be needed is a greater understanding of how current rehabilitation strategies promote physiological recovery. There is accumulating evidence for the positive effects of aerobic exercise on recovery, but a lack of research that thoroughly investigates the mechanisms underlying this. The in-lab experimental study contributing to this thesis targeted this gap in the research by collecting neurophysiological datasets pre- and post-exercise. Functional connectivity measures and small-world properties were extracted and across variables there was evidence that physiological responses of SRC athletes differ from healthy controls. This altered response may reveal an adaptive, compensatory mechanism, still more research is needed before drawing strong conclusions.

List of publications considered for dissertation

(published)

Coenen, J., & Reinsberger, C. (2023). Neurophysiological markers to guide return to sport after sport-related concussion. *Journal of Clinical Neurophysiology, 40,* 391–397. https://doi.org/10.1097/WNP.0000000000000996

Coenen, J., Strohm, M., Reinsberger, C. (2024) Impact of moderate aerobic exercise on small-world topology and characteristics of brain networks after sport-related concussion: an exploratory study. *Scientific Reports, 14,* 25296. https://doi.org/10.1038/s41598-024-74474-6

(submitted)

Coenen, J., van den Bongard, F., Delling, C.A., & Reinsberger, C. (submitted). Differences in network functional connectivity in response to sub-symptomatic exercise between elite adult athletes after sport-related concussion and healthy matched controls: a pilot study. *Journal of Neurotrauma.*

List of other publications

Peer-reviewed
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van den Bongard, F., Gowik, J. K., **Coenen, J.,** Jakobsmeyer, R., & Reinsberger, C. (2024). Exercise-induced central and peripheral sympathetic activity in a community-based group of epilepsy patients differ from healthy controls. *Experimental Brain Research*, 1-10.

Delling, C.A., Jakobsmeyer, R., **Coenen, J.,** Christiansen, N., & Reinsberger, C. (2023). Home-Based Measurements of Nocturnal Cardiac Parasympathetic Activity in Athletes during Return to Sport after Sport-Related Concussion. *Sensors*, *23*(9), 4190.

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van den Bongard, F., **Coenen, J.,** & Reinsberger, C. (2022). Fitness, performance, and cardiac autonomic responses to exercise in people with epilepsy. *Epilepsy & Behavior*, *135*, 108869.

Accepted abstracts
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Coenen, J., Delling, C., van den Bongard, F., Jakobsmeyer, R. & Reinsberger, C. (2023) Central and peripheral autonomic activity pre- to post-submaximal exercise after a sport-related concussion. Sports Medicine and Health Summit. Hamburg, Germany, June 2023. [Oral presentation, published in *Deutschen Zeitschrift für Sportmedizin*]

Coenen, J., van den Bongard, F., Delling, C., Jakobsmeyer, R. & Reinsberger, C. (2022) Autonomic response to submaximal exercise after a sports-related concussion. 6th International Consensus Conference on Concussion in Sport. Amsterdam, Netherlands, October 2022. [Poster presentation, published in *British Journal of Sports Medicine*, doi: 10.1136/bjsports-2023-concussion.254]

Coenen, J. & Reinsberger, C. (2022) Digitalization within a neurophysiological investigation of return-to-sport post-concussion. Wir feiern die Forschung der Zukunft. Paderborn, Germany. [Poster award - 3rd place]

Delling, C., **Coenen, J.,** Jakobsmeyer, R. & Reinsberger, C. (2022). Cardiac autonomic effects of submaximal exercise in athletes post concussion. European College of Sport Science Congress. Sevilla, Spain, August 2022. [Published in *European Journal of Sport Science*]

Coenen, J., van den Bongard, F., Delling, C. & Reinsberger, C. (2022) Network functional connectivity response to submaximal exercise after a sport-related concussion. European College of Sport Science Congress. Sevilla, Spain, August 2022. [Oral presentation, published in *European Journal of Sport Science*]

Delling, C., **Coenen, J.** Jakobsmeyer, R. & Reinsberger, C (2022) Nächtliche und belastungsinduzierte Aktivität im Autonomen Nervensystem während und nach Return-to-Sport nach sportassoziierte Concussion. Leichte Schädel-Hirn-Traumata und Kopferschütterungen im Sport – Forschung und Transfer für die Praxis. *Federal Institute of Sport Science*, Berlin, Germany, June 2022.

Coenen, J., Delling, C., Jakobsmeyer, R. & Reinsberger, C. (2022). Exercise induced activity in the central autonomic network after sports related concussion. Leichte Schädel-Hirn-Traumata und Kopferschütterungen im Sport – Forschung und Transfer für die Praxis. *Federal Institute of Sport Science*, Berlin, Germany, June 2022.

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Coenen, J., van den Bongard, F., Stroehlein, J., & Reinsberger, C. (2021) Neurophysiological Response to Exercise During Return-to-Sport Post-concussion. Sport, Medicine and Health Summit. Virtual, April 2021. [Poster presentation, Published in: *Deutschen Zeitschrift für Sportmedizin,* 72 (3)]

van den Bongard, F., Stroehlein, J. K., **Coenen, J**., Jakobsmeyer, R., & Reinsberger, C. (2021) Exercise-induced changes in functional brain network activity and peripheral autonomic parameters in epilepsy patients. Sport, Medicine and Health Summit. Virtual, April 2021. [Published in: *Deutschen Zeitschrift für Sportmedizin*, 72 (3), S. 145]

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Figures and tables list

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List of abbreviations

ACC	anterior cingulate cortex
ACRM	American Congress of Rehabilitation Medicine
ADHD	attention deficit hyperactivity disorder
ANS	autonomic nervous system
BCT	Brain Connectivity Toolbox
BCTT/BCBT	Buffalo concussion treadmill (/bike) test
BDNF	brain-derived neurotrophic factor
BEM	Boundary Element Method
BFI	Brain Function Index
BNA	Brain Network Activation
BOLD	blood-oxygen-level dependent
CAN	central autonomic network
CI	Concussion Index
CISG	Concussion in Sports Group
CO_2	carbon dioxide
COVID-19	Coronavirus - 2019
CP	clustering coefficient
CT	computer tomography
CTE	chronic traumatic encephalography
CTRL	control group
DAI	diffuse axonal injury
DMN	default mode network
ECG	electrocardiogram
EDA	electrodermal activity
EEG	electroencephalography
ERP	event related potentials
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCS	Glascow coma scale
GE	global efficiency
GSR	Galvanic skin response
HF	high frequency
HR	heart rate
HRt	heart rate threshold
HRV	heart rate variability
ICA	Independent Component Analysis
IQR	interquartile range

LF	low frequency
LF/HF	low frequency to high frequency
LP	path length
maxHR	maximal heart rate
Mdn	median
MN	minimum norm
MRI	magnetic resonance imaging
mTBI	mild traumatic brain injury
NIRS	near-infrared spectroscopy
PCC	posterior cingulate cortex
PFC	pre-frontal cortex
PLV	phase locking value
PNS	parasympathetic nervous system
PPCS	prolonged (/persistent) post-concussive symptoms
qEEG	quantitative electroencephalography
RMSSD	root mean square of successive differences
ROI	regions of interest
RPE	rating of perceived exertion
RPM	revolutions per minute
RTS	return to sport
SCAT	Standardized Concussion Assessment Tool
SNS	sympathetic nervous system
SRC	sport-related concussion
SWI	small-world index
TBI	traumatic brain injury
TES	traumatic encephalography syndrome
VAS	visual analogue scale
VIS	visual network
VO_{2peak}	peak oxygen consumption
WB	whole brain

Note. alphabetical order

1 Introduction

"A lot of people think we're gladiators, but we're human beings. We get injured and we've got the rest of our lives to worry about.'' New York Jets offensive lineman Damien Woody

Sport-related concussion (SRC) has been referred to by some as a *silent epidemic* (Dewan et al., 2018; Giza et al., 2017). However, over the years this sport-related injury has gained increasing attention and awareness. There appears to be a collective concern for the potential long-term effects (i.e., mental health problems and neurological disease) of having a concussion history (Patricios et al., 2023). However, the magnitude of these risks is not well understood (Manley et al., 2017).

Each year an estimated 69 million individuals will suffer from traumatic brain injury (TBI), with the majority of cases being mild (81%), followed by moderate and severe (Dewan et al., 2018). Concussion, a mild form of traumatic brain injury, occurs in collision and contact sports at a high incidence rate (Prien et al., 2018). Of those athletes who sustain a mild traumatic brain injury (mTBI), some may never seek medical attention, so the previously mentioned numbers may be underrepresented. Even for those who do seek medical attention, concussion cases may be a challenging encounter for clinicians due to varied symptom expression (Kontos, Sufrinko, et al., 2019; Mucha & Trbovich, 2019), and lack of objective markers (Herring et al., 2021; McCrory et al., 2017).

A concussion occurs when a force is exerted onto the body or directly to the head, which causes the brain to shift within the skull (Barth et al., 2001). The acceleration and deceleration can cause a diffuse axonal injury (DAI), which affects particularly the white matter (i.e., axons), and is not detectable with conventional neuroimaging methods (Giza & Hovda, 2014). However, this pathology is assumed to be reflected in the overt signs and symptoms of a concussion (Giza & Hovda, 2014; Patricios et al., 2023). In pursuit of establishing objective markers to aid clinical decision-making, a greater understanding of how the pathophysiology of a concussion is expressed in the overt signs and symptoms is needed (Herring et al., 2021; Patricios et al., 2023). This will be elaborated on in the following section (*2.2.1 Patho-mechanisms/-physiology*).

In the past year, two high-impact papers were published in the field of SRC: (1) *The American Congress of Rehabilitation Medicine's* (ACRM) *Diagnostic Criteria for Mild Traumatic Brain Injury* (Silverberg et al., 2023), and (2) *The Concussion in Sports Group's (CISG) Consensus Statement on concussion in sport: the 6th International Conference on Concussion in Sport* (Patricios et al., 2023). The first provides diagnostic criteria through an operational definition of mTBI, while the second proposes a conceptual definition. A desired aim of the ACRM and CISG is to have a unified conceptual and operational definition for mTBI/SRC, to be used to inform clinical practice and reliably identify cases for research. Unfortunately, these definitions are limited when it comes to addressing clinical outcomes (e.g., typical vs. prolonged recovery).

Typical concussion cases experience spontaneous symptom resolution within the first few weeks after injury. In the past, it was common practice for a clinician to prescribe strict rest to an athlete, until their symptom resolved or returned to baseline (pre-injury) levels. But athletes who are exposed to strict rest are removed from the benefits of exercise and social interactions, which could result in concurrent disturbances (i.e., sleep disruptions and physical deconditioning) (Kontos et al., 2023). Now, with the new return to sport (RTS) strategy, clinicians are encouraged to prescribe gradual reintroduction of symptom-limited daily activities directly after injury. Followed by, the implementation of light, then moderate aerobic exercise (Leddy et al., 2023; Patricios et al., 2023). Importantly, this aerobic exercise should not exacerbate symptoms, more than mildly (i.e., more than 2 points on a 1 (no symptoms) – 10 (severe symptoms) point scale). In research, this type of exercise has been shown to speed up recovery (Leddy, Haider, Ellis, et al., 2019), and aid in the recovery of persisting post-concussion symptoms (PPCS) cases (Leddy, Haider, et al., 2018).

The emerging evidence that supports the use of aerobic exercise as a non-pharmaceutical means to aid in the recovery process, echoes the idea that *exercise is medicine* (Leddy, Haider, et al., 2018). The principle behind this concept is that the health care system should think of exercise as medication, which may be prescribed to patients (Sallis, 2009). As with medication, the dosage matters and should be based on the characteristics of the patient (Leddy, Haider, et al., 2018). Correspondingly, light to moderate intensity thresholds may be set by estimating the patient's predicted maximal heart rate (maxHR) and then calculating 55% of maxHR for light intensity exercise and 70% for moderate intensity (Patricios et al., 2023).

Although studies have suggested mechanisms for how aerobic exercise may promote recovery after a concussion (Leddy, Wilber, & Willer, 2018; Tan et al., 2014), there is a lack of research which thoroughly investigates these mechanisms. For that reason, the works included in this thesis particularly investigated athletes' neurophysiological response to moderate intensity exercise during their recovery process.

2 Current State of Research

"Over the past decade, there has been major progress in the methods for evaluation of sport-related concussion and in determining the natural history of clinical recovery after injury. Critical questions remain, however, about the acute neurobiological effects of SRC on brain structure and function, and the eventual time course of physiological recovery after injury."
(McCrea et al., 2017)

Over the past *two* decades, concussions in sport have gained increasing attention and awareness, in research and media coverage. Incidence rates have also been on the rise (Gardner et al., 2019). Although participation in sports appears to come with an inherent risk of injury (Roe et al., 2017), it is also associated with great health benefits. It is a challenge to equate the benefits against the possible risks (Giza et al., 2017).

As neuroscientific methods continue to develop, it affords an increasingly detailed investigation into brain structures and functions post-injury (Nathan W. Churchill et al., 2017; McCrea et al., 2017). Research using neuroscientific means has also demonstrated that physiological recovery proceeds clinical recovery (i.e., asymptomatic), which opens a critical question about the ultimate time course of recovery (McCrea et al., 2017). Clinically, there is great interest to establish markers that may compliment current concussion management strategies (Patricios et al., 2023; Silverberg et al., 2023). Beyond diagnostics, a marker which may support RTS decisions is highly sought after (Tabor et al., 2023).

Currently, the advisement of training load and progressions through the RTS strategy relies heavily on overt symptom expression (Patricios et al., 2023). Meanwhile, an underlying neurophysiological response to exercise continues to be proposed as a mechanism for recovery (Leddy, Haider, et al., 2018; Leddy, Wilber, & Willer, 2018; Tan et al., 2014). A relevant gap in research is the thorough investigation of neurophysiological response to RTS recommended exercise. This comprehensive chapter (*2 Current state of research*) will build a foundation with the current state of research for the experimental work which follows. In doing so, topics such as: (1) the pathophysiology of concussion, (2) recovery and rehabilitation strategies and (3) state of research on neurophysiological markers to guide RTS will be elucidated.

1.1 The Human Brain: Networks

Before exclusively detailing concussion related topics, a brief introduction to brain networks and network neuroscience follows. The conceptualization of the human brain as a complex network, both at the structural and functional level (Bassett & Sporns, 2017; Sporns, 2011) is pivotal to the experimental work. The brain as an interconnected system, relies on both functional *segregation*, and *integration* of information from different brain regions (Braun et al., 2001; Friston, 2011; Rubinov & Sporns, 2010). Functional segregation implies that the origin of a function stems from a particular cortical area, which is specialized to handle the perceptual or motor demands (Friston, 2011). The segregated cortical area may then involve other specialized areas, through functional integration to support more complex functions. There is growing evidence that segregation and integration of networks is altered in disease (Braun et al., 2001; Engels et al., 2015), and after brain injury (Hillary & Grafman, 2017).

2.1.1 Functional Networks

Previous works have identified numerous functional brain networks, each with their own specific patterns of neural communication and spatiotemporal interaction between regions (Bressler & Menon, 2010). One functional brain network – the default mode network (DMN), is hypothesized to play a significant role in intrinsic thought (Raichle, 2015), task-negative (resting-state) conditions (Dunkley et al., 2018), and task-switching facilitations (Dunkley et al., 2018).

Furthermore, studies which investigated this popular resting-state network, have discussed its potential role in health and disease (Hallquist & Hillary, 2019). For example, patient groups with neurological disorders commonly present increased functional connectivity within the DMN (Hillary et al., 2015). *Hyperconnectivity* therefore appears to be a fundamental response to neurological disease in brain networks (Hillary et al., 2015). The increased functional connectivity may exist to counter the neuropathology while maintaining behaviour. This response is not limited to neurological disease, but also has been reported as a response to acquired brain injury (Hillary & Grafman, 2017).

