# Concussions and repetitive head impacts in sports: Functional testing, neuroimaging, interventions and brain injury biomarkers

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## Functional testing, neuroimaging, interventions and brain injury biomarkers

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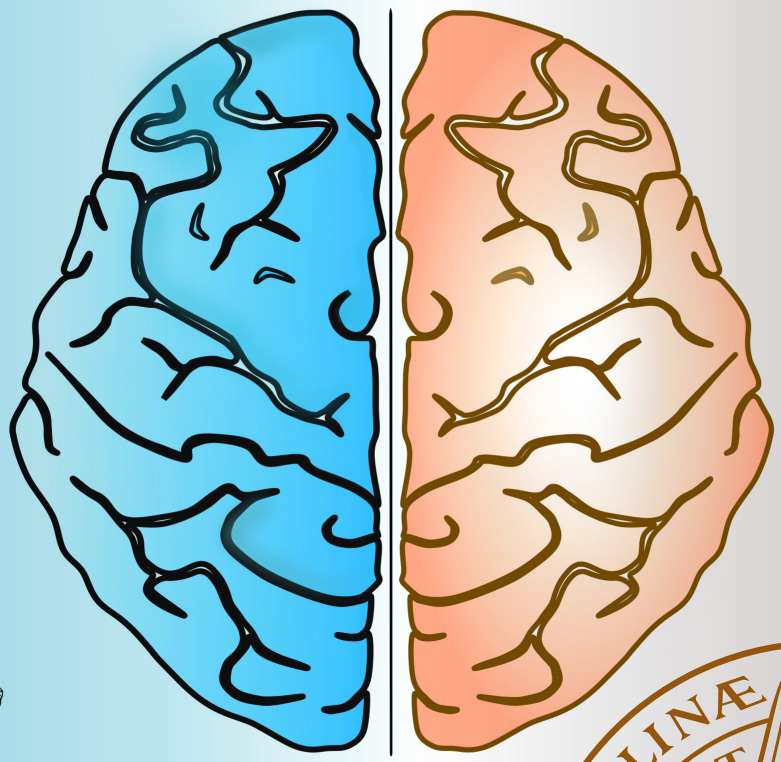

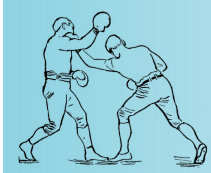

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DOCTORAL DISSERTATION

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**Title and subtitle**: Concussions and repetitive head impacts in sports: Functional testing, neuroimaging, interventions and brain injury biomarkers

**Abstract:** A sport-related concussion (SRC) may result in a variable number of acute symptoms. At long-term, some SRCs lead to persistent post-concussive symptoms (PPCS), defined as symptoms lasting more than four weeks post-SRC. Repetitive head impacts (RHI), insufficient to cause SRCs, may also cause short- and long-term brain health problems. Commonly, strenuous exercise leads to increased core and brain temperatures that may exacerbate SRCs and RHIs. To date, interventions with proven benefit used in the acute management of RHI and SRC are scarce. This thesis aimed to investigate mechanisms of vestibular system-related symptoms in PPCS athletes, explore the brain's perivascular spaces as indicators of glymphatic system function in PPCS athletes and boxers, and evaluate the effects of a head-and-neck cooling intervention on blood brain injury biomarker levels and clinical symptoms when applied immediately post-fight in boxers.

**Paper I-II**: Twenty-one PPCS athletes and 21 healthy controls were evaluated by

ultra-high field strength (7T) magnetic resonance imaging (MRI) and a battery of vestibular tests including posturography. PPCS athletes showed vestibular impairment related to dysfunction of the inferior vestibular nerve, as well as impaired postural control.

**Paper III**: Using 7TMRI in 21 boxers, 18 PPCS athletes and 20 controls, only boxers displayed enlargement and increased diffusivity of the perivascular spaces, indicating altered brain clearance systems.

**Paper IV–V:** Forty active boxers were included in a clinical trial where 19 boxers were randomized to receive early head-and-neck cooling, and 21 to routine post-fight management. Post-fight GFAP levels were lower ($p<0.05$) on day 6 post-fight in boxers receiving the cooling intervention, initiated at ca 10 minutes post-fight, than in controls. The intervention slightly lowered clinical symptoms scores ($p=0.08$), and levels of the axonal injury marker NF-L decreased by 1.0 ± 1.1 pg/mL in the intervention group and increased by 1.71 pg/mL ±1.07 in controls ($p= 0.07$).