The following regions make up the DMN: orbital frontal cortex, medial prefrontal cortex/anterior cingulate cortex, lateral temporal cortex, inferior parietal lobe, posterior cingulate and para-/hippocampal cortex (Raichle, 2015) As the DMN sits centrally in the brain consisting of discrete, bilateral cortical areas (Raichle, 2015), it relies on white matter tracts for neural communication. This makes it particularly vulnerable to insult. After neurological disruption via. TBI there is an increased connectivity in the posterior cingulate cortex (PCC) (Sharp et al., 2014). While the response to mTBI is less clear. There have been reports of increased connectivity over the right pre-frontal cortex (PFC), with reduced connectivity in the parietooccipital region for mTBI patients less than 3 months post-injury (Virji-Babul et al., 2014), and reports of no significant connectivity differences in the DMN at 10 days after mTBI (Zhang et al., 2012). Both studies compared a patient group to a group of control athletes.

2.1.2 Network Neuroscience

Network neuroscience provides a powerful framework for gaining new insights into both healthy and pathological brain function characteristics. Networks neuroscience is derived from network science, which provides tools to examine and descriptively report network characteristics (Bassett & Sporns, 2017). Of interest in the field of neuroscience, are measures which relate to local and global connections of a network, echoing the significance of *segregation* and *integration* of information. Graph theory, a branch of mathematics which is used to explore properties of graphs (/networks), is perhaps most transferable to neuroscience (Bassett & Bullmore, 2017; Bassett & Sporns, 2017; Vecchio et al., 2017).

2.1.3 Graph Theory

In graph theory, networks are defined by a set of nodes and edges, and their interrelations (Bassett & Sporns, 2017; Stam et al., 2016). When defining a network in neuroscience, nodes and edges can be representative of neurons and axons on a microscopic scale, or cortical brain regions and their interrelations on a macroscale (Bassett & Bullmore, 2017; Bassett & Sporns, 2017). Human studies rely often on non-invasive techniques for data acquisition, resulting in networks constructed of cortical brain regions and their interrelations. Analyses may be conducted in binary or weighted form. Binary graphs increase the contract by applying a threshold which converts the continuous edge weights to either 1 (suprathreshold) or 0 (subthreshold) (Achard et al., 2006; Bassett & Bullmore, 2017). Binary networks tend to be simpler to characterize and more easily defined for statistical comparisons (Rubinov & Sporns, 2010). Weighted graphs, afford differentiation between stronger or weaker connections (Bassett & Bullmore, 2017), therefore may retain more relevant information appropriate to investigate the complexities of brain connectivity (Bassett & Bullmore, 2017). The decision to use binarized or weighted or both matrices is a critical discussion point.

Network neuroscience tends to reveal *nonrandom* graph topologies (Bassett & Sporns, 2017), also known as small-world network topologies (Bassett & Bullmore, 2017). This topology is said to represent efficient communication between different brain regions (Braun et al., 2001). To determine if a network has a small-world topology, two common graph measures: clustering coefficient (CP) and path length (LP), are calculated. CP is the probability of two neighbouring nodes, to be directly connected to each other (Bassett & Bullmore, 2017; Rubinov & Sporns, 2010; Watts & Strogatz, 1998). LP is the minimum number of edges needed to make a connection between two nodes (Watts & Strogatz, 1998), with shorter paths implying greater integration (Rubinov & Sporns, 2010). CP and LP are measures of functional segregation and integration, respectively. Small-world topology is expected in healthy brains, by exhibiting efficient communication on both a local (segregated) and global (integrated) level (Bassett & Bullmore, 2017; Braun et al., 2001). To depict this, the Watts-Strogatz model begins with a lattice network, where each node is connected to it's nearest neighbour, and goes along till the network is random (Bassett & Sporns, 2017; Watts & Strogatz, 1998). In the middle of lattice and random is small-world topology.

Departure of brain networks from a small-world topology has been shown in neurological patients (Braun et al., 2001; Fornito et al., 2015; Hallquist & Hillary, 2019; Hillary et al., 2015; Vecchio et al., 2017), and after brain injury (Hillary & Grafman, 2017; Imms et al., 2019). In TBI patients there are reports of longer LP (Cao & Slobounov, 2010; Imms et al., 2019; Sharp et al., 2014), which may imply that a detour is taken. This is likely a compensatory mechanism, taken to get around disconnection caused by TBI (Hillary & Grafman, 2017). Graph theory, therefore, may be a unique and powerful tool which reflects the neuropathology of TBI.

1.2 Definition (mild) Traumatic Brain Injury & Concussion

Concussions are a form of mTBI (Mayer et al., 2017). However, as a diagnostic label, *concussion* may be used interchangeably with mTBI (Silverberg et al., 2023). Still, in this text the label used will represent that of the source. This term *mild* exists because TBIs present on a spectrum, ranging from mild, to moderate, and severe. The diagnosis criterion for each is based on the Glasgow coma scale (GCS: Table 1) and conventional neuroimaging techniques. What constitutes as moderate to serve TBI, is a GCS score less than 13 (3 to 8 for severe, and 9 to 12 for moderate) and the presence of structural damage visible on computed tomography (CT) or magnetic resonance imaging (MRI) scans. Mild injuries are diagnosed by a GCS score greater than 13 (to a maximum achievable score on the scale of 15), and an absence of evidence for structural injury on conventional neuroimaging scans. Without the clinical presence of structural damage, an mTBI/concussion is defined as a rather functional injury (McCrory et al., 2017).

Table 1 *Glasgow Coma Scale*

Behaviour	Response	Score
Best eye response	Spontaneously To speech To pain No response	4 3 2 1
Best verbal response	Oriented to time, place and person Confused Inappropriate words Incomprehensiable sounds No response	5 4 3 2 1
Best motor response	Obeys commands Moves to localized pain Flexion withdrawal from pain Abnormal flexion (decorticate) Abnormal extension (decerebrate) No response	6 5 4 3 2 1
Total score:	*Best response* *Comatose client* *Totally unresponsive*	15 8 or less 3

To establish a unified operational and conceptual definition of mTBI and SRC, the ACRM and CISG respectively each published a high-impact paper (Patricios et al., 2023; Silverberg et al., 2023). These definitions are meant to inform clinical practice and uniformly identify cases for research. Operationally, there exists specific criteria which must be met to diagnose mTBI. The first criterion dictates that a biomechanically plausible mechanism for injury exists, followed by the presentation of one or more clinical signs, at least two acute symptoms, and at least one clinical finding attributable to brain injury (Silverberg et al., 2023). Conceptually, SRC is a TBI that is caused by a direct blow to the head or elsewhere to the body, resulting in an impulsive force transmitted to the brain. The force initiates a neurotransmitter and metabolic cascade, with a possible axonal injury (Patricios et al., 2023). SRC results in a range of signs and symptoms that present immediately post-injury or evolve over time, followed by spontaneous symptom resolution within days, or prolonged recovery (Patricios et al., 2023).

1.2.1 Patho- mechanisms /-physiology

Initiated by a force exerted onto the head or elsewhere on the body, this force transmits to the brain causing it to accelerate (or decelerate), and revolve within the skull (Barth et al., 2001). While the human brain is fastened within the skull, upon impact inertia is distorted – changing the object's speed or direction. Simulations of the linear versus rotational forces have demonstrated that the linear acceleration causes little deformation, while the rotational acceleration induces distortion (Noble & Hesdorffer, 2013). Therefore, the rotational forces are likely to have the greatest impact on the pathology.

A resulting DAI proves that axons are particularly vulnerable to these biomechanical forces (Giza & Hovda, 2014). Post-mortem investigations into the DAI described pathological damage to the white matter, corpus callosum and brain stem (Adams et al., 1989). DAI appears to induce microhemorrahages, disconnection, mechanoporation, stretching and beading of axons, and disruptions of axonal transport (Giza & Hovda, 2014). The diffuse nature of this injury leads to the disruption of functional brain networks, making it difficult to localize, and contributing to the heterogeneity of patients' clinical presentations (Kutcher & Giza, 2014).

The new *neurometabolic cascade*, attempts to further make sense of the underlying pathophysiology of a concussion, and how this is linked to the clinical characteristics (Giza & Hovda, 2014). At this time, much research on this topic stems from animal models for TBI/mTBI, as it is not possible to conduct concussion inducing experiments on humans. The acute pathophysiology, initiated by biomechanical force is characterized by an intracellular efflux of potassium and influx of calcium concentrations along with hyperacute increased release of glutamate. The ionic influx appears also in migraine cases, coined as a spreading depression (Charles, 2018). This may explain why headache is a commonly reported symptom after a concussion (Register-Mihalik et al., 2018). Efforts are then made to restore homeostasis, and cause hyperglycolysis - defined as an increase in glucose consumption (Bergsneider et al., 1997). Coupled with a reduced cerebral blood flow post-injury, the mismatch between the energy supply and demand worsens an energy crisis (Giza & Hovda, 2014). Identifying the duration of metabolic vulnerability is a challenge, with practical implications. Research indicates that a repeat injury during this period of vulnerability has significant consequences on the pathophysiology and recovery time (Vagnozzi et al., 2008). This supports the current recommendation to immediately remove an athlete from play (or practice) even if there is suspicion of a concussive injury. This action of immediate removal is intended to remove the risk of further potential injury (Patricios et al., 2023).

1.3 Rest & Exercise

After an athlete is removed from play, commences a series of clinical assessments. The results of the post-injury assessments are then used to inform clinical concussion management decisions. Such as, deciding when an athlete is ready to begin their RTS progressions, and when an athlete is ready to return to unrestricted sports participation. This is what will be elaborated on in the following sections.

1.3.1 Acute to Subacute Phase Post-injury

Removal of a player from the field is meant to avoid subsequent injury, as well as provide the health care professional with the opportunity to conduct an office assessment (Patricios et al., 2023). Actual or suspected loss of consciousness, seizure, tonic posturing, ataxia, poor balance, confusion, behavioural change and amnesia are signs which warrant immediate removal from the field (Echemendia, Burma et al., 2023). Once removed, the Standardized Concussion Assessment Tool (SCAT) now in it’s 6th Edition (Echemendia, Brett, et al., 2023), can be used to conduct a multimodal evaluation of the athlete’s current status. The SCAT contains multiple relevant domains of assessment, such as: consciousness, memory, symptoms, cognition, balance, and cervical spine. The received information is valid acutely post-injury (within 72 hours) and briefly beyond (up to 5-7 days) to make a probable diagnosis. Beyond aiding in probable diagnosis, only the symptom checklist from the SCAT has demonstrated clinical utility in tracking recovery and may be used to inform RTS decisions (Echemendia et al., 2017).

Typical concussion cases tend to experience spontaneous symptom resolution within the first few weeks after injury, for adults this is around 14 days post-injury (Harmon et al., 2019; McCrory et al., 2017). In the past, it was common practice for a clinician to prescribe strict rest to an athlete, until their symptoms resolved. However, athletes who are prescribed strict rest are removed from the benefits of exercise and social interactions, which could result in concurrent disturbances (i.e., sleep disruptions and physical deconditioning) (Kontos et al., 2023). C*ocoon therapy* (i.e., strict rest) is no longer recommended and clinicians are now recommending a more active approach to recovery (Leddy et al., 2023; Leddy, Haider, et al., 2018; Leddy, Wilber, & Willer, 2018). Studies from the past, mostly from animal research, suggested that rest be beneficial to allow the brain to recover from the acute metabolic crisis of concussion (Leddy, Wilber, & Willer, 2018). In humans, rest was also reported to prevent the risk of subsequent injury and worsening of symptoms (Giza & Hovda, 2014). However, prolonged periods of strict rest, result in physical deconditioning (Tan et al., 2014) and negative post-injury behaviours (Kontos et al., 2023). Negative post-injury behaviours may include: bad sleep hygiene and reduced social and sport interactions (by not attending school or practices) post-injury, which may in turn exacerbate affective symptoms (Kontos et al., 2023). The evolving evidence from pilot studies and clinical trials (Haider, Leddy, et al., 2019; Leddy, Haider, Ellis, et al., 2019; Leddy, Haider, Hinds, et al., 2019) continuously reveal the benefits of initiation of exercise during the recovery process. It appears to be both appropriate and necessary to prescribe an active approach to SRC recovery. An active approach has additionally been shown to reduce the risk for prolonged symptoms and reduce the negative consequences strict rest may have on an athlete's athletic, academic, and vocational performance (Leddy, Wilber, & Willer, 2018).

1.3.2 Physical Activity and Exercise

After a short period of relative rest (i.e., symptom-limited daily activities), an athlete is to initiate their RTS process (Patricios et al., 2023). The CISG, in their latest consensus statement, provides a step-by-step strategy (Table 2) to incrementally increase intensity and demands, with the goal to integrate an athlete back to unrestricted sports participation in a safe and timely manner (Patricios et al., 2023). How and when the athlete makes progressions through the steps is heavily based on their symptom expression at rest and in response to exercise. Noteworthy, each step should typically take a minimum of 24 hours, and no more than a mild symptom exacerbation (i.e., more than 2 points on a 10-point scale) should be present during the last lowest stage achieved (Patricios et al., 2023).

Table 2 *Return-to-sport (RTS) strategy*

Step	Exercise strategy	Activity at each step	Goal
1	Symptom-limited activity	Daily activities that do not exacerbate symptoms (e.g., walking)	Gradual reintroduction of work/school
2	Aerobic exercise **2A – light** (up to approximately 55% maxHR) then **2B – moderate** (up to approximately 70% maxHR)	Stationary cycling or walking at slow to medium pace. May start light resistance training that does not result in more than mild or brief exacerbation* of concussion symptoms	Increase heart rate
3	Individual sport-specific exercise Note: if sport-specific training involves any risk of inadvertent head impacts, medical clearance should occur prior to Step 3	Sport-specific training away from the team environment (e.g., running, change of direction and/or individual training drills away from the team environment.) No activity at risk of head impact.	Add movement, change of direction
Steps 4-6 should begin after the resolution of any symptoms, abnormalities in cognitive function and any other clinical findings related to the current concussion, including with and after physical exertion.			

4	Non-contact training drills	Exercise to high intensity including more challenging training drills (e.g., passing drills, multiplayer training) can integrate intro a team environment	Resume usual intensity of exercise, coordination and increased thinking
5	Full contact practice	Participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6	Return to sport	Normal game play	

*Mild and brief exacerbation of symptoms (i.e., an increase of no more than 2 points on a 0–10 point scale for less than an hour when compared with the baseline value reported prior to physical activity). Athletes may begin Step 1 (i.e., symptom--limited activity) within 24 hours of injury, with progression through each subsequent step typically taking a minimum of 24 hours. If more than mild exacerbation of symptoms (i.e., more than 2 points on a 0–10 scale) occurs during Steps 1–3, the athlete should stop and attempt to exercise the next day. Athletes experiencing concussion--related symptoms during Steps 4–6 should return to Step 3 to establish full resolution of symptoms with exertion before engaging in at--risk activities. Written determination of readiness to RTS should be provided by a healthcare professional before unrestricted RTS as directed by local laws and/or sporting regulations.

Note. adapted from Concussion in Sports Group (Patricios et al., 2023) consensus statement.

The emerging evidence that supports the use of exercise as a non-pharmaceutical means to aid in the recovery process, echoes the idea that *exercise is medicine* (Leddy, Haider, et al., 2018). The principle behind this concept is that the healthcare system should think of exercise as medication, which may be prescribed to patients (Sallis, 2009). As with medication, the dosage matters and should be prescribed considering relevant characteristics of the patient (Leddy, Haider, et al., 2018). Correspondingly, light to moderate intensity thresholds may be set by estimating the patient's age predicted maxHR and then calculating 55% of maxHR for light intensity and 70% for moderate intensity (Patricios et al., 2023). Clinicians with access to exercise testing may safely prescribe aerobic exercise of a greater intensity, based on 90% of the individual's heart rate (HR) threshold (HRt), uncovered by taking the maximum HR achieved on an exercise test, at which point more than mild symptom exacerbation occurred (Leddy et al., 2023).