We found that PPCS athletes suffer from a high burden of balance-related problems, reducing their quality of life, and identified inferior vestibular nerve dysfunction and impaired postural stability as contributors to these symptoms. Active boxers had alterations of their perivascular spaces, potentially indicating impaired glymphatic system function. Finally, reduced levels of brain injury biomarkers by early head-and-neck cooling indicate that rapid normalization of brain temperature may attenuate secondary brain injury mechanisms following a boxing bout.

**Key words:** Sports-related concussion, repetitive head impact, persistent post-concussive symptoms, traumatic brain injury, ultra-high field strength MRI, glymphatic system, brain temperature, selective head-and neck cooling

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MADE IN SWEDEN

*To my father Seyed Morteza*

# Table of Contents

# Popular scientific summary (populärvetenskaplig sammanfattning)

Beskrivning av huvudtrauma inom idrottsevenemang sträcker sig 3000 år tillbaka, till Homeros epos Iliaden och Odysséen från antikens Grekland. Det beskrivs "ett slag mot käken som gjorde att Euralyos föll ner till marken utan kontroll över sin kropp". Under senare år gav Hippokrates den första medicinska förklaringen till huvudskada genom att nämna förlorat medvetande som följd av trauma mot huvudet under idrottsevenemang (gladiatorerna). Oron för huvudtrauma inom idrott kan spåras tillbaka till antikens Grekland, där boxning ansågs vara den mest livshotande och vanligaste orsaken till död och svåra skador. Historiskt sett gav Al-Razi (ca 865–925 e.Kr) den tidigaste kända klassificeringen av huvudskador och beskrev både trauma utan synlig skallskada och symtom efter slag mot huvudet. Hans iakttagelser kan ses som en tidig beskrivning av det vi idag kallar hjärnskakning (på engelska concussion).

Trots att dagens kontaktidrott skiljer sig markant från den som utövades under gladiatorernas tid kan vi peka på flera kända idrottare som har uppmärksammat riskerna med idrottsrelaterade hjärnskakningar och upprepat- repetitivt- trauma mot huvudet. Inom boxning har vi sett Muhammad Alis uttalade Parkinsonism, och uttalanden från den amerikanska fotbollsspelaren Brett Favre, som har sagt: "Jag skulle inte låta min son utöva sporten."

En idrottsrelaterad hjärnskakning uppstår vid direkt slag mot huvudet eller vid ett indirekt slag mot kroppen där kraften överförs till hjärnan och leder till störningar i hjärnans funktion. Symtomen som uppstår till följd av traumat karaktäriseras som en störd funktion i hjärnan och kan yttra sig som till exempel försämrad balans, nedsatt kognitiv förmåga, övergående dimsyn eller kortvarig medvetslöshet.

Dessa symptom kan, om de kvarstår, hindra idrottaren både från återgång till idrottande samt vardagsliv som skola/jobb. Efter en bekräftad hjärnskakning är det viktigt att de rehabiliteras enligt den så kallade hjärntrappan som utgörs av 6 steg. Vanligtvis försvinner symtomen inom 7–10 dagar, men i 15–20 % av fallen kan återhämtningen ta längre tid. Kvarstående symtom i mer än fyra veckor efter idrottsrelaterad hjärnskakning ökar risken för övergång till en subkronisk fas med persisterande symtom. Förlängd återhämtning har i dagsläget kopplats till hög initial symtombörda vid skadetillfället, upprepade hjärnskakningar, försämrat balanssystem, samt kvinnligt kön.

Repetitiva slag mot huvudet som ej når tröskelnivån för en hjärnskakning kan medföra likvärdiga konsekvenser som en diagnosticerad hjärnskakning på lång sikt. Den risken avspeglas hos boxare, där en boxare under en sex minuter lång boxningsmatch utsätts för mer än 40 slag mot huvudet. Teoretiskt kan antalet slag mot huvudet under ett år överstiga 1000, om man räknar med träning.

Även om en hjärnskakning inte utvecklas är inte repetitiva huvudtrauman ofarliga; den samlade effekten av yttrar sig snarare över tid som en långsam försämring av hjärnans funktion. Det är visat att långsiktiga förändringar i hjärnan kan uppstå hos idrottare inom kontaktsport, även om de aldrig diagnostiserats med hjärnskakning. Tidiga tecken syns som skador på nervtrådarna och andra förändringar i hjärnans vita substans. När skadorna sedan förvärras visar studier vid obduktion ansamlingar av onormala proteiner i hjärnan, något som är typiskt för sjukdomen chronic traumatic encephalopathy (CTE).