Results from clinical studies have reported the benefits of participation in aerobic exercise after a concussion, such that it appears to speed up recovery, which may in turn reduce the risk for delayed recovery (Leddy, Haider, Ellis, et al., 2019; Leddy, Haider, Hinds, et al., 2019). In one study, adolescent male athletes were recruited within 10 days post-injury and were assigned to either an aerobic exercise intervention group or relative rest prescription (Leddy, Haider, Hinds, et al., 2019). Recovery times, defined as the return to baseline symptoms, exercise tolerance and/or as judged by physician examination, were significantly shorter in the aerobic exercise group. With an average recovery time of 8 days. Furthermore, no patient in the aerobic exercise group experienced delayed recovery, identified as more than 30 days to recover. The relative rest group recovered on average in 24 days, and 4(/30) participants in this group experienced delayed recovery. This study suggests that early participation in aerobic exercise speeds recovery and reduces the number of patients who experience prolonged recovery. In another study, patients who were recruited within the first 10 days after a concussion, were assigned to an aerobic exercise intervention or stretching intervention (Leddy, Haider, Hinds, et al., 2019). Those who took part in the aerobic exercise intervention recovered within a median of 13 days. Of the 52 participants participating in the aerobic exercise intervention, 50 had recovered by 30 days post-injury. In this study, aerobic exercise was shown to improve recovery, more so than a placebo-like stretching intervention ($p = 0.048$).

Physical activity participation, more generally via. self-reports and trackers, was also associated with a faster recovery (Coslick et al., 2020; Rademacher et al., 2023; Seehusen et al., 2021). Through self-reports, physical activity participation was categorized as the following: 0 = none other than daily activities, 1 = light exercise, including walking, 2 = moderate exercise, which increases their heart rate, 3 = heavy exercise, including participation in sport specific drills without contact, 4 = introducing contact activity in a somewhat controlled setting, and 5 = full participation in competition (Coslick et al., 2020). This study showed that moderate levels of physical activity participation prior to and following a concussion, elicited a more rapid recovery (i.e., return to sport). A limitation of the previously mentioned study was the use of self-reports. To overcome this limitation trackers may be used to objectively measure physical activity participation. A study which investigated 32 adolescent athletes with a recent concussion history (within 14 days) quantified steps per day and exercise frequency, duration and intensity (Seehusen et al., 2021). The group which took longer to recover (≥ 28 days) had significantly fewer steps per day, than to the group who recovered less then 28 days post-injury (8,158 vs. 11,147 steps per day; $p = 0.02$). The median step count for those who recovered less than 28 days was approximately 11,000 steps/day, while the group who took longer to recover had only, on average 6,600 steps/day. Note that this number is well below the reported normative value of 12,000 to 16,000 steps/day (Tudor-Locke et al., 2011). The group which experienced a longer recovery (≥ 28 days) also had fewer total minutes of exercise participation per week (117 vs. 219 minutes; $p = 0.01$), however, there was no significant group difference for the intensity of exercise, as measured by average HR (p = 0.796) and peak HR (p = 0.383). Using a wrist-worn sensor, physical activity intensity may be categorized based on the individual's age-predicted maxHR. In a later cohort study, 54 participants were instructed to wear an activity tracking sensor for one week (Rademacher et al., 2023). Physical activity data was categorized in the following 3 zones: sedentary – below 50% of maxHR, light – 50-60% of maxHR, and moderate to vigorous physical activity – 70 – 100% of maxHR. Results showed that more time in moderate to vigorous physical activity zones was associated with faster symptom resolution. Specifically, engaging in more than 30 minutes per day was associated with a sooner time to symptom resolution (21 ±16 days vs. 42 ±30 days). This is an evolving field of research, and future studies should continue to explore the effect that frequency, duration and intensity of physical activity participation has on concussion recovery.

When discussing the benefits of physical activity and exercise participation, as it relates to concussion recovery, it is appropriate to explore what may be going on in the brain of healthy individuals and post-injury patients. The benefits that *moderate* aerobic exercise has on brain function post-brain injury have not yet been thoroughly explored in humans. However, the outward consequence of faster recovery, and reduced incidence of delayed recovery, suggest that some adaptive biological processes occur. For example, aerobic exercise stimulates the release of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF). BDNF plays a vital role in promoting neural plasticity and neurogenesis (Di Liegro et al., 2019), by this means aiding in the brain's recovery post-injury (Roig et al., 2013). Furthermore, participation in physical activity improves cerebral vascular control, which appears to be altered due to brain injury (Tan et al., 2014). Thereby, using *mild to moderate* exercise to increase the demand for oxygen to the brain, in turn, increases cerebral blood flow (Tan et al., 2014). Exercise at this intensity, therefore targets a response that compensates for the pathology of brain injury (e.g., reduced cerebral blood flow (Giza & Hovda, 2014)).

To assess cerebrovascular response and symptom burden during exercise, 40 concussed patients were evaluated within 3 weeks post-injury, compared to 37 controls (Howell et al., 2021). At rest, there was a moderate statistically significant relationship between cerebrovascular response and carbon dioxide (CO_2) levels for the patient group (p = 0.01), which did not exist for the control group (p = 0.21). Furthermore, the patient group had a change in CO_2 (as measured by fraction of end-tidal CO_2), which significantly correlated with cerebral blood flow velocity during exercise ($p < 0.01$). Change in CO_2 in the patient group also significantly contributed to symptom exacerbation on the exercise test ($p < 0.05$). The increase in CO_2 levels (i.e., vasoactivity), may be the basis for the exercised-induced symptom exacerbation after a concussion (Howell et al., 2021), and may be used to inform exercise interventions.

In a prospective experimental study, cerebral blood flow velocity was associated with a limited exercise tolerance, which resolved after exercise intervention (Clausen et al., 2016). Nine female athletes, who were on average 9 weeks post-injury, were compared to 13 matched-control athletes. Cerebral blood flow velocity was measured during a treadmill test at baseline (pre-intervention) and every 3-weeks until symptoms no longer exacerbated on the treadmill test for the patient group. Controls were only measured once, as it was assumed their data should not change significantly while keeping with their regular training. Six of the 9 patients completed the 12-week aerobic exercise intervention. The aerobic exercise was performed for 20 minutes per day, 5 to 6 days per week, working at a threshold of 80% of their maxHR achieved on the initial treadmill test. Pre-intervention, patients had significantly higher cerebral blood flow velocity during exercise, than controls ($p \leq 0.05$). Post-intervention cerebral blood flow was significantly lower than pre-intervention measures ($p \leq 0.05$).

The effects of physical activity and exercise participation on the pathology of a concussive injury (i.e., DAI) are still largely unknown (Tan et al., 2014). However, given the influence of exercise on cerebral blood flow, and reports of physical activity participation enhancing recovery, the benefits of prescribing an active recovery (vs. rest) strategy are evident.

1.3.3 Prolonged Recovery

Although the majority of concussion patients experience spontaneous symptom resolution, and/or successfully return to sport within two weeks from injury (McCrory et al., 2017), these cases tend to be single, uncomplicated cases (Rohling et al., 2012). There exists a subpopulation, deemed the *miserable minority,* who experience persisting symptoms beyond typical recovery trajectories (Rohling et al., 2012). It is not fully understood why some cases do not recover in the typical trajectory; however, many possible confounding factors have been presented. In one study, with 294 patients, simply having a history of a previous concussion was associated with a higher risk for delayed recovery, with symptoms lasting more than 28 days ($p = 0.006$) (Miller et al., 2016). In another study, with 531 patients from youth to adults (age 7 to 26), a higher initial symptom burden was associated with longer lasting symptoms (Meehan et al., 2014). While majority (86%) of patients with a low initial symptom score < 13, experienced symptom resolutions within 28 days post-injury. Further risk factors for prolonged recovery included pre-existing conditions, such as: attention deficit hyperactivity disorder (ADHD) (Miller et al., 2016) and migraines (Kontos, Elbin, et al., 2019), as well as being of the female sex (Kontos, Elbin, et al., 2019; Miller et al., 2016). With this in mind, not only concussion history, but also characteristics about the patient are imperative to making concussion prognosis predictions.

Formerly known as post-concussion syndrome (Hiploylee et al., 2017), prolonged recovery is more commonly now called *prolonged (/persisting) post-concussive symptoms* (PPCS). PPCS is the nomenclature used to label cases where recovery exceeds 3 months. PPCS could result from single case mTBI, complicated mTBI or repetitive head impacts (Mayer et al., 2017). As multiple factors may simultaneously contribute to PPCS, multimodal assessments leading to multimodal treatment is recommended (Mayer et al., 2017). Assessments may include vestibular, oculomotor, psychological, sleep, cervical and autonomic nervous system evaluations (Harmon et al., 2019). The results from the assessments are used to recognize the *clinical domain /profiles* of the patients (Harmon et al., 2019). Although these profiles may also be used to recognize the complexity of a concussion at diagnosis, they are particularly valuable for identifying complexities in persisting symptom cases (Harmon et al., 2019). Briefly, as an example, an athlete who presents with migraine/headache symptoms should have a physical exam which checks for occipital and neck tenderness, as well as for tight neck muscles. This is because the underlying cause of the headache symptoms may be a cervical dysfunction. If this is the case, the prescribed treatment should align with the athlete's profile (in this case, migraine/headache). Treatment may therefore consist of manual therapy to attend to the tenderness. Of note, the above example is an oversimplification for explanatory purposes, as many patients will present in overlapping profiles, and require multiple interventions provided by a multidisciplinary team with specific expertise (Harmon et al., 2019). This is something to consider.

Targeted interventions post-injury evidently facilitate recovery (Schneider et al., 2023; Schneider et al., 2014). In a randomized controlled trial, 31 patients post-concussion with persisting dizziness, neck pain and/or headache symptoms were assigned to an intervention group or control (Schneider et al., 2014). Both groups received once weekly physiotherapy, where they performed range of motion exercises, stretching and postural exercises (i.e., considered the standard of care). The intervention group additionally received cervical spine physiotherapy and vestibular rehabilitation for 8 weeks. A greater proportion of patients treated with the cervical spine physiotherapy were medically cleared to RTS following the 8-week intervention, than from the control group ($p = 0.002$).

Aerobic exercise intervention for PPCS cases also appears to be beneficial (Mercier et al., 2020; Schneider et al., 2023). The justification for aerobic exercise intervention stems from previous studies with non-concussed patients reporting that exercise intervention reduces headache frequency, fatigue, improves mental health, cognition and sleep (Mercier et al., 2020). Since the former listed symptoms often appear in PPCS cases, exercise interventions prescribed to these patients should lead to symptom reduction and support recovery (Mercier et al., 2020). In an outpatient research setting, 33 adolescents (ages 12 to 17 years old), who had sustained an mTBI and were still symptomatic 4 to 16 weeks post-injury, were randomly assigned to an aerobic exercise program or stretching program (Kurowski et al., 2017). There was a significant group by time interaction for self-reported symptoms ($p = 0.044$). Translating to a greater improvement (i.e., reduction in symptoms) with the aerobic exercise intervention, than stretching. Nevertheless, both groups did demonstrate improvements from baseline, indicating that stretching and low intensity activity may still elicit benefits. At this time studies investigating aerobic exercise intervention as an effective treatment for adults with PPCS are limited, but it appears research is underway, with study protocols published (Mercier et al., 2020; Sullivan et al., 2018).

Beyond the miserable minority and prolonged recovery, there is a collective concern for the potential long-term (/chronic) effects of concussion (Patricios et al., 2023; Prien et al., 2018). Although, the magnitude of the risk for long-term effects is not well understood (Izzy et al., 2021; Manley et al., 2017; McKee et al., 2009). A retrospective cohort study of 9205 adult patients with concussion history, matched with non-concussion controls, was conducted to assess the risk for chronic medical diagnoses in patients with and without concussion history (Izzy et al., 2021). During the up to 10 years follow-up, there was a significantly higher risk for developing cardiovascular hypertension, obesity, and diabetes mellitus for those with a concussion history. For psychiatric and neurological risks, there was an increased risk for depression, psychosis, stroke and epilepsy. The same group of researchers a year later published a study which assessed risk for chronic medical diagnosis, this time in patients with mTBI, or moderate to severe TBI, compared to controls (Izzy et al., 2022). Similar results were presented, such that there was an increased risk for hypertension, diabetes, and ischemic stroke or transient ischemic in the groups exposed to TBI – mild or moderate to severe, compared to controls. As a next step, further investigations are needed to understand the causality or directionality of these risks. In turn, this may be used to advise screening and preventative programs (Izzy et al., 2022).

Additionally and almost exclusively in the context of sports, there is a possible risk for developing traumatic encephalography syndrome (TES) and the associated neuropathologically diagnosed chronic traumatic encephalopathy (CTE) (Katz et al., 2021), after receiving multiple concussive impacts. Mechanisms for CTE, mimic that of the pathophysiology of a concussion and DAI. Such that, rotational acceleration and deceleration forces, leads to the shearing of axons at time of injury, and a series of changes thereafter (McKee et al., 2009). However, not exclusively concussion history contributes to these diagnoses, instead substantial exposure to repetitive head impacts is required (Katz et al., 2021). Still, worth mentioning as much attention and concern for long-term effects is directed at CTE. This progressive neurodegeneration may present as clinical features in the cognitive domain (e.g., episodic memory), as behavioural and personality changes, psychiatric disorders, and/or motor problems (Katz et al., 2021; McKee et al., 2009). Guidelines for prevention have proposed that the easiest way to reduce incidence rates of CTE is to limit the number of concussions and exposure to head impacts (McKee et al., 2009). This includes but is not limited to immediate removal from play in the case of a suspected concussion.

Attending to the idea of prevention - one of the emphasized topics of the CISG (Patricios et al., 2023), policy and rule changes have been enforced which limit the number and duration of impacts in training and competition (Eliason et al., 2023). Furthermore, concussion management strategies highlight the importance of recognition followed by immediate removal of an athlete from the field to limit secondary injuries (Echemendia, Burma, et al., 2023). A more complex prevention strategy may reduce premature return to *unrestricted* sport and/or competition. With this in mind, the next section highlights the importance of understanding physiological SRC recovery.

1.4 Physiological Recovery

Physiological recovery appears to exceed that of clinical recovery (i.e., asymptomatic or symptom resolution) (Kamins et al., 2017). However, limiting consensus is the heterogeneity of the modalities and markers used to track physiological recovery. There is evidence that a reduced cerebral blood flow, persists beyond time of clinical recovery (Kamins et al., 2017; Meier et al., 2015). In a cohort of 44 collegiate football athletes, 17 sustained a concussion and were assessed approximately 1-day, 1-week and 1-month post-injury (Meier et al., 2015). Although neuropsychiatric symptoms may resolve by 1-week, serial analysis showed that cerebral blood flow within the patient group was significantly lower at 1-day and 1-week, compared to 1-month post-injury ($p < 0.001$). Although it exceeds symptom resolution, a decreased cerebral blood flow appears to normalize 1-month post-injury. When comparing patient datasets to the control group, the significantly lower cerebral blood flow, which existed 1-week post-injury ($p = 0.05$), was no longer statistically significant 1-month post-injury ($p = 0.86$). This mirrors the neurometabolic cascade of a concussion (Giza & Hovda, 2014), which was discussed earlier (*2.2.1 Patho- mechanisms /-physiology*).