Det som särskiljer huvudtrauman inom idrott från andra hjärntrauma är att de ofta sker på grund av den fysiska ansträngningen under förhöjd hjärntemperatur som kan bli i nivå med feber, vilket kan öka hjärnskaderisken. För varje grad Celsius som hjärntemperaturen stiger ökar också hjärnans energibehov med 6–8 %. Dessutom är hjärnan redan ett mycket energikrävande organ och konsumerar hela 20 % av vårt totala energibehov. Den ökade risken för hjärnskada efter kontaktidrott har påvisats med förhöjda biomarkörer för hjärnskada, och nivåerna av biomarkörer blir ännu högre vid idrottsrelaterad hjärnskakning.

Som en möjlig behandling av idrottare har vi studerat användning av selektiv kylning av huvud- och halsregionen efter både idrottsrelaterade hjärnskakningar och repetitivt trauma mot huvudet. Syftet är att sänka hjärntemperaturen till normal temperatur, med motiveringen att detta kan ha en skyddande effekt och därmed minska symtom och hjärnskadan. Tidigare visade en klinisk studie på 132 elithockeyspelare med idrottsrelaterad hjärnskakning en lovande effekt, med snabbare återgång till sport genom tidigare symtomfrihet hos de spelare som kyldes, än hos kontroller.

**Artikel 1:** Tjugoen idrottare med symtom efter hjärnskakning under mer än sex månader jämfördes med friska kontroller gällande symtombörda, balanstester och magnetkamera (MR)-undersökning av hjärnan. Resultaten visade att idrottare med kvarstående symtom upplevde nedsatt livskvalitet och uttalade symtom. Alla deltagare (100 %) rapporterade trötthet, och 85 % hade balansrelaterade problem. Balanstesterna visade skador på den nedre balansnerven hos dessa idrottare, vilket kan förklara deras balansproblem.

**Artikel 2:** Tjugo idrottare med persisterande symtom i över 6 månader efter en idrottsrelaterad hjärnskakning jämfördes med 12 aktiva idrottare som fungerade som friska kontroller. Undersökning av så kallad postural kontroll genomfördes för att jämföra hur mycket energi som krävdes för att upprätthålla balansen i stående. Resultaten visade att idrottare med persisterande symtom efter hjärnskakning använde betydligt mer energi för att hålla balansen än de friska kontrollerna. Dessutom förlitade sig dessa idrottare i större utsträckning på synen för att korrigera balansen jämfört med kontroller.

**Artikel 3:** Tjugoen aktiva boxare och 18 idrottare med persisterande symtom efter hjärnskakning jämfördes med 20 matchade friska kontroller med hjälp av högupplöst MR. Syftet var att undersöka hjärnans dränagesystem- det glymfatiska

systemet. Aktiva boxare visade ett konstant mönster av förstorade perivaskulära utrymmen som tecken på ett överansträngt glymfatiskt system, jämfört både med symtomatiska idrottare och friska kontroller.

**Artikel 4:** Protokoll som låg till grund för den randomiserade, blindade studien om nedkylning av idrottare inkluderade en powerberäkning, som visade att det krävdes totalt 40 boxare för att uppnå tillförlitliga resultat, med målet att påvisa en 20 % skillnad i biomarkörer mellan grupperna efter sex dagar.

**Artikel 5:** Totalt 40 aktiva boxare inkluderades, varav 19 boxare randomiserades till huvud- och halskylning efter boxningsmatch, medan 21 boxare följde det standardiserade protokollet för återgång till spel. Resultaten visade en signifikant effekt av avkylningen, med snabbare normalisering av hjärnskademarkören GFAP efter sex dagar. En liknande trend observerades för hjärnskademarkören NF-L ($p = 0.07$), och de kylda boxarna hade färre symtom jämfört med kontrollerna ($p = 0.08$).

I denna avhandling har vi visat att idrottare med persisterande symtom efter idrottsrelaterad hjärnskakning lider av uttalade kvarstående symtom i form av trötthet, balansproblem, depression och ångest.