1.4.1 Electrophysiological Investigations

Electrophysiological investigations, through means of electroencephalography (EEG), have revealed various event-related potentials (ERP) and EEG markers that present acutely post-injury or persist chronically. In a study with the aim to better understand the association between brain function and time since injury, symptoms and working memory, 45 patients with mTBI and 40 controls were recruited (Gosselin et al., 2012). For the association analysis, the N350 and P300 ERP components were selected. N350 amplitude (more negative) was associated with time since injury ($r = -.31$, $p = 0.006$). The mTBI patient group had a significantly smaller amplitude for P300, compared to controls ($p < 0.01$). Additionally, P300 amplitude in the mTBI group was associated with depression symptoms ($r = -0.31$, $p = 0.006$), and worse performance (slower reaction time ($r = -0.41$) and lower accuracy ($r = 0.34$)) on a working memory task ($p < 0.05$). Although no association was found between P300 and time since injury, this component due to it’s sensitively to general cerebral dysfunction (Polich, 2004), may particularly elucidate the pathophysiology of injury and related cognitive deficits. Consequently, P300 is the most commonly studied component in the field of SRC (Tabor et al., 2023). However, further investigations are needed. In a different study, using an independently developed quantitative EEG (qEEG) discriminant for mTBI, 59 high school American football athletes who sustained a concussion, were compared to 31 non-injured matched control athletes. Using this qEEG discriminate, statistically significant group differences were reported at time of injury ($p < 0.001$) and 8 days post-injury ($p = 0.008$) (Barr et al., 2012). Interestingly, group differences for post-concussion symptoms only existed at time of injury, not 8 days post-injury. At 45 days after injury, there was no statistically significant differences between groups for symptoms, nor for the qEEG discriminant score ($p = 0.15$). These findings reveal a physiological recovery which exceeds post-concussion symptoms resolution.

Brain Network Activation (BNA), derived from EEG recordings, indexes temporal and spatial changes in brain activity, as well as brain network functional connectivity (Eckner et al., 2016; Kiefer et al., 2015; Reches et al., 2017). In a case study, involving a high school hockey player EEG measurements were obtained at baseline (pre-season), at injury (within 18 hours), for landmarks at return to learn (3 days post-injury) and return to play (8 days post-injury), plus three additional follow-up time points (21 days, 50 days, and 116 days) (Kiefer et al., 2015). At the initial post-injury visit there was a decreased amplitude of the ERPs and a decreased BNA score, which was still evident at 21 days post-injury. Despite having returned to learn and sport by day 8 post-injury, physiological alterations were still detected 21 days post-injury. The amplitude of ERPs and BNA composite score returned to baseline values by the later two follow-up time points (50 days and 116 days). Another study using BNA, with a greater sample of 86 athletes with a concussion, compared to 81 controls, assessed the clinical utility of BNA in SRC management (Reches et al., 2017). Initial evaluations of the patient group were performed between 2-10 days after injury (mean: 3.7 days). The follow-up visit was either approximately one week after the initial visit, or when the subject was asymptomatic. Results showed that symptom scores were higher for the SRC patient group than the control group at both visits ($p < 0.0001$). Within the SRC patient group, the symptom score was significantly higher at the initial visit vs. follow-up ($p < 0.0001$). Additionally, there was a significant difference for BNA score between SRC patients and the control group at initial visit ($p < 0.05$), which did not exist at the follow-up visit. BNA scores may have the potential to elucidate brain function and therefore physiological recovery after SRC, but before it is introduced into clinical practice further clinical trials are needed.

An EEG feasibility study, exposed 9 student athletes with a history of mTBI who were cleared to begin their RTS process, and 9 age-matched controls to a progressive moderate intensity (70% maxHR) bike test (Gay et al., 2015). At baseline (pre-exercise), groups exhibited similar measures of absolute power across frequency bands. During the bike test, no athlete experienced symptom exacerbation, and all were able to reach the intensity (70% maxHR) goal. Statistical analysis revealed significant differences in alpha ($p = 0.001$), beta ($p = 0.004$), delta ($p = 0.002$), and theta ($p = 0.000$) power between groups *X* condition (mTBI vs. controls and pre- to post-bike tests). Previous studies, with healthy individuals have also revealed increases in power after exercise (Schneider et al., 2010), which indicates that exercise appears to affect brain function. More specifically, a higher absolute power particularly in the theta band may evolve from injury and pathophysiological changes, as an elevated theta power has been repeatedly reported in TBI research (Montgomery et al., 1991). Taking a different perspective, the elevated power brought on by exposure to physical stress may depict an adaptive physiological response (Gay et al., 2015).

Although electrophysiological investigations continue to report altered brain function beyond symptom resolution, consensus is limited due to inconsistencies of methods and results. Future greater studies are warranted in this field, which carefully consider EEG guidelines (e.g., American Clinical Neurophysiology Society Guidelines (Acharya et al., 2016)) to limit inconsistencies and strengthen cross-study comparisons.

2.4.2 Autonomic Nervous System

Physiological alternations post-concussion injury have been reported and discussed within the autonomic nervous system (ANS) (Esterov & Greenwald, 2017; Mercier et al., 2022; Pertab et al., 2018; Purkayastha et al., 2019). Although this injury occurs centrally - by definition in the brain, the alterations within the ANS often are studied peripherally. Briefly, the ANS embraces two branches, the sympathetic (SNS) branch - also referred to as the fight-flight response and the parasympathetic (PNS) branch - which encompasses the rest-digest aspect (Waheed & Vizzard, 2023). The ANS plays a vital role in regulating many physiological processes, such as regulating blood pressure, HR and cerebral blood flow (Pertab et al., 2018). Heart rate variability (HRV), estimated from beat-to-beat changes in HR, permits non-invasive insights into ANS function and recovery in healthy athletes (Aubert et al., 2003).

A case-control repeated measures study recruited 52 university athletes, 26 with a concussion and 26 controls (Hutchison et al., 2017). Physiological measures of HRV were collected, along with psychological measures of stress (via. questionnaires) at three different time points indicative of recovery milestones. The time points were as follows: (1) taken within 1-week post-injury (symptomatic phase), (2) after resolution of symptoms and the start of RTS (exercise progression phase), (3) 1-week after medical clearance of return to play. At the initial visit, concussed athletes had greater symptom scores than the controls. At this time point, not only were symptoms worse for this concussed group but also psychological scores for sleep quality and mood scales. By time point 2 (exercise progression) only symptoms were significantly higher for the concussed group. With-in group analyses revealed a statistically significant decline in symptoms for the concussed athletes from the symptomatic phase (mean group symptom score ± standard deviation: 23 ±8), to the start of RTS (7 ±8), to 1-week post return to play (3 ±4). In fact, from time point 1 to 3 there was a significant improvement in all self-report scales for the concussion group. Physiologically, RR intervals (i.e., intervals between successive heartbeats) were significantly lower for concussed athletes at all three time points, compared to controls. LF/HF (low frequency to high frequency) ratio was greater for the concussed athletes than the controls even after return to play. These results point to a suppression of HRV for the concussed group, which exceeds that of symptom resolution.

In another study, 11 athletes with a concussion history were recruited alongside 11 matched uninjured teammates, to examine if concussed athletes exhibit differences in HRV values compared to controls (Senthinathan et al., 2017). Post-concussed athletes were evaluated at the same three distinct time points as described above (Hutchison et al., 2017). Using HR monitors, datasets were collected in seated resting condition. Analysis in the frequency domain of HRV revealed a group *X* phase interaction ($p = 0.03$) for the low frequency (LF) band, which is presumed to reflect the baroreceptor activity and sympathetic activity (Aubert et al., 2003). For the high frequency (HF) band, supposed to be an indicator of parasympathetic activation (Aubert et al., 2003), a group *X* phase interaction ($p = 0.03$) also existed. Investigation into the LF/HF ratio, which allegedly represents sympathovagal balance (Gall et al., 2004), revealed elevated values for the concussion group at the initial visit, which declined at RTS initiation and 1-week after return to play. Many HRV measures showed a greater change between initiation of RTS and 1-week after return to play, than within 1 week since injury and symptom resolution. This may indicate that concussed athletes are back to participating in activities before they are physiologically recovered – visit 1 to 2. It may also suggest that initiation of these activities facilitates an athlete's recovery – visit 2 to 3 (Senthinathan et al., 2017).

When it is true that physiological recovery exceeds that of clinical recovery, simply monitoring post-concussion symptoms to inform RTS decisions seems subpar. There is an apparent need for the identification and establishment of objective markers which may inform RTS decision-making (Tabor et al., 2023). In the next section and corresponding paper, the clinical utility of a few neurophysiological markers will be discussed with respect to their suitability in guiding RTS.

1.5 Neurophysiological (markers) for RTS

Paper #1 – Neurophysiological Markers

Coenen, J., & Reinsberger, C. (2023). Neurophysiological markers to guide return to sport after sport-related concussion. *Journal of Clinical Neurophysiology. 40,* 391–397. https://doi.org/10.1097/WNP.0000000000000996

SRC are one of the most challenging encounters for clinicians, due to the injury's complexity and heterogeneity. Because of this, there is a call to establish objective markers to aid in clinical decision-making. The primary aim of this narrative review was to overview *state-of-the-art* neurophysiologic methods (e.g., qEEG), that are appropriate to investigate the complex pathophysiological process of a concussion. A secondary aim was to discuss the clinical utility of evidence-based markers, to be used in SRC management.

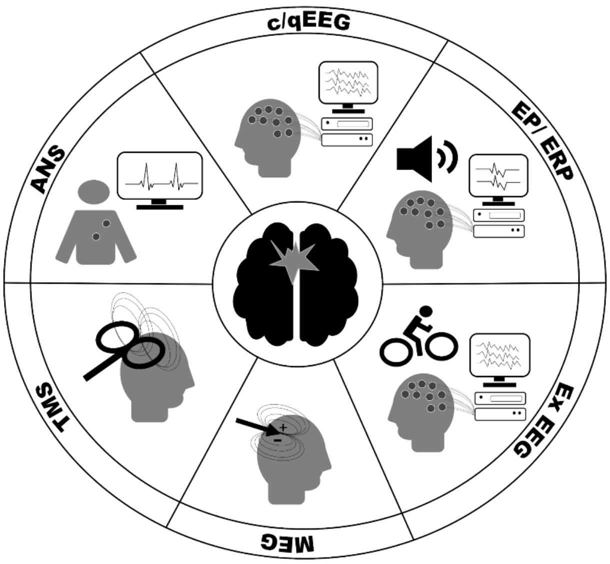
Attempts to use conventional EEG in the past could only draw limited insights about the acute pathophysiology accompanying a concussion, and could not predict nor confirm post-concussion symptoms (Amyot et al., 2015). Despite these limitations, conventional EEG has a place in neurocritical care - monitoring persons with moderate-to-severe TBIs (Amyot et al., 2015). As quantitative EEG becomes more readily available, spectral analysis and functional connectivity analysis are employed to investigate the complexities of mTBI (Rapp et al., 2015). In the spectral power analysis domain, associations between mTBI and the different frequency bands have been revealed. This injury appears to invoke a decrease in alpha power, and an increase in delta, theta and beta power (Rapp et al., 2015). However, not always consistently and measurement conditions appear to matter. A systematic review consolidating the literature on resting-state EEG reported a decrease across all power brands (Conley et al., 2018). Strong conclusions from EEG functional connectivity analysis are additionally difficult to draw, as study results are inconsistent. For example, one study reports an increased connectivity in the prefrontal cortex (Virji-Babul et al., 2014), while another one reports decreased frontal connectivity (Cao & Slobounov, 2010).

It may be that lack of consistency in data collection conditions, data processing and analysis methods underlie these ambiguous results. However, with a growing body of research using resting-state conditions, future stronger conclusions may be revealed. At this time, resting-state EEG appears to be an affordable and sensitive method for assessing pathologic mechanisms and mechanisms for recovery post-concussion (Conley et al., 2018).

By investigating HRV parameters post-concussion, valuable information has been revealed regarding the response of the ANS to this injury (Bishop et al., 2018; Pertab et al., 2018). Investigation into this system seems applicable because of it's central command (i.e., central autonomic network (CAN)), which is hypothesized to be affected by a concussive injury (Goldstein et al., 2002). In addition, there is suspicion that ANS dysfunction (Mercier et al., 2022) is the basis for post-concussion exercise intolerance (Pelo et al., 2023). Furthermore, there is empirical evidence to suggest that HRV is a useful tool for monitoring the status of a concussed athlete during their recovery (Bishop et al., 2018). However, due to a lack of adherence to guidelines for standardization of methods (Taskforce (Sassi et al., 2015)) comparisons between studies are limited and the drawing of conclusions is difficult.

Till now, there is no single neurophysiological marker (Figure 1) that might serve as a clinical standard for guiding the progressions through the RTS strategy. However, some EEG-derived markers show clinical utility potential, when combined with a clinical multimodal concussion assessment. Future research projects may use machine learning - predictive modeling techniques, to reveal potential objective markers for RTS. In the meantime, neurophysiological investigations continue to advance our knowledge and understanding of SRC related pathologies and trajectories of recovery.

Figure 1 *Current Neurophysiological Methods Available for Investigation of Sport-related Concussions*



Note. Figure generated for Paper #1. EEG, electroencephalography; c/qEEG, conventional and quantitative EEG; EP, evoked potentials; ERP, event-related potentials; exEEG, exercise response EEG; MEG, magnetoencephalography; TMS, transcranial magnetic stimulation; ANS, autonomic nervous system.

Author contributions: JC and CR discussed the topic and outline for the review. JC conducted a literature search and wrote the first draft of the manuscript. CR provided feedback on all versions of the manuscript and submitted the final version.

Before getting into the experimental work contributing to this thesis, a few final remarks remain pertaining to neurophysiological markers. Echoing the latest consensus statement on concussion in sport, advanced technologies such as those investigating neurophysiology, are a valuable research tool not yet suitable for clinical practice (Patricios et al., 2023; Tabor et al., 2023). Still, the establishment of markers which may inform RTS decisions is highly sought out (Tabor et al., 2023). The works which follow, utilized advanced technologies and methods, to explore neurophysiology during RTS. The aim was not to identify or establish a suitable marker, but rather to contribute to a greater knowledge and understanding of how the current RTS strategy may promote (neuro)physiological recovery. As this may precede that of establishing a marker for RTS. In due time, the results of the experimental work presented here may contribute to the establishment of an objective marker for RTS decisions.

3 Research Aims and Questions

The overall research aim of the experimental work was to investigate neurophysiological response to moderate aerobic exercise (up to 70% maxHR) in a prospective cohort study design. The focus was on athletes with a SRC history, who are in their RTS strategy. The pathophysiology of a concussive injury (i.e., neurotransmitter and metabolic cascade, with DAI) has already been extensively studied in animal models, with a lack of studies in humans (Giza & Hovda, 2014). This leads to many assumptions being made regarding the pathophysiological process of injury, and mechanisms for recovery (Ellis et al., 2018; Leddy, Haider, et al., 2018; Tan et al., 2014). Aerobic exercise kept below symptom exacerbation has been shown to promote recovery in SRC cases (Leddy, Haider, Ellis, et al., 2019; Leddy, Haider, Hinds, et al., 2019). The mechanisms underlying this positive effect of exercise, are however unclear.

This thesis will address the following research questions, to expose the research aim:

1) Are there neurophysiological markers which exist with clinical utility in the field of SRC, particularly markers which may be used to inform athletes' RTS? progressions (paper #1 – narrative review)

2) How does functional connectivity (as a measure of brain function) in whole brain, and relevant networks respond to moderate exercise (up to 70% maxHR) in a group of athletes within their RTS strategy, compared to matched controls? (paper #2 – original research manuscript)

3) How do small-world properties in whole brain and relevant networks change in response to moderate exercise (up to 70% maxHR), in a group of athletes within their RTS strategy, compared to matched controls? (paper #3 – original research manuscript)

4 Publications and Results

Three publications contribute to this dissertation. The first provided a literature overview of neurophysiological markers and was already outlined in *Chapter 2 Current state of research.* The next two publications are original research manuscripts which utilized the same laboratory experimental procedure and participants. The in-lab procedure will be described in the next sections. Followed by a presentation of the main results from each publication.

4.1 In-lab Procedure

4.1.1 Participants

Participants were recruited between January 2019 and June 2022 through contact with local sports clubs, contact with the athletes directly and as patients coming to the Sports Medicine Institute concussion clinic. In total 58 adult elite athletes were recruited for this study, with 27 of these athletes recruited for the patient group (SRC group). As an inclusion criterion for the SRC group, athletes had to have been clinically diagnosed with a concussion, according to the CISG conceptual definition (Patricios et al., 2023). Additionally, they needed to have been medically cleared to initiate their RTS strategy (Patricios et al., 2023), meaning cleared to participate in mild to moderate aerobic exercise. For every SRC athlete, a matched control (CTRL) athlete was recruited with the following (matching) criteria: sex, age (±5 years), height (±20 cm), weight (±10 kg), and when possible matched for sport and position. Due to the unforeseen obstacle of the COVID-19 pandemic, at one moment the study was on hold. Followed by a time when sports were only occurring in a limited capacity, resulting in very few (sport-related) concussions occurring. When it was allowed to go back into the lab, a few extra controls were invited to participate in the study as a precaution in case things got shut down again. For this reason, there is a slight imbalance in the number of participants per group. The matching criteria mentioned above was applied when pairing these particular controls to a patient. One control who was recruited for the study, suffered from a concussion during the project, and was invited back again – this time to participate as SRC athlete. This athlete's control dataset was then excluded from further analysis and replaced by another dataset. Exclusion criteria for participation in this study were: not being physically active, diagnosed with a cardiovascular disease, and for the control group they should not have experienced a concussion or head trauma within the past year (past 365 days). The flowchart presented on the next page provides an overview of the study design, with a few additional details (Figure 2).

The study was conducted in accordance with the Declarations of Helsinki and approved by the ethics committee of the Westphalian Medical Board (2018-522-f-S). Written informed consent was obtained from all participants. The trial was registered at the German Clinical Trial Register (DRKS00029207).

Figure 2 *Flow Chat of Study Design*

Recruitment, Eligibility, Inclusion

- contact with local sports clubs, with the coaches and the athletes themselves
- informed consent and demographic information were collected upon arrival at the lab
- concussion history questionnaire and symptom checklist were filled out by all athletes
- athletes within their RTS strategy made up the SRC group
- matched healthy control athletes did not have a recent (> 365 days) concussion history

In Lab Protocol

n = 58 athletes (n = 26 SRC athletes, n = 31 controls, n = 1 control → SRC)

Resting-state (pre-exercise)	**Exercise test**	**Resting-state (post-exercise)**
8 minutes supine position eyes closed resting-state	2-minute warm up progressive protocol +25 Watts/ 2 minutes till moderate intensity or maximum exertion 2-minute cool down	3 x 8 minutes supine position eyes closed resting-state with a 2-minute pause in-between to avoid drowsiness
Measurement outcomes of the resting-state measurements and exercise test		
3-lead ECG 128-channel EEG Captrack GSR module RPE scale VAS symptoms SRSS E4 multimodal sensor	12-lead ECG RPE scale VAS symptoms E4 multimodal sensor	3-lead ECG 128-channel EEG GSR module RPE scale VAS symptoms SRSS E4 multimodal sensor

Analysis

n = 42 matched (n = 21 SRC athletes, n = 21 matched controls)

Measurements & outcomes:	*Exclusion criteria:*
3-lead ECG: heart rate, RMSSD, LF/HF ratio GSR module: mean EDA 128-channel EEG: functional connectivity (PLV) for WB, DMN, CAN, VIS RPE scale, VAS symptoms and SRSS as subjective measures	n = 15 *excluded* (participated only in all-out protocol (n = 8), not matched with SRC athlete (n = 6), participated first as control, then as SRC athlete (n = 1), symptomatic despite years since concussion (n = 1))

Note. RTS: return to sport, SRC: sport related concussion, ECG: electrocardiogram, EEG: electroencephalography, GSR: galvanic skin response, RPE: rating of perceived exertion, VAS: visual analog scale, SRSS: short recovery and stress scale, RMSSD: root mean square of successive differences, LF/HF: low frequency high frequency ratio, EDA: electrodermal activity, PLV: phase locking value, WB: whole brain, DMN: default mode network, CAN: central autonomic network, VIS: visual network

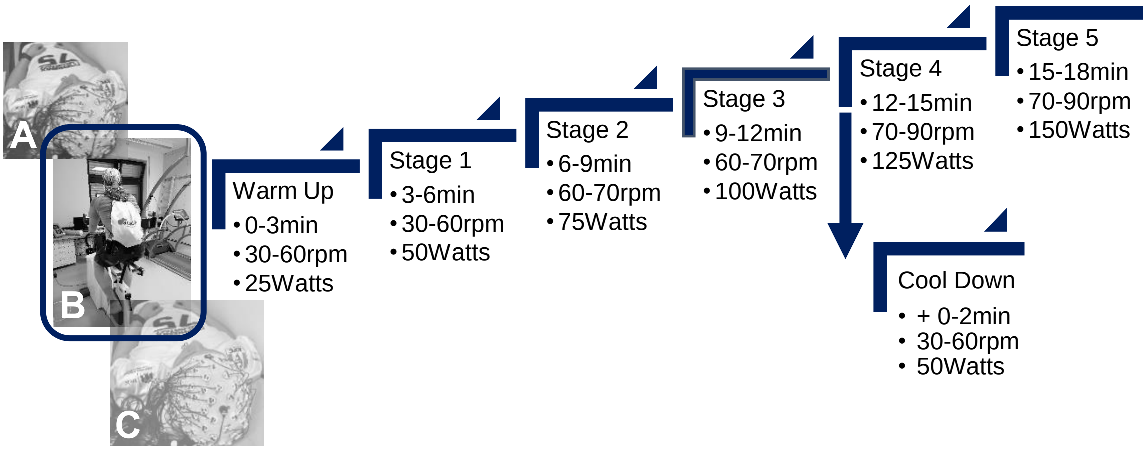
4.1.2 Concussion History and Symptomology

All athletes that were recruited for this study, were asked to fill out a questionnaire upon arrival at the lab. This questionnaire gathered important information about the athlete's age, sports participation characteristics (e.g., sport type and years of sport participation) and concussion history. Concussion history characteristics of interest for this study were: 1) have you ever experienced a concussion, when yes how many and 2) when was your last experienced concussion. All participants were additionally asked to fill out the symptom checklist found within the SCAT- 5th edition (Echemendia et al., 2017). A Likert scale from 0 = no symptom to 6 = severe was used to assess symptom expression. The symptom checklist was used to calculate the number of symptoms (maximum of 22 (22x1)) and the post-concussion symptom score (maximum of 132 (22x6)). Further information was gathered about the athlete's sleep quality from the previous night, with questions asking them to report how many hours they slept and at which time they awoke. In addition, athletes were asked to provide information about the presence of neurodevelopment deficits (e.g., ADHD) and neurological comorbidities (e.g., epilepsy).

4.1.3 Exercise Test

In-lab all athletes participated in a progressive standardized ergometer exercise test, to moderate or maximum exertion. Both tests started at a 25-watt workload followed by incremental increases of 25 watts every 2 minutes. The revolutions per minute were controlled by the athlete and monitored by the researcher with the following recommendations: 50-60 revolutions per minute (RPM) at 24-60 watts, 60-70 rpm at 60-100 watts, 70-90 rpm at >100 watts (Figure 3). Throughout the exercise test - every two minutes, the participants were asked to provide their symptom expression (via. a visual analogue scale (VAS) (Leddy & Willer, 2013) and their rating of perceived exertion (RPE) (Borg, 1990). These scales (i.e., VAS and RPE) were also used during the pre- and post-exercise resting-state EEG measurements to gather subjective information. The moderate intensity exercise test considered components of the YMCA bike test and the Buffalo Concussion Treadmill (/bike) test (BCTT/BCBT) (Haider, Johnson, et al., 2019; Leddy & Willer, 2013). Moderate, for the purpose of this study was defined as 70% of the athlete's age calculated maxHR. This was calculated with the following equation: 206.9 – (0.67*age) (American College of Sports Medicine, 2010). Once the athlete reached their exercise goal (moderate or maximal exertion), they were instructed to slow their pace back to 50-60 rpm for a 2-minute cool down.

Figure 3 *In-Lab Protocol (moderate aerobic exercise test)*



Note. A: pre-exercise, resting-state measurement, B: exercise test, C: post-exercise, resting-state measurement, rpm: revolutions per minute

4.2 Data Recording and Processing Procedure

The following neurophysiological datasets were obtained pre- and post-exercise: 1x 128-channel EEG, 1x 3-lead electrocardiogram (ECG), 1x Galvanic skin response (GSR). The following sections will detail the data recording conditions of the resting-state measurements and the processing steps for the EEG datasets. The EEG datasets were analyzed for the two experimental works contributing to this thesis. The data extracted from the ECG and GSR will be touched upon in the *Outlook* subchapter, for this reason, are mentioned here.

The ActiCHamp system from Brain Products (Brain Products GmbH, Germany) was used in this study. The ground electrode was positioned at FPz, and FCz was used as the reference electrode. The cap was positioned according to the international 10-10 system (Acharya et al., 2016), using the nasion and union as landmarks. Electrode impedance was kept below 25 kΩ and the recording sampling rate was 1000 Hz. Using CapTrack software (Brain Products GmbH, Germany), individual electrode locations were registered before the first resting-state, to be applied later in the data processing. The participants were instructed to lay comfortably in supine position, with their eyes closed. They were given verbal instructions to relax, but also to stay awake before each of the 8-minute resting-state conditions.

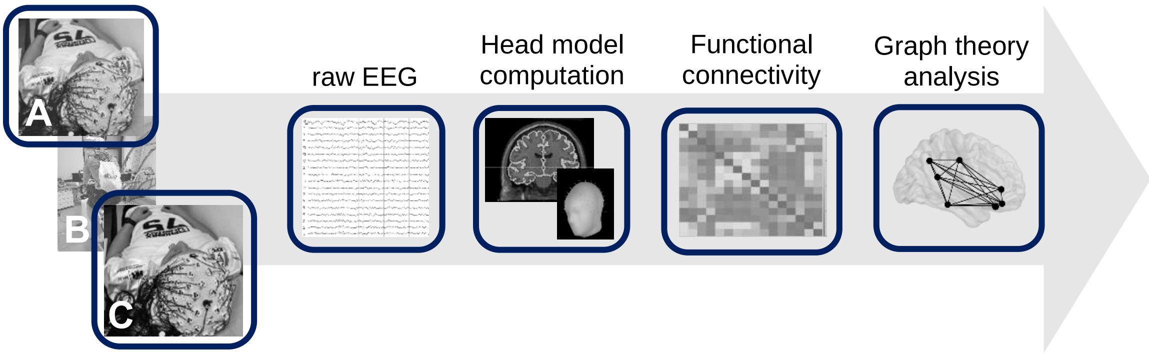
The first preprocessing steps were done in BrainVision Analyzer (version: 2.1.2, Brain Products GmbH, Germany). Datasets were down sampled to 250 Hz. Following, a Butterworth Filter with a low cutoff of 1 Hz and a high cutoff of 30 Hz was applied, alongside a notch filter (50 Hz). The notch filter was additionally applied to reduce spikes at 50 Hz due to the electrical line. Next, the reference channel was changed to average. Bad channels were identified at this stage by visual inspection and were replaced by topographic interpolation by Spherical Splines method. Channels were checked for bridges first using MATLAB-based eBridge algorithm (Alschuler et al., 2014). This algorithm identifies signals as probable bridges when they are highly similar. The identified channels were then additionally checked using a coherence threshold (> .80) method in Analyzer. When both criteria identified the channels as bridged, the channels were interpolated. Common artifacts, such as eye movements and electrocardiographic artifacts were identified by Independent Component Analysis (ICA), InfoMax algorithm (Langlois et al., 2010). Once identified these artifact components were rejected. Four artifact free epochs (2048 points/epoch; (Engels et al., 2015)) per recording were exported for further processing and analysis.

4.2.1 Functional Connectivity

The artifact free epochs were uploaded into Brainstorm software (Tadel et al., 2011), run through MATLAB (The MathWorks Inc. Optimization Toolbox, version: 9.4 (R2022b), Natick, Massachusetts) commands. In preparation for functional connectivity analysis, the following two main steps were necessary: (1) constructing a head model, and (2) solving the inverse problem by source estimation. An individual MRI was not available for each participant, therefore, a default anatomy – Conlins27 (Aubert-Broche et al., 2006; Holmes et al., 1998) was used. However, in efforts to individualize each head model, the electrode positions on the scalp recorded by CapTrack were used to warp the default anatomy to fit the participant’s measurements. Boundary Element Method (BEM) was used to construct the head model (Gramfort et al., 2010), followed by source estimation by minimum norm (MN) imaging estimation (Baillet et al., 2001) As recommended in previous literature for connectivity analysis from high-resolution EEG, MN estimator combined with a phase synchronization measure is optimal (Hassan et al., 2014). Phase locking value (PLV), which measures the degree of synchronization between signals (Hassan et al., 2014), was calculated for each epoch and then averaged together. Initially, PLV was calculated in the theta (7-13 Hz), alpha (7-13 Hz) and beta (7-13 Hz) band. However, during preliminary analyses significant results consistently were revealed only within the alpha frequency band (Coenen et al., 2022). It appears that PLV based network metrics have a high association with alpha relative power, clustering coefficient and betweenness centrality (Demuru et al., 2020), for this reason the alpha band exclusively was focused on in proceeding analyses.

PLV matrices (68 x 68), between all regions of the Desikan Killany atlas (Desikan et al., 2006) were exported from Brainstorm. For the different relevant networks, regions of interest (ROI) were selected based on previous literature a priori (Schoffelen & Gross, 2009). For whole brain (WB), all 68 ROI available within the atlas were used. For the DMN regions of the medial prefrontal cortex, medial temporal lobe, posterior cingulate and parietal cortex were identified and used for analysis (Kabbara et al., 2017; Raichle, 2015; Zhang et al., 2012). The CAN comprises the midcingulate cortex, insula and amygdala (Beissner et al., 2013). For this network, 24 ROI were selected. The visual network (VIS) was included in this study as a control network. Regions in the occipital lobe were selected for this network (Kabbara et al., 2017). The data processing procedure is visually displayed below (Figure 4).

Figure 4 *EEG Data Processing, from Raw to Parameter Extraction*



Note. A: pre-exercise, resting-state measurement, B: bike exercise test, C: post-exercise, resting-state measurement, EEG: electroencephalography

4.2.2 Graph Theoretical Analysis

The PLV-based matrices resulting from the previous procedure may be further explored using graph theoretical analysis. This analysis can be done weighted or binarized. Addressing both in this study, was an attempt to weigh the costs and benefits of each method (Bassett & Bullmore, 2017). The connection between two nodes was determined by the PLV between the different ROI. Consideration for an appropriate threshold for connection (i.e., edges) tried to balance between information loss and exclusion of non-significant connections. In attempts to balance this, investigations were conducted using several plausible thresholds (van Wijk et al., 2010). However, as network measures are unstable across absolute thresholds (Garrison et al., 2015), proportional thresholds were used. The PLV matrices were thresholded proportionally from 10% to 50%, by increments of 10% to include several gradations of possibly influential connections (Churchill et al., 2021; Rubinov & Sporns, 2010).

The idea here was to explore small-world topology, to elucidate brain function. Here, the balance between segregation and integration is compared to a random graph. Small-worldness was evaluated based on the small-world index (SWI): $\sigma = \frac{\gamma}{\lambda}$, where networks with a higher value than 1 depict small-world topology (Humphries & Gurney, 2008). Detailing this equation: γ is the normalized CP - the ratio between the CP of the network divided by the random network CP and λ is the normalized LP - calculated as the LP of the network divided by the corresponding random LP.

The graph theoretical analysis was conducted using tools from the Brain Connectivity Toolbox (BCT) (Rubinov & Sporns, 2010), run through MATLAB. Segregation estimated by CP was extracted using the function *'clustering_coef_bu'* and *'clustering_coef_wu'* for the binary and weighted graphs, respectively. Integration as average LP was calculated with the function *'charpath'* across graphs. At this point, 50 null (random) network models with similar size, density, and degree distribution were generated (Rubinov & Sporns, 2010; Tsirka et al., 2011). These were used to calculate the normalized CP (γ), and the normalized LP (λ) values for the small-world index.