Hos idrottare med hjärnskakning kunde vi lokalisera en skada på den nedre balansnerven (*artikel 1*) samt tecken på ökad energi för att hålla balansen och ökat beroende av synen vid stående *(artikel 2)*, vilket kan bidra till uttalad trötthet. Resultaten ligger i linje med tidigare forskning som visat att idrottare efter hjärnskakning använder synen i betydligt högre grad för att upprätthålla balansen under krävande moment jämfört med friska kontroller.

Detta förändrar den normala fördelningen i balanssystemet, som bygger på flera komponenter, inklusive ytlig känsel samt förmågan att känna av sin egen position och rörelser (proprioception).

Vidare visade högupplösta magnetkameraundersökningar förstorade perivaskulära utrymmen hos aktiva boxare samt ökad diffusivitet. Detta tyder på ett överansträngt rensningssystem i hjärnan hos aktiva boxare vilket inte påvisades hos idrottare med persisterande symtom efter hjärnskakning eller friska kontroller *(artikel 3)*. Slutligen visade tidig selektiv huvud- och halskylning efter boxningsmatch en signifikant snabbare normalisering av hjärnskadeproteinet GFAP *(artikel 4&5)*. Det påvisar betydelsen av förhöjd hjärntemperatur och indikerar att kylningen potentiellt kan minska vissa skadliga processer i hjärnan efter upprepade slag mot huvudet. Sammanfattningsvis syftade studierna i denna avhandling till att identifiera orsaker till balansrelaterade problem hos idrottare med symtom efter hjärnskakning. Hjärnskademekanismer hos idrottare som drabbats av hjärnskakningar och hos boxare som utsatts för upprepade huvudtrauman undersöktes. Slutligen utvärderades potentialen för en intervention hos boxare, mätt med hjärnskademarkörer, att minska risken för hjärnskador och förbättra återhämtningen.

# Abbreviations

LOC Loss of Consciousness

CSF Cerebrospinal fluid

CTE Chronic traumatic encephalopathy

cVEMP Cervical vestibular evoked myogenic potentials

DHI Dizziness Handicap Inventory

DKI Diffusion kurtosis imaging

DTI Diffusion tensor imaging

RTP Return to play

GFAP Glial fibrillary acidic protein

HADS Hospital Anxiety Depression Scale

MRI Magnetic resonance imaging

mTBI Mild traumatic brain injury

NFL Neurofilament light

S100B S100 calcium-binding protein B

PPCS Persistent post-concussive symptoms

QoL Quality of life

SCAT Sport Concussion Assessment Tool

SRC Sport-related concussion

RHI Repetitive head impact

TBI Traumatic brain injury

Tau Tubulin-associated unit

BD-tau Brain derived tubulin-associated unit

vHIT Video head impulse test

VNG Videonystagmography

# List of Papers

*Paper I*

Gard A, **Al-Husseini A**, Kornaropoulos EN, De Maio A, Tegner Y, Björkman-Burtscher I, Markenroth Bloch K, Nilsson M, Magnusson M, Marklund N. Post-Concussive Vestibular Dysfunction Is Related to Injury to the Inferior Vestibular Nerve. J Neurotrauma. 2022 Jun;39(11-12):829-840. doi: 10.1089/neu.2021.0447.

*Paper II*

**Al-Husseini A**, Gard A, Fransson PA, Tegner Y, Magnusson M, Marklund N, Tjernström F. Long-term postural control in elite athletes following mild traumatic brain injury. Front Neurol. 2022 Sep 12;13:906594. doi: 10.3389/fneur.2022.906594.

*Paper III*

Shanbhag, N. C., **Al-Husseini, A**., Duarte Coello, R., Valdés Hernandez, M. del C., Barisano, G., Hett, K., Gard, A., Jung, L. B., Nilsson, M., Markenroth Bloch, K., Newcombe, V. F. J., Menon, D. K., Wardlaw, J., Marklund, N., & Kornaropoulos, E. N. (manuscript under submission). *Impaired perivascular space diffusivity indices in elite boxers: A 7T MRI study of glymphatic system. (Submitted for publication)*

*Paper IV*

**Al-Husseini A**, Tegner Y, Blennow K, Zetterberg H, Marklund N. Effects of Selective Head-and-Neck Cooling on Brain Injury-Related Biomarker Levels and Symptom Rating Following a Boxing Bout: Protocol for an Exploratory Randomized Trial. JMIR Res Protoc. 2025 Jun 16;14:e68954. doi: 10.2196/68954.