4.3 Statistical Analysis

IBM SPSS Statistics (version: 28.0, IBM Corporation, Armonk, New York, United States) was used for the statistical analyses. The data was first assessed for normality using Shapiro-Wilk test ($p < 0.05$, reject the hypothesis of normality). Between group differences, were determined by computing independent t-tests or Mann-Whitney U tests, depending on the normality test results. When applicable equal variances were assessed by Levene-Test ($p < 0.05$, reject the assumption of equal variance). In paper #2, the within-group analyses were conducted using Paired t-test or Wilcoxon signed-ranked test. The effect size Cohen's d was computed for normally distributed data, while Pearson's r was computed for non-normally distributed or non-metric data. To investigate network topology divergencies between groups in response to exercise in paper #3, a mixed-ANOVA was performed on the binary and weighted graph parameters.

The level of significance was set to $p \leq 0.05$ (2-tailed) a priori. Respecting the undirected hypotheses, in both studies two-tailed statistical tests were conducted. To correct for multiple comparisons in Paper #2 Bonferroni correction was applied and an adjusted level of significance $p \leq 0.0125$ (i.e., 0.05/4) was considered. In contrast for paper #3 the significance level of $p = 0.05$ was not further adjusted because of the study's exploratory approach (Armstrong, 2014). Despite the increased risk of incorrectly identifying significant effects, this approach prioritizes the identification of potential associations to direct future investigations.

In paper #3, a chi-square test of independence was conducted to examine the association between the presence of small-world topology and SRC. If the expected cell frequency in the chi-square test was lower than five, the Monte Carlo method with 10000 samples was used to estimate the significance. The effect size Pearson's r was calculated to compliment the results of the chi-square test.

Tables in the results section will present mean (± standard deviation) for data that was normally distributed, and median (Mdn) and interquartile range (IQR) for non-normally distributed datasets.

4.4 Results

4.4.1 Clinical and Participant Characteristics

Datasets from 42 (/58) participants were analyzed for the experimental works. Twenty-one athletes made up the SRC patient group and 21 matched controls built the CTRL group. Participant characteristics are displayed in Table 3. This sample of athletes were actively participating in a range of sports, although most were involved in contact or collision sports, such as soccer (n =13), basketball (n =12), and American football (n =7). There were no significant group differences for participant characteristics of: age (*p* = 0.822), height (*p* = 0.443), neither weight (*p* = 0.821). The patient group had a greater symptom score (Mdn =10) than the controls group (Mdn =1) on the SCAT5 symptom checklist (*p* =.000).

Table 3 *Demographic and Participant Characteristics of Athletes*

	SRC patient group	CTRL control group	p-value	Cohen's d[a]/ r (effect size)[b]
Sex	17 males	17 males		
Age (years)	23.69 ± 4.99	24.03 ± 4.68	0.822[a]	0.070[a]
Height (cm)	181.81 ± 12.37	184.48 ± 9.78	0.443[a]	0.239[a]
Weight (kg)	79.29 ± 14.17	80.29 ± 14.31	0.821[a]	0.070[a]
BMI	23.79 ± 2.10	23.38 ± 2.27	0.548[a]	-0.187[a]
Sport	Soccer (6) Basketball (6) Am. Football (2) Other (7)	Soccer (7) Basketball (6) Am. Football (5) Other (3)		
Number of concussions	1.76 ± 1.26 (range = 1-5)	0.62 ± 1.12 (range = 0-4)	0.003[a*]	-0.959[a]
Days since last concussion (days)	31.71 ± 41.98 (range = 2-140)	> 365		

Symptom Number	Mdn = 7 (7)	Mdn = 1 (2)	0.000[b*]	-0.63[b]
Symptom Score	Mdn = 10 (21)	Mdn = 1 (3)	0.000[b*]	-0.63[b]

[a] Student t-test
[b] Mann- Whitney test
* $p < 0.05$
** $p < 0.001$
mean ± standard deviation
Mdn = median (IQR= interquartile range)

Physiological response to the moderate aerobic exercise test, measured by HR did not significantly differ between groups. Although, HR was slightly higher for controls (75 ±13 bpm) vs. patients (71 ±10 bpm) pre-exercise, it was not statistically significantly different (p = 0.321). At moderate intensity, average HR was 138 bpm for both groups (SRC: 138 ±8 bpm, CTRL: 138 ±5 bpm, p = 0.859). After the cooldown, mean HR was 107 bpm for patients (107 ±11 bpm) and controls (107 ±10 bpm, p = 0.978) Peak moderate exercise performance was similar between groups, as measured by maximum watts achieved (SRC: 169 ±48 W, CTRL: 172 ±48 W, p = 0.816), power to weight ratio ((P2W) SRC: 0.50 ± 0.15 W/kg, CTRL: 0.47 ± 0.10 W/kg, p = 0.728), and duration (SRC: 14 ±4 min, CTRL: 14 ±4 min, p = 0.816). RPE at moderate aerobic exercise intensity did not differ between groups, with a mean of 13 for both groups (SRC: 13 ±3, CTRL: 13 ± 2, p = 0.453). VAS symptom expression did significantly differ between groups throughout the exercise test. While the control group consistently reported 0 symptoms, SRC patients reported symptoms ranging from 0 – 4 pre-exercise, 0 – 5 at moderate intensity exercise and 0 - 4 after cool down. In Table 4, are the exercise performance characteristics.

Table 4 *Exercise Performance Characteristics of Athletes*

		SRC patient group	CTRL control group	p-value	Cohen's d[a]/ r (effect size)[b]
Pre-exercise	HR (bpm)	71.05 ± 10.40	74.86 ± 12.63	0.304[a]	0.321[a]
	RPE	7.43 ± 2.46	7.05 ± 1.21	0.538[b]	-0.04[b]
	Symptoms (VAS)	0.86 ± 0.94	0 ± 0	0.000[b**]	-0.65[b]
Moderate Exercice	HR (bpm)	137.86 ± 7.83	137.48 ± 5.41	0.859[a]	-0.055[a]
	RPE	12.62 ± 2.52	13.19 ± 2.28	0.453[b]	-0.12[b]
	Symptoms (VAS)	1.81 ± 1.84	0 ± 0	0.000[b**]	-0.65[b]

	Watts (W)	169.05 ± 48.12	172.62 ± 48.12	0.816[a]	0.072[a]
	P2W (W/kg)	0.50 ± 0.15	0.47 ± 0.10	0.728[a]	-0.108[a]
	Time (min)	13.52 ± 3.85	13.81 ± 3.85	0.816[a]	0.072[a]
Post-exercise	HR (bpm)	106.86 ± 11.37	106.95 ± 9.88	0.978[a]	0.009[a]
	RPE	9.90 ± 2.21	8.71 ± 1.64	0.062[b]	-0.29[b]
	Symptoms (VAS)	1.42 ± 1.43	0 ± 0	0.000[b]**	-0.67[b]

[a] Student t-test
[b] Mann- Whitney test
* $p < 0.05$
** $p < 0.001$
mean ± standard deviation

Paper #2 – Networks Functional Connectivity

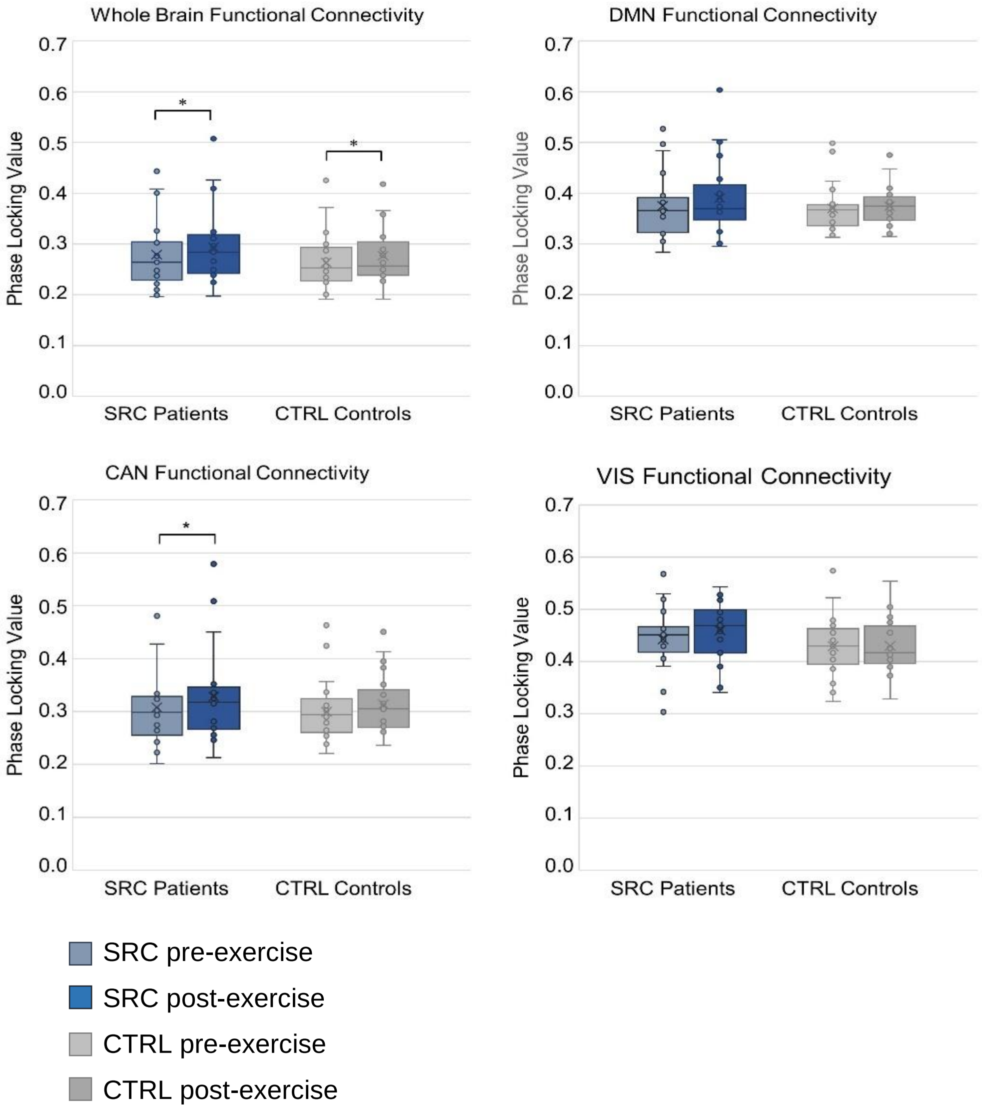
Coenen, J., van den Bongard, F., Delling, C.A., & Reinsberger, C. (submitted). Differences in network functional connectivity in response to sub-symptomatic exercise between elite adult athletes after sport-related concussion and healthy matched controls: a pilot study. *Journal of Neurotrauma.*

The aim of this study was to explore functional connectivity, in the WB and in relevant networks, in response to moderate intensity (70% maxHR) aerobic exercise. Particularly, interested in the neurophysiological response to exercise in a group of adult elite athletes post-concussion, during their RTS strategy, compared to healthy matched controls. Functional connectivity was calculated by PLV within the alpha band (7-13 Hz). WB connectivity analysis recruited all 68 ROI available within the atlas. To extract presumably relevant networks and investigate network connectivity, 24 ROI constructed the CAN, 14 ROI constructed the DMN, and 8 ROI built a control network (VIS).

The main results of the network functional connectivity analysis are as follows. First, for WB there was a significant increase in activity in both groups from pre- to post-exercise (SRC: 0.264 to 0.284, $p = 0.011$ and CTRL 0.253 to 0.257, $p = 0.011$). Second, within the CAN, network connectivity significantly increased from pre- to post-exercise for the SRC group (0.298 to 0.317, $p = 0.003$). There was an increase in activity in the control group, but it did not remain statistically significant when controlling for multiple testing (0.294 to 0.305, $p = 0.020$). Third, within the DMN the SRC group appears to have a greater response to exercise (0.366 to 0.370, $p = 0.028$) vs. controls (0.368 to 0.375, $p = 0.401$), but with the adjusted p-value this increase in connectivity is not statistically significant. Finally, as anticipated the control network (VIS) did not differ significantly pre- to post- exercise for the SRC group (0.452 to 0.469, $p = 0.156$), neither the control group (0.430 to 0.418, $p = 0.385$) (Figure 5).

Increased CAN connectivity in response to exercise, as revealed by this study, may have exposed a potential underlying mechanism for cardiac autonomic alterations post-injury. Relating this back to previous literature, particularly the *hyperconnectivity hypothesis* reported in TBI literature, an increase in connectivity occurs to reduce behavioural deficits post-injury. Unfortunately, as this study is underpowered it limits the confidence in these results. Therefore, future greater studies are needed, that additionally investigate connectivity within the CAN in a sample of SRC athletes.

Figure 5 *Box Plots of Phase Locking Value*



Note. PLV: phase locking value, as functional connectivity parameter, for whole brain (WB), central autonomic (CAN), default mode (DMN), and visual (VIS) networks pre- and post- sub-symptomatic exercise task, during sport-related concussion (SRC) patients return to sport compared to matched controls (CTRL). *p < 0.0125 (Bonferroni's correction applied)

Author contributions: JC and CR conceptualized the research aims for the project. JC, FvdB and CD were involved in data collection and data processing. JC conducted the data analysis and wrote the first manuscript draft. FvdB, CD and CR critically reviewed and edited all previous drafts before submission.

Publication status: The initial submission was done by JC on 09.12.2023. More recently, a revised manuscript with responses to the reviewers' comments was submitted 10.10.2024. It is currently under review.

Paper #3 – Small-world Topology and Characteristics

Coenen, J., Strohm, M., & Reinsberger, C. (2024). Impact of moderate aerobic exercise on small-world topology and characteristics of brain networks after sport-related concussion: An exploratory study. *Scientific Reports.* https://doi.org/10.1038/s41598-024-74474-6

Using graph theoretical analysis, previous studies have reported a departure from a small-world topology after brain injury. Therefore, graph analysis may be a unique and powerful tool to explore divergences in response to moderate aerobic exercise, between SRC athletes and healthy matched controls. In this study, by calculating CP as a measure of segregation, PL for integration and small world index to denote the synergy between the two, differences between groups were in fact revealed.

The main results of the study were as follows: Pre-exercise, DMN-CP values were higher for the SRC group (0.2 4± 0.11), compared to matched controls (0.16 ± 0.09, *p* = 0.007). Post-exercise, WB-PL values were significantly higher for the SRC group (2.14 ± 0.07) than controls (2.10 ± 0.06, *p* = .041). Additionally, post-exercise a significant association was found between SRC and the absence of small-world topology (SWI ≤1) in the WB network (*p* = 0.048). The absence of small-world topology was identified in five SRC athletes who either were in the early acute recovery phase post-injury (n = 3) or exhibited both cumulative concussion history and high symptom severity (n = 2). Table 5 outlines the characteristics of the SRC athletes with an absence of small-world topology.

Table 5 *Characteristics of the SRC Athletes with an Absence of Small-World Topology*

Variables	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Age (years)	29.61	18.75	18.5	30.98	27.53
Height (cm)	183	178	183	212	177
Weight (kg)	81	70	74	109	79
Sex (male/female)	male	male	male	male	male
Sport	basketball	soccer	soccer	basketball	Am. football
Number of concussions	1	1	1	5	4
Days since last concussion	4	2	7	19	116
Symptom number	1	1	7	12	17
Symptom severity	1	4	14	28	52

Note. Concussed athletes without small-world topology in the weighted WB with a threshold of 40%. Am. Football: American football

Based on these findings, it appears that moderate aerobic exercise during an athlete's RTS induces a different network response than that reported for the healthy matched controls. Furthermore, that an absence of small-world topology post-exercise, appears to particularly present in SRC athletes who are only a few days post-injury. Although, the clinical relevance of these findings needs to be interpreted with caution, may this study encourage and direct future studies to use graph theoretical analysis with a greater sample and if possible, a longitudinal study design.

Author contributions: JC and MS share the first author position on this paper because of their contributions. JC, MS and CR together conceptualized the research aims for the project. JC was involved with data collecting and data processing. MS conducted the graph theoretical analysis. The first draft was written by JC and MS, which then received critical feedback and edits from CR.