*Paper V*

**Al-Husseini, A**., Blomstrand, E., Tegner, Y., Blennow, K., Zetterberg, H., & Marklund, N. (manuscript under submission). *Reduced brain injury biomarker levels by early selective head and neck cooling in elite boxers: A randomized clinical trial. (Submitted for publication)*

# Other scientific contributions

**Al-Husseini A**, Fazel Bakhsheshi M, Gard A, Tegner Y, Marklund N. Shorter Recovery Time in Concussed Elite Ice Hockey Players by Early Head-and-Neck Cooling: A Clinical Trial. J Neurotrauma. 2023 Jun;40(11-12):1075-1085. doi: 10.1089/neu.2022.0248.

# Author´s contribution to the papers

**Paper I**

Analysis and interpretation of vestibular data. Project administration, including recruitment of healthy control and PPCS participants, and performing examinations including MRI scanning and medical history collection. Co-authorship throughout the manuscript preparation process.

**Paper II**

Analysis and interpretation of posturography data. Project administration, including recruitment of healthy control and PPCS participants, and performing examinations. Manuscript drafting in collaboration with co-authors.

**Paper III**

Project administration, including recruitment of participants across all cohorts and collection of all MRI data. Interpretation of data with respect to repetitive head impacts and neuroimaging findings. Critical review of the manuscript and contribution to the submission process.

**Paper IV**

Conceptualisation of the study design and development of the methodology. Responsible for obtaining national approval from the Swedish Boxing Association for study conduct. Visualisation, drafting, and revision of the manuscript in response to comments from co-authors and reviewers. Final approval of the manuscript and responsibility for the publication process.

**Paper V**

Conceptualisation of the study design and development of the methodology together with supervisors. Project administration, including recruitment and administration of examinations including MRI scanning and medical history collection of all boxers across Sweden. Analysis and interpretation of all data. Visualisation, drafting, and revision of the manuscript incorporating feedback from co-authors and supervisors.

# Abstract

A sport-related concussion (SRC) may result in a variable number of acute symptoms. At long-term, some SRCs lead to persistent post-concussive symptoms (PPCS), defined as symptoms lasting more than four weeks post-SRC. Repetitive head impacts (RHI), insufficient to cause SRCs, may also cause short- and long-term brain health problems. Commonly, strenuous exercise leads to increased core and brain temperatures that may exacerbate SRCs and RHIs. To date, interventions with proven benefit used in the acute management of RHI and SRC are scarce. This thesis aimed to investigate mechanisms of vestibular system-related symptoms in PPCS athletes, explore the brain's perivascular spaces as indicators of glymphatic system function in PPCS athletes and boxers, and evaluate the effects of a head-and-neck cooling intervention on blood brain injury biomarker levels and clinical symptoms when applied immediately post-fight in boxers.

Paper I-II: Twenty-one PPCS athletes and 21 healthy controls were evaluated by ultra-high field strength (7T) magnetic resonance imaging (MRI) and a battery of vestibular tests including posturography. PPCS athletes showed vestibular impairment related to dysfunction of the inferior vestibular nerve, as well as impaired postural control.

Paper III: Using 7TMRI in 21 boxers, 18 PPCS athletes and 20 controls, only boxers displayed enlargement and increased diffusivity of the perivascular spaces, indicating altered brain clearance systems.

Paper IV–V: Forty active boxers were included in a clinical trial where 19 boxers were randomized to receive early head-and-neck cooling, and 21 to routine post-fight management. Post-fight GFAP levels were lower ($p<0.05$) on day 6 post-fight in boxers receiving the cooling intervention, initiated at ca 10 minutes post-fight, than in controls. The intervention slightly lowered clinical symptoms scores ($p=0.08$), and levels of the axonal injury marker NF-L decreased by $1.0 \pm 1.1$ pg/mL in the intervention group and increased by 1.71 pg/mL $\pm 1.07$ in controls ($p= 0.07$).

We found that PPCS athletes suffer from a high burden of balance-related problems, reducing their quality of life, and identified inferior vestibular nerve dysfunction and impaired postural stability as contributors to these symptoms. Active boxers had alterations of their perivascular spaces, potentially indicating impaired glymphatic system function. Finally, reduced levels of brain injury biomarkers by early head-and-neck cooling indicate that rapid normalization of brain temperature may attenuate secondary brain injury mechanisms following a boxing bout.