Publication status: The paper was submitted to *Scientific Reports* on 26.04.2024 by JC. The paper was accepted on 26.09.2024 and published on 25.10.2024.

5 Discussion

A main objective of this dissertation was to contribute an increased knowledge and understanding of brain function during an athlete's RTS strategy. As identified by the narrative review (**paper #1** – neurophysiological markers), there is a lack of studies which investigate the neurophysiological response to exercise during an athletes' RTS. To attack this gap in the research, the experimental works (**paper #2** – networks functional connectivity and **paper #3** – small-world topology and characteristics) set out to investigate neurophysiological responses to moderate aerobic exercise (up to 70% maxHR) in a prospective cohort study. The study design focused on adult elite athletes with SRC history, who were still within their RTS strategy, and compared their responses to a group of healthy matched control athletes.

5.1 Functional Connectivity

Paper #2 included in this thesis investigated network functional connectivity in WB, CAN, DMN and VIS. WB connectivity increased significantly in both groups in response to moderate aerobic exercise. Connectivity within the CAN increased significantly from pre- to post-exercise only within the SRC athlete group. DMN connectivity also increased pre- to post-exercise in the SRC athlete group, however, the statistical significance did not hold after correcting for multiple testing. These two distinct (DMN and CAN) networks have been previously reported or hypothesized to be altered by SRC injury (Mercier et al., 2022; Zhang et al., 2012). In contrast, no alteration in network connectivity was revealed for the control network (i.e., VIS).

In line with previous research, there were no significant group differences at rest, but exposure to a physical stressor, such as exercise, seemed to reveal alterations (Gay et al., 2015; Zhang et al., 2012). In a previous study, using EEG methods, 9 student-athletes who were previously diagnosed with a concussion, were compared to 9 control student-athletes (Gay et al., 2015). Aerobic exercise (till 70% maxHR), on a bike ergometer resulted in higher delta, theta, alpha, and beta absolute power values for the mTBI group, compared to controls ($p < 0.05$). The significant power increase presented frontally, centrally, and posteriorly ($p < 0.05$). Within the alpha band, the mTBI group had significantly greater absolute power values during the bike test frontally ($p = 0.012$). After the bike test, the mTBI group had significantly greater alpha power values centrally ($p = 0.001$) and posteriorly ($p = 0.005$). This previous work described the capability of exercise to expose abnormalities in EEG measures, otherwise not present in strict resting conditions. Knowing this, the experimental work contributing to this thesis went beyond spectral analysis and explored functional connectivity within WB and relevant brain networks.

There was an increase in connectivity within the DMN for the SRC group, which can be discussed in relation to previous findings. Research using other neuroimaging methods, such as functional MRI (fMRI), have also explored connectivity patterns within the DMN in response to exercise post-concussion (Zhang et al., 2012). An fMRI study recruited 14 sport-related mTBI athletes who were 10 ±2 days post-injury and 15 control athletes, to explore the functional integrity of the DMN at rest and in response to exercise. All athletes were exposed to the same aerobic exercise bike test mentioned in the previous paragraph (Gay et al., 2015; Zhang et al., 2012). After exercise, there was a significant decrease in the magnitude of connections within the DMN for the mTBI group, compared to controls. Particularly, between the PCC and medial prefrontal cortex (p = 0.010), as well as PCC and left lateral parietal cortex (p = 0.047) (Zhang et al., 2012). Similarly, within the functional connectivity analysis conducted for paper #2 contributing to this thesis, there appears to be a greater response to exercise within the DMN for the SRC group, compared to controls. However, this finding needs to be interpreted with caution as it did not remain statistically significant upon considering an adjusted p-value (p = 0.028, *corrected* $p < 0.0125$).

More recent fMRI studies investigated the functional connectivity of resting-state brain networks, in strictly resting-state conditions. In one study, 12 acutely (≤ 2 months) post-concussion adolescents (mean age = 16 years old), and 10 healthy matched controls were recruited (Borich et al., 2015). Within the DMN, there was increased connectivity within the PCC area for the concussion group, compared to controls (p < 0.01). In another study, 12 adult patients (mean age = 38 years old) from a trauma centre, were compared to 16 adult healthy controls (Iraji et al., 2015). Results showed reduced connectivity in PCC and precuneus regions for the patient group, compared to controls (p < 0.001). In addition, they reported increased connectivity between the PCC and other ROI of the brain (e.g., dorsolateral PFC, p < 0.01).

Relating this back to the functional connectivity results reported in paper #2, which found no group differences in strictly resting conditions, makes one wonder. Due to inconsistent results, variation of neuroimaging methods and different measurement conditions, comparisons across studies are limited. Still, despite the inconsistent direction (increase vs. decrease) of reported results, there appears to be an altered connectivity response to injury. A combination of original research studies, reviews and theoretical work in (network) neuroscience, is relied on to further discuss the results of this thesis in the following sections.

5.1.1 Hyperconnectivity Hypothesis

Hyperconnectivity has been presented as a common network response to neurological insult (Hillary et al., 2015). It has been presented as an explanation for increased connectivity in studies with neurological patients (Hallquist & Hillary, 2019; Hillary et al., 2015), as well as brain injury patients (Hillary & Grafman, 2017; Hillary et al., 2014). In response to the SRC/mTBI related DAI, normal neural pathways are disrupted, which in turn affects (functional) brain networks. To compensate for injury, while maintaining behavioural and cognitive function, the brain may attempt to establish new pathways. Thereby increasing spatiotemporal interaction between signals, as measured by functional connectivity parameters (Bressler & Menon, 2010).

Increased functional connectivity post-injury has been revealed across different modalities and by estimating different parameters, delivering accumulating support for the hyperconnectivity hypothesis. In one study, applying resting-state EEG to 29 student-athletes before (baseline) and shortly after (day 7 post-injury) sport-related mTBI, patterns of brain connectivity within the alpha frequency were observed (Cao & Slobounov, 2010). Using coherence as a measure of functional connectivity between 19 ROI (19 electrodes), results showed a significant decrease in long-distance (9 ±2 cm) connectivity, and a significant increase in short-distance (7 ±3 cm) connectivity post-injury ($p < 0.05$). Another study calculated temporal correlations (i.e., spontaneous fluctuations) between blood-oxygen-level dependent (BOLD) signal time series from fMRI scans to estimate functional connectivity (Mayer et al., 2011). Connectivity within and between the DMN and fronto-parietal task network was explored, in addition to clinical assessments and neuropsychological test results. Twenty-seven adult mTBI (GCS: 13-15) patients within 21 days post-injury, showed hyperconnectivity between DMN and lateral prefrontal cortex, as well as between right prefrontal cortex and posterior parietal cortex, compared to 26 matched controls ($p < 0.05$). More recently, functional connectivity patterns of adolescent (10-18 years old) concussion patients were compared to adolescent (10-18 years old) orthopaedic injury patients (Healey et al., 2022). From resting-state fMRI scans, functional connectivity was estimated by correlation coefficients between BOLD time series of WB and regions corresponding to a priori selected networks of interest. There was increased functional connectivity reported for the concussion patient group within the regions of the salience network, specifically between the right frontoinsular cortex and the left anterior cingulate cortex

(ACC) ($p = 0.001$) and right ACC ($p = 0.002$). Additionally, there was increased connectivity between the salience network and regions of the DMN (e.g., PCC and PFC, $p < 0.05$), as well as regions of the central executive network (e.g., dorsolateral pre-frontal cortex, $p > 0.05$) for the concussion group.

Although the selected ROI may differ between studies, and methods also, continually there are reports of increased connectivity for the concussion patient groups, compared to controls. Accruing further support for the relevance of the hyperconnectivity hypothesis in concussion cases. The potential adaptive mechanism of increased connectivity may provide insights into recovery trajectories, and in time may inform post-concussion rehabilitation (Healey et al., 2022). With this, attention is brought back to the work included in this thesis. There was a significant increase in CAN connectivity in response to moderate aerobic exercise only for the SRC group ($p = 0.003$). This occurred, despite both groups achieving similar moderate aerobic exercise performance, as measured by HR, P2W, and RPE ($p > 0.05$). In line with the hyperconnectivity hypothesis, one could speculate that increased functional connectivity within the CAN is an adaptive response. A response which enables patients to achieve similar exercise performances. However, as an abundance of the research which supports hyperconnectivity is drawn from strictly resting-state conditions, and this study found significant results only in response to exercise, comparisons are limited. Therefore, it is additionally important to discuss the literature on exercise-induced brain connectivity patterns in humans.

5.1.2 Exercise-induced Brain Connectivity

Even an acute bout of exercise has been shown to alter brain network functional connectivity (Alfini et al., 2020; Moore et al., 2022; Schmitt et al., 2019; Weng et al., 2017; Won et al., 2021). In one study, 12 healthy young adults (mean age = 23 years old) and 13 healthy older adults (mean age = 66 years) were exposed to an active moderate (65% of maxHR) exercise condition (Weng et al., 2017). For comparison, in a counterbalanced order, participants were additionally exposed to a (control) passive exercise condition where their legs were moved by motorized pedals to resemble the active bike exercise procedure. Study results showed that 30 minutes of moderate-intensity aerobic cycling induces increased connectivity, as measured by synchrony between brain regions (e.g., PFC, temporal pole and hippocampus, $p < 0.05$, uncorrected). Such a result did not show in the passive condition. Increased connectivity in response to active exercise appeared in ROI associated with affect and reward processes, learning and memory and regions associated with attention and executive control (Weng et al., 2017). In another study, functional connectivity was evaluated in response to different aerobic exercise intensities, conducted on a treadmill (Schmitt et al., 2019). For this, 25 healthy male athletes participated in both a low intensity (35% under lactate threshold) and a high intensity (20% above threshold) exercise test. Results showed that from pre- to post-exercise conducted at a low intensity, functional connectivity increases in brain networks particularly associated with cognition and attentional processes (i.e., fronto parietal network, $p = 0.033$). In response to exercise conducted at a high intensity, increased functional connectivity rather presented in affective brain networks (i.e., affective and reward network, $p = 0.015$). Taken together, even a single bout of exercise appears to have a positive response on brain function.

In the experimental work included in this thesis, a single bout of moderate intensity exercise increased WB functional connectivity in both athlete groups (SRC and CTRL). This WB response may point to the benefits of exercise in general. However, CAN connectivity significantly increased from pre- to post-exercise only within the SRC group. Therefore, it seems appropriate to discuss the significance of this network, as it pertains to SRC.

5.1.3 Central Autonomic Network

Within the theoretical background (*2.4.2 Autonomic nervous system*), physiological alternations post-concussion in the ANS were presented (Esterov & Greenwald, 2017; Mercier et al., 2022; Pertab et al., 2018; Purkayastha et al., 2019). Alterations within the CAN post-injury have been hypothesized to be the source of autonomic dysfunction post-injury (Esterov & Greenwald, 2017; La Fountaine, 2018; Mercier et al., 2022; Pertab et al., 2018), as well as a contributor to the exercise intolerance experienced by some patients (Leddy, Haider, et al., 2018; Tan et al., 2014).

Previous studies have addressed the topic of exercise intolerance by investigating HR threshold (Haider, Johnson, et al., 2019; Leddy, Hinds, et al., 2018) and HR recovery (Memmini et al., 2021). In one study examining adolescent athletes (14-19 years old), a lower HR at test termination on the BCTT at the first visit – within 10 days post-injury, was statistically associated with prolonged symptoms (> 21 days post-injury, $p = 0.003$) at the second visit (Leddy, Hinds, et al., 2018). Suggesting that normal vs. abnormal exercise tolerance within the first week post-injury, may have prognostic utility, and may serve as a physiological marker for tracking concussion recovery (Leddy, Hinds, et al., 2018). Another study, which recruited 33 male adolescent hockey athletes, grouped them based on their concussion history (with vs. without a concussion history) (Memmini et al., 2021). All athletes were exposed to a 20-minute aerobic exercise test

(60% to 70% of their maxHR), in addition to a pre- and post-exercise resting-state measurement. All athletes were asymptomatic at the time of testing. Still, athletes with a concussion history showed suppressed cardiac autonomic recovery post-exercise, compared to controls ($p < 0.01$). Furthermore, there appeared to be a cumulate effect of concussion history, such that HR recovery rate was significantly different between players with a single concussion history, compared to those with a history of multiple concussions (more than 1, $p < 0.05$). Therefore, despite clinical recovery (i.e., asymptomatic), long-term cardiac autonomic alterations may persist, and those with a cumulative concussion history may be most affected. Taken together, HR thresholds and HR recovery rates may prove valuable in pursuit of establishing physiological markers for SRC recovery monitoring. Although the experimental work included in this thesis did not reveal group differences for HR at moderate intensity (mean HR = 138 bpm), centrally there was a significant increase in CAN connectivity for the patient group. This novel finding might expose a potential underlying mechanism for cardiac autonomic alterations post-injury.

To discuss this from another angle, aerobic exercise has also been shown to improve cerebral blood flow, therefore oxygenation (Lal et al., 2018; Rooks et al., 2010). A systematic review with the aim to quantify the effects of exercise on cerebral oxygenation, gathered studies measuring hemodynamic response, through means of near-infrared spectroscopy (NIRS). The review reports that trained healthy individuals were able to attain higher cortical oxygen levels than untrained individuals. Additionally, that a quadratic response to incremental exercise exists, such that oxygenation rises between moderate (30% to 60% peak oxygen consumption (VO_{2peak})) to hard (60% to VO_{2peak}), then falls at very hard intensities ($\geq VO_{2peak}$) (Rooks et al., 2010). The transfer of this back to the field of SRC, implies that training status (trained vs. untrained) and intensity of exercise play a role in seizing the benefits of aerobic exercise.

A concussion injury follows a complex cascade of events, which leaves the brain in a state of energy crisis (Giza & Hovda, 2014). By recommending exercise at a moderate intensity post-injury, one may target this energy crisis by promoting increased cerebral blood flow and oxygenation (Leddy, Haider, et al., 2018; Leddy, Wilber, & Willer, 2018; Tan et al., 2014). This, although not explicitly investigated till now, is often reported as the reason why sub-symptom threshold exercise interventions promote recovery (Haider, Leddy, et al., 2019; Leddy, Haider, Ellis, et al., 2019), and reduce the likelihood of prolonged recovery (Leddy, Haider, Hinds, et al., 2019). Although still not a clear picture, functional connectivity increases in WB and the CAN, in response to moderate aerobic exercise might be the basis for restoring autonomic function post-injury.

5.2 Small-world Topology and Characteristics

Although discussions about brain network topology have existed for decades (Bassett & Bullmore, 2017; Watts & Strogatz, 1998), there is limited research on this topic in the field of SRC (N W Churchill et al., 2021). Generally, the brain tends to reveal *nonrandom* graph topologies (Bassett & Sporns, 2017), and is often referred to as a small-world network (Bassett & Bullmore, 2017). Despite reports of small-world topology remaining after mTBI/SRC injury, alterations within CP and LP parameters might reflect concussion pathology.

Paper #3 contributing to this thesis explored alterations in network topology and characteristics of WB and the DMN, in a group of SRC athletes within their RTS strategy, compared to healthy matched controls. Between group analysis pre-exercise (baseline), revealed differences in DMN-CP. Post-exercise the SRC group has elevated WB-LP. Furthermore, post-exercise there was an association between SRC and absence of small world topology (SWI ≤1, $p = 0.048$). In line with previous studies, a greater LP for patients might reflect decreased global connectedness (Cao & Slobounov, 2010; Imms et al., 2019; Li et al., 2022). By calculating small-world properties from resting-state EEG datasets of 29 student-athletes before (baseline) and shortly after (day 7 post-injury) sport-related mTBI, despite small-world like topology remaining, alterations were revealed in network properties (Cao & Slobounov, 2010). There was a significant elevation in LP ($p < 0.001$), and a reduction in CP (although non-significant; $p > 0.01$) from baseline to post-injury. In a resting-state fMRI study, 88 adult (mean age = 40 years old) mTBI patients were recruited within the first 7 days post-injury, parallel to 85 matched controls (mean age = 39 years old) to explore network properties between groups (Li et al., 2022). LP (as well as CP) values were significantly higher in the patient group, compared to matched controls ($p < 0.01$). These results echo alterations in small-world properties described also for neurological patients (Miraglia et al., 2022; van Diessen et al., 2013). Which trends towards an unfavourable deterioration from small-world topology for patients, and more network randomness (Fathian et al., 2022; Stam, 2014).