# 1 Introduction

## Traumatic brain injury (TBI)

TBI can be defined as an alteration of brain function, or other evidence of brain pathology, caused by an external force [1]. TBI is a major health concern worldwide, and a leading cause of death, disability, and emergency department visits [2]. It is a most common neurological disorder and acknowledged as a significant health concern both in the acute setting as well as chronically at long-term [3]. Annually, 50–60 million people sustain a TBI, and it is expected to remain one of the top injury-related causes of mortality and disability to the year 2030 [3]. Worldwide, age-adjusted TBI incidence is estimated at 259 per 100,000 people [4] and in Europe, the incidence varies geographically between 47-694 per 100.000 people, with 2.1 million hospital discharges. The annual mortality range is 9 to 28 per 100,000 people [5], and additionally, TBI-related deaths in Europe are estimated at 82.000 annually [3]. Nearly three times more TBI cases are observed in low- and middle-income countries (LMICs). This can be the result of poor traffic regulations and limited access to healthcare facilities [5]. Although the overall incidence of TBI is lower in high-income countries, cases with persistent post-TBI symptoms are more readily detected due to the availability of specialized care units and follow-up care [3, 6].

The most common injury mechanisms of TBI include falls, motor vehicle accidents, violence, sport-related injuries, accidents at home or work, and suicide attempts [5]. Even though the number of traffic collisions is decreasing, the rate of TBI related to falls is increasing particularly in the elderly [5, 7]. TBI is a vastly heterogeneous disorder, with a large variation in how the trauma affects the brain as well as patient presentation and outcome. TBI classification is based on several criteria, including findings on structural neuroimaging, duration of loss of consciousness (LOC) and post-traumatic amnesia (PTA), and the level of consciousness as measured by the Glasgow Coma Scale (GCS) score (Table 1). TBI evaluations are mostly based on the GCS score and are classified into mild (mTBI), moderate or severe TBI [8, 9]. In the US, 36.4% of self-reporting individuals had experienced at least one mTBI during their lifetime [9, 10].

While this classification is easy to remember and use, it lacks prognostic accuracy and patient classified as “mild” may have a poor recovery, and those presenting as “severe” may have a full recovery. For this reason, a new classification has been proposed based on clinical presentation, biomarker levels, neuroimaging results and individual patient factors. This CBI-M (clinical, biomarkers, imaging- modifiers) classification is expected to gain importance in TBI management in the coming

years [11]. Taken together, these challenges highlight the need of multimodal assessment of the TBI patient and of developing improved classifications in order to better guide clinical decisions, and for improved prognostication.

**Table 1. Glasgow Coma Scale and TBI Classification**
Classification of traumatic brain injury (TBI) by clinical examination based on three response domains; Eye opening, Verbal response and motor response using the Glasgow Coma Scale (GCS)

| Response domains | Response | Score |
|---|---|---|
| **Eye opening response** | Spontaneous | 4 |
| | To speech | 3 |
| | To pain | 2 |
| | No response | 1 |
| **Verbal response** | Oriented | 5 |
| | Confused | 4 |
| | Inappropriate | 3 |
| | Incomprehensible | 2 |
| | No response | 1 |
| **Motor response** | Obeying | 6 |
| | Localizing pain | 5 |
| | Withdrawal to pain | 4 |
| | Flexion to pain | 3 |
| | Extension to pain | 2 |
| | No response | 1 |
| **Injury severity based on GCS** | | |
| **Mild TBI** | | **13-15** |
| **Moderate TBI** | | **9-12** |
| **Severe TBI** | | **3-8** |

# Sport-related concussion and repetitive head impacts

Concussion is, by definition, a mild traumatic brain injury (mTBI). Although the terms "concussion" and "mTBI" are often used interchangeably in the literature, there are definitional differences. For instance, a sport-related concussion (SRC)- the topic of this thesis- does not require LOC for diagnosis and management [12-14]. An SRC is defined as a TBI caused by an external traumatic force applied directly to the head and neck region, or indirectly transmitted to the brain through the body, during exercise-related activities. Symptoms typically appear within minutes to hours after trauma and are not attributable to other injuries, comorbidities or drugs [15, 16]. It is worth noting that SRC is considered, in general, to reflect a functional disturbance rather than a structural neuropathology. Standard neuroimaging (e.g. computed tomography (CT), T1- and T2-weighted magnetic resonance imaging (MRI)) does not typically reveal structural abnormalities, although specialized neuroimaging research modalities using e.g., ultra-high field 7T MRI, as used in this

thesis, may detect widespread changes not least in the white matter, the clinical significance of which has not yet been determined [17, 18].

## Concussion and boxing history

The earliest clinical description of head injury dates to the Egyptians 1600 years BC, which were first translated in the early 1920s in the Edwin Smith surgical papyrus. These ancient texts described clinical symptoms such as loss of consciousness and speechlessness in head-injured patients [19]. An ancient description of concussion is traceable back the Hippocratic corpus in Greece during the 5th–4th century BC and sounds similar to a TBI with loss of consciousness, as observed today. It was translated as: "In cerebral concussion, whatever the cause, the patient becomes speechless... falls down immediately, cannot see and hear…" [20]. Recognition of the transient symptoms experienced after a head trauma was first noted in the 10th century in the Middle East by the, in those times, well-known physician Rhazes al-Razi. Later, a concept similar to "commotio" was described during the Renaissance, though it initially received little attention [21]. Despite the description of transient symptoms and clinical insight of concussion during the 10th century, the concept that concussions could lead to long-term consequences came from Martland in 1928. He described "punch-drunk" in former boxers, later referred to as dementia pugilistica, and identified *postmortem* features such as perivascular microhemorrhages, which Martland believed could be related to "replacement gliosis". He associated these findings with long-term exposure to repeated head impacts in boxing [20]. In the 1970s, Corsellis and colleagues provided a classical clinicopathological description of dementia pugilistica, which served as a basis for later neuropathological comparisons. At the beginning of the third millennium, Ann McKee's team conducted a series of neuropathological analyses of a former NFL player. The attention to the *post-mortem* diagnosis of Chronic Traumatic Encephalopathy (CTE) and the number of athletes diagnosed with CTE, markedly increased in the second decade of the 2000s. An attempt to associate clinical symptoms to the neuropathological findings of CTE at autopsy was made, named Traumatic Encephalopathy Syndrome (TES) [22].

Although outside the focus of this thesis, Traumatic Encephalopathy Syndrome (TES) can be defined as a group of progressive symptoms associated with exposure to repetitive head impacts that cannot be explained by another neurological, psychiatric, or medical condition [23, 24] (*vide infra)*.

## Epidemiology of concussions

TBI is the umbrella term in neurotraumatology; of all TBIs, mTBI accounts for 90% and is, by definition, considered a form of concussion (Figure 1)[3]. Sport-related concussions occur across all sports, with the highest incidence reported in American football, ice hockey, rugby, soccer, and basketball [25]. Among combat sports, boxing demonstrates the highest incidence of concussion [26].

A comprehensive worldwide TBI epidemiology study estimated that1.2–30% of all TBIs are sports-related, while a more specific and recent estimate suggest that 10% of all TBIs occur in a sports context [27]. These data argue for a global SRC incidence rate of approximately 31.5 new cases per 100,000 people per year [5, 28]. In a Swedish ice hockey study spanning 29 seasons, the incidence of SRC was estimated to an average 77 cases per 1,000 games, accounting for 17% of all injuries [29]. In addition, among American high school athletes, SRCs accounted for 8.9 % of all athletic injuries and 5.9% of collegiate athletic injuries [30]. Regardless, these numbers are presumably an underestimation due to the incomplete reporting of SRCs by health care or the medical teams. Globally, the incidence of SRCs has increased across all sports and age groups, with higher rates among females [31].

In studies of boxing-related injuries, concussions accounted for 12.3% of injuries, second only to skin lacerations (21.4%). One study on boxing-related injuries that analyzed professional boxers observed a higher rate (21% vs. 33%) of concussions when compared to earlier studies of amateur boxers [32, 33]. Additionally, SRC is associated with an increased risk of sustaining orthopedic injuries, a relationship examined in studies comparing injury odds ratios pre- and post-concussion, as well as relative to uninjured athletes [34].

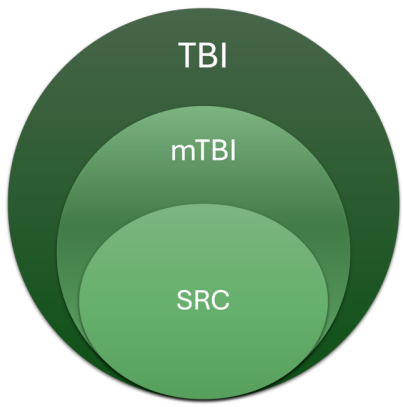


**Figure 1.** The term traumatic brain injury (TBI) includes all brain injuries caused by trauma, regardless of aetiology or severity. Mild TBI (mTBI) depends on the severity of the injury, while sports-related concussion (SRC) refers to a brain injury specifically induced during sports activities.