The idea of hyperconnectivity as a compensatory adaptive mechanism to injury has already been discussed in a previous section (*5.1.1 Hyperconnectivity hypothesis*), as it is depicted by increased functional connectivity. Though, through exploration of graph characteristics hyperconnectivity may also be revealed. An increased CP translates to increased local connectivity, which has been previously reported as a common compensatory response to neurological insult. This further supports the adaptiveness of the hyperconnectivity hypothesis (Hillary & Grafman, 2017; Nakamura et al., 2009). Whether and how this explains the increased CP pre-exercise reported in paper #3 remains unclear, as this group difference does not persist post-exercise.

The experimental work contributing to this thesis, explored small-world topology and network characteristics between two groups (SRC and CTRL), not only in strictly resting conditions but also pre- to post- moderate aerobic exercise. The novelty of this approach in the field of SRC research may be viewed as a strength of this study. However, due to a lack of previous research applying graph theoretical analysis and moderate aerobic exercise in this field, comparisons to other studies are limited. As a compromise, the following will discuss this study's results to previous research investigating healthy athletes (Büchel, Lehmann, et al., 2021; Büchel, Sandbakk, & Baumeister, 2021; Tamburro et al., 2020). In a study with 14 male active adults (mean age = 26 ±4 years old), who regularly cycled at least twice a week, functional connectivity and brain network efficiency from EEG datasets was examined (Tamburro et al., 2020). Within the alpha band, global efficiency (GE) significantly increased in response to exercise initiation, which could be due to an increase in alertness and preparedness (GE = 0.587, p = 0.008). This increase was followed by a decrease during periods of exhaustive cycling (GE = 0.556, p = 0.008), which may be due to higher efforts making it harder to integrate information between brain regions. Another study, again exploring an exercise test in blocks of increasing intensity, with active adult participants (mean age = 25 years old), found that low (50% VO_{2peak}) to moderate (70% VO_{2peak}) intensity enhances network characteristics, while exhaustive (90% VO_{2peak}) intensity impaired characteristics (Büchel, Sandbakk, & Baumeister, 2021). More specifically, within alpha-1 band (8-10.5 Hz), there was a significant main effect for condition (intensity) on CP (p = 0.036), LP (p = 0.028) and SWI (p = 0.042). Relating this back to the work done for this thesis, which only evaluated the response to moderate exercise intensity (70% maxHR), still healthy active controls showed lower WB-LP, compared to the SRC group. This may resemble better connectedness at moderate intensity, matching the results of enhanced efficiency (Tamburro et al., 2020), and pointing to exercise-induced benefits on brain function. Discussing this result from the other direction, higher WB-LP values for the SRC group post-exercise, may reflect decreased connectedness due to the DAI (Vecchio et al., 2017). However, as pre-exercise WB-LP values did not significantly differ between groups, moderate intensity exercise may have played a role in aggravating these results.

The association between the absence of WB small-world topology (SWI ≤1) and SRC, points to patients exhibiting less efficient information exchange (Bassett & Bullmore, 2017; Vecchio et al., 2017). The absence was identified in 5 (of the 21) SRC patients. Further investigation into participant characteristics revealed that they were either in the early acute recovery phase or had a cumulative concussion history with a high symptom severity score. Although the majority of the SRC patients recruited for this study were in the subacute phase (i.e., 8-89 days post-injury (Elbin et al., 2014)), 3 patients (/5) were in the early acute phase (i.e., ≤ 7 days post-injury). The other 2 (/5) may be characterized by having a cumulative concussion history with a high symptom severity. Unfortunately, further statistical investigations into the effect of clinical characteristics on the (absence of) small-world topology were not possible due to the low and heterogeneous sample. However, if future studies replicate these results in a larger sample, taking care of clinical characteristics, then exploring the clinical utility of an absence of small-world topology as a potential marker may ensue.

5.2.1 Neurophysiological Markers

With this sub-chapter, this thesis comes full circle. From presenting the current state of the research on neurophysiological markers, and their potential clinical utility in paper #1 to closing the discussion here, that future greater powered studies are needed in this pursuit. The establishment of objective markers, which may aid in clinical decision making is highly sought out (Patricios et al., 2023; Tabor et al., 2023). Due to the complexity of SRC injuries resulting in subtle (to serve) heterogeneous signs and symptoms and variant recovery trajectories, in addition to a limited utility of conventional methods (i.e., CT and MRI), clinicians rely on clinical assessment results and subjective reports from the athletes (Tabor et al., 2023). Parallel to developments and advances in neuroscientific technologies, methods such as, (quantitative) EEG may particularly be able to provide important insights into the pathophysiology of SRC (Conley et al., 2018) and mechanisms for recovery.

A novel EEG processing technique, which derived a BNA score from ERPs, is under investigation for it’s utility as a potential objective marker for SRC management (Eckner et al., 2016; Kiefer et al., 2015; Reches et al., 2017). Studies which investigated the BNA were already described within a previous sub-chapter (*2.4.1 Electrophysiological investigations*). As a brief summary, changes in BNA scores during the recovery process may help clinicians qualitatively describe and quantitatively evaluate brain function (Kiefer et al., 2015), but future studies are needed (Reches et al., 2017). In clinical practice, BrainScope® (BrainScope Company Inc, USA) medical devices index brain function from novel quantitative EEG methods (Hanley et al., 2018). A Brain Function Index (BFI) and Concussion Index (CI) were designed to reflect abnormalities which result from a mTBI/concussive injury. Features which relate to changes in frequency spectra, functional connectivity and complexity were considered in the design. In combination with multimodal concussion assessments (i.e., including SCAT), the indexes may provide clinicians with additional relevant information to help make clinical decisions (Bazarian et al., 2021; Hanley et al., 2018; Jacquin et al., 2021). In one study, which examined 207 concussion patients and 373 athlete controls, on day 0 (within 72 hours post-injury) CI scores were significantly lower for the concussion group, compared to controls ($p < 0.001$) (Bazarian et al., 2021) At follow-up, in this case at return to play, there was a significant increase in CI from day 0, within the patient group ($p < 0.001$). Such a marker (in this case an index), has the potential to provide valuable information to clinicians at the point of diagnosis, and for monitoring recovery (Bazarian et al., 2021). Of note, both the BFI and CI have received (Food and Drug Administration (FDA)) clearance to be used in emergency departments alongside standard clinical assessments.

A systematic review from some years ago focused on resting-state EEG studies in the field of SRC, as a reliable technique to identify functional neurophysiological changes after a concussion (Conley et al., 2018). The systematic review included 16 studies, all of which reported some abnormality in resting-state EEG activity after a concussion, however, the methods and analytical approaches differed which limited comparisons. Compared to power-based analyses (i.e., characterizing the strength or magnitude of activity within each frequency band), connectivity (/coherence) based analyses are better suited to reflect neural communication and network dynamics alterations. Therefore, may better reflect the pathology of SRC, and related DAI. However, in this domain results were inconsistent with one study reporting decreased frontal to parietal connectivity (Cao & Slobounov, 2010), and another reporting increased frontal connectivity and decreased parietal-occipital connectivity (Virji-Babul et al., 2014). Inconsistencies in this case may rather reflect methodological differences than neurophysiological ones. A lack of consistency and replicability of results impairs consensus and halts the transfer of research findings to clinical use.

Although the experimental works included in this thesis aimed not to identify nor validate any markers for clinical use, instead the aim was to contribute to an increased understanding of brain function post-injury. Still, the results may have provided insights into the pathology of SRC (e.g., functional disconnection), and revealed mechanisms for recovery (e.g., targeting the central origin of cardiac ANS symptoms). In line with the pursuit of establishing objective markers, which may help clinicians make RTS decisions, it seemed appropriate to investigate the response to moderate aerobic exercise as recommended within the current RTS strategy (Patricios et al., 2023). Furthermore, this was identified as a relevant gap in the research, when it comes to neurophysiological markers for RTS (paper #1). In both experimental works (papers #2 and #3), through (quantitative) resting-state EEG applications pre- and post-exercise, valuable insights into brain function post-concussion were revealed. By including a moderate aerobic exercise test neurophysiological alterations for the SRC group were exposed, which otherwise were not present in strictly resting conditions (pre-exercise). The main results may be summarized as follows: First, significantly increased connectivity within the CAN in response to exercise, which occurs only for the SRC group, may have exposed the origin of cardiac autonomic alterations post-injury (La Fountaine, 2018). Second, higher LP in WB post-exercise for the SRC group compared to controls may reflect functional disconnection due to injury (Vecchio et al., 2017), with an adaptive compensatory response necessary to maintain connectedness (Hillary & Grafman, 2017). Third, the uncovering of an association between absence of small-world topology and SRC post-exercise, which may have been driven by clinical characteristics, warrants future investigations.

5.3 Limitations

The experimental works of this thesis are not without limitations. The following will detail the limitations which may particularly influence the interpretation and application of the main results. Beginning with the participants' characteristics of the sample. The inclusion criteria 18 years to 40 years old limits the generalizability of these results to pediatric and adolescent athletes. However, as an abundance of previous literature explored adolescent athletes' response to the BCTT and BCBT, this study points towards the feasibility (i.e., sub-symptom) of a moderate aerobic exercise test with elite adult athletes. A second limitation rooted in the participants' characteristics, is the small, under powered and rather heterogeneous (i.e., days since concussion, and the number of previous concussions) sample. Unfortunately, due to this, it did not afford the exploration of subgroups based on concussion characteristics (e.g., time since injury). This point particularly limited any further investigation into the characteristics of the SRC athletes, which may have particularly driven the small-world topology (/or absence of small-worldness) results. A future longitudinal study, which collects data from the acute phase to subacute (defined as up to 3 months post-injury) (Mayer et al., 2017), may track the trajectory of this alterations and provide additional valuable insights. One must also be aware that neurophysiological measures are rather heterogeneous, and variable (Ding et al., 2022). With only one measurement point available, day-to-day fluctuations in these measures were not controlled for. Further promoting future studies to consider a longitudinal study design.

In addition, methodological limitations related to EEG and network neuroscience should be mentioned and briefly discussed. The analysis conducted for paper #2 and #3, was heavily hypotheses based - meaning that specific networks of interest, previously reported or hypothesized to be altered by a concussive injury were selected a priori. These networks were explored by calculating mean values over the network, not node-to-node connections. This decision was made to reduce the risk of Type-1 error, but it is important to mention as this may be the reason why although other studies have reported altered connectivity within the DMN post-concussion, (Cao & Slobounov, 2010; Virji-Babul et al., 2014; Zhang et al., 2012) this study failed to do so. In this field of research, drawing clear conclusions is often limited due to methodological inconsistencies such as this.

6 Conclusions and Outlook

This dissertation and considered publications have contributed to an increased knowledge and understanding of a neurophysiological response (i.e., within WB and relevant brain networks) to moderate aerobic exercise, during athletes' RTS. This increased understanding may be used to inform future studies about the feasibility of implementing a moderate aerobic exercise test, with quantitative EEG applications.

6.1 Outlook

This outlook section will focus on the altered CAN connectivity for the SRC group, in response to moderate aerobic exercise. This result may have exposed an underlying mechanisms for cardiac autonomic alterations post-injury (Esterov & Greenwald, 2017; La Fountaine, 2018). Furthermore, it may have revealed a mechanism by which moderate aerobic exercise promotes recovery after a concussion (Leddy, Wilber, & Willer, 2018; Tan et al., 2014). The emerging evidence for the promotion of *exercise is medicine* post-concussion (Leddy, Haider, et al., 2018) till now has come from clinical trials exposing participants and patients to sub-threshold exercise tests and interventions (Haider, Johnson, et al., 2019; Leddy, Haider, Ellis, et al., 2019; Leddy, Haider, Hinds, et al., 2019), with limited investigations into the response within the central nervous system (the brain). Future studies are needed, to validate these results with a greater sample and studies with longitudinal designs that may track recovery trends.

Another consideration for future studies should be the application of the results to the field (literally). It may not be realistic to assume that athletes and clinicians have access to EEG technologies. It is more likely that they have access to ECG and/or ANS sensors. Therefore, investigations into the association between CAN and peripheral (autonomic) neurophysiological parameters should also be considered a next logical step. This idea is further supported by the notion that not central, but peripheral ANS monitoring in sports is already being done to recommend training load and recovery (Bellenger et al., 2016).

6.1.1 BelaNCo Project

An underway sequel project - *Belastungsinduzierte Anpassungen funktionell autonomer Netzwerke nach sportassoziierter Concussion* (BelaNCo), aims to further explore the response of the CAN to aerobic exercise during an athlete's RTS, compared to healthy matched controls. Beyond the central autonomic response of the CAN, the sequel project may also consider peripheral ANS data. This is because the transfer to the field (of sports) is of utmost importance. The BelaNCo study aims to identify opportunities for peripheral ANS monitoring of central alterations, during athletes' RTS. This is further motivated because, as already mentioned, peripheral ANS monitoring in sports is already being done to recommend training load and recovery (Bellenger et al., 2016).

Preliminary investigations and two conference contributions already began to explore the peripheral ANS response to moderate aerobic exercise, and its association with central CAN connectivity. Parasympathetic cardiac activity – as measured by root mean square of successive differences (RMSSD) (Malik et al., 1996), decreased more significantly and with less variability after exercise, for SRC athletes (Mdn = 56.94 to 40.16, $p < 0.001$) than matched controls (Mdn = 52.90 to 43,13; $p = 0.016$). LF/HF is considered by some to reflect sympatho/vagal balance (Malik et al., 1996), therefore presumed to reflect a balance between SNS and PNS. In this preliminary analysis, only the SRC group showed a significant increase in LF/HF from pre- (Mdn = 0.66) to post-exercise (Mdn = 0.77, $p = 0.036$) (Coenen, van den Bongard et al., 2024). As the interpretation of the LF/HF remains controversial during short measurements (5 minutes vs. 24 hours), because it may be that PNS (not SNS) drives the LF in resting-state conditions (Shaffer & Ginsberg, 2017), this particular result will not be further discussed here. To investigate the sympathetic activity more clearly, mean electrodermal activity (EDA) was calculated from the GSR datasets. EDA reflects sympathetic innervation and historically was used to measure psychophysiological stress (Boucsein, 2012; Posada-Quintero & Chon, 2020). In the preliminary investigations, the SRC group showed a significant increase from pre-(Mdn = 1.82), to post-exercise (Mdn = 2.30, p =0.043). Although a similar (increase) response existed for the control group (Mdn = 1.60 to 2.36), results marginally missed statistical significance ($p = 0.053$) (Coenen, Delling, et al., 2023). After exercise, there was also a significant positive correlation between EDA and CAN connectivity ($p \leq 0.05$). This may highlight the capability of a physical stressor to elicit a more pronounced central (sympathetic) response.

Taken all together, this thesis and the works included contribute to an increased knowledge and understanding of neurophysiological responses to moderate aerobic exercise, during RTS. Furthermore, results may have exposed a potential underlying mechanism for cardiac autonomic alterations post-injury. Still, more work is needed to be done in this field in pursuit of establishing objective neurophysiological markers which may aid in clinical RTS decisions. Not only central but also peripheral ANS makers should be considered in this pursuit.

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Research Papers

Research papers

Coenen, J., & Reinsberger, C. (2023). Neurophysiological markers to guide return to sport after sport-related concussion. *Journal of Clinical Neurophysiology, 40,* 391–397.doi: 10.1097/WNP.0000000000000996

Coenen, J., Strohm, M., Reinsberger, C. (2024) Impact of moderate aerobic exercise on small-world topology and characteristics of brain networks after sport-related concussion: an exploratory study. *Scientific Reports, 14,* 25296. doi:10.1038/s41598-024-74474-6

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