## Repetitive head impacts

Repetitive head impacts (RHI) refer to head impacts that may or may not result in acute symptoms sufficient for a concussion diagnosis [35]. This type of mainly asymptomatic cranial impacts is also referred to as a sub-concussive event [36]. Increasing evidence suggests that RHI may lead to long-term neurological consequences such as neurocognitive impairment and white matter abnormalities on

neuroimaging [37]. RHI occur in various contact sports such as rugby, American football, boxing, football and the martial arts. Boxing and football offer the best opportunity to study cumulative RHIs, distinguishable from SRCs, since in these sports RHI are intentional such as in headers or head strikes.

## Head impacts in boxing

Basic rules in boxing include no strikes under the belt, the occipital part of the head and to stop fighting after the command to "break" from the referee is called out. Boxing bouts vary in the number of rounds dependent on whether the bout is at the amateur or professional level. Each boxing round lasts 3 minutes, followed by a 1-minute break. The highest number of rounds in professional boxing is 12. The boxers wear either 8- or 10-oz gloves, depending on the weight class they are competing in. The boxing bout either ends by referee decision, technical knockout (TKO), or knockout (KO). Symptoms that increase TKO susceptibility include signs of imbalance and boxers not defending themselves properly by guarding their heads. There is always a medical doctor at the ring side, evaluating the boxer's condition under the bout and post-bout. Additionally, the coaches of each boxer can end the match prematurely by throwing the towel into the rink if the coach has a high suspicion that their boxer has gained too many strikes to the head risking brain injury. The rate of total landed strikes in a typical Olympic 3x3 minutes boxing bout is on average 50 strikes/bout with a 5:1 head-to-body ratio [38].

Since 1920, the cumulative burden of RHIs associated with boxing has been known to produce neurological impairments, originally named dementia pugilistica and now referred to as chronic traumatic encephalopathy (CTE; see previous paragraph)[39]. A previous clinical explanation for symptoms associated with head trauma in boxing was termed chronic traumatic brain injury (CTBI), which was characterized by symptoms in three domains: motor, cognitive, and behavioural. It has been observed that 20% of professional boxers develop a form of chronic TBI during their careers [40] and 40% of retired boxers suffer from symptoms related to chronic brain injury [26].

The most commonly known injury in boxing is a knock-out [41]. When analyzing the mortality reported in the Velazquez boxing fatality collection, a marked reduction in mortality was observed from 1983 and onwards, when the number of rounds were reduced from 15 to 12 [42]. This change occurred after the death of the light-weight boxer Duo Koo Kim, who suffered from neurological deterioration following a bout that included a high number of blows to the head, finally resulting in a knockout [26]. In this case, the cause of death was a subduralhematoma, the most common injury observed in fatal boxing fights [43].

# Pathophysiology

Concussion can metaphorically be explained as a system that suddenly overheats, since a sudden impact to the head increases the energy demand that forces the brain to work beyond its energy capacity. This is followed by impaired brain performance reflected in appearance of symptoms. By unknown mechanisms the brain later enters a stabilization phase with a gradual normalization of the energy metabolic situation and restoration of symptoms in a majority of cases. This metaphor shows the transient neurological symptoms that typically define an SRC and the symptoms that may persist.

Concussion biomechanics are shaped by both anatomy and head kinematics. Rapid acceleration and deceleration load the rigid skull and are especially harmful across regions and tissue layers with different densities. Consequently, rotational (and some linear) accelerations induce shear strains in neural tissue [44] (Figure 2), and it is well established that rotational acceleration is generally more deleterious than linear acceleration for strain-mediated brain injury. This is supported by head-impact measurements in National Football League athletes [45], and by boxing biomechanics showing that a hook punch generates proportionally greater rotational than translational acceleration in concussive events [46]. Rotational forces may act in horizontal, axial or coronal planes, with the coronal plane posing the greatest risk for injury [44]. Across all forms of TBI, increased force correlates with greater injury [47]. Some studies have attempted to set concussion thresholds at 70-75 G in linear acceleration or rotational acceleration at 5022 rad/s2. These limits remain uncertain as to the lowest level of acceleration needed to induce a concussion [46, 48].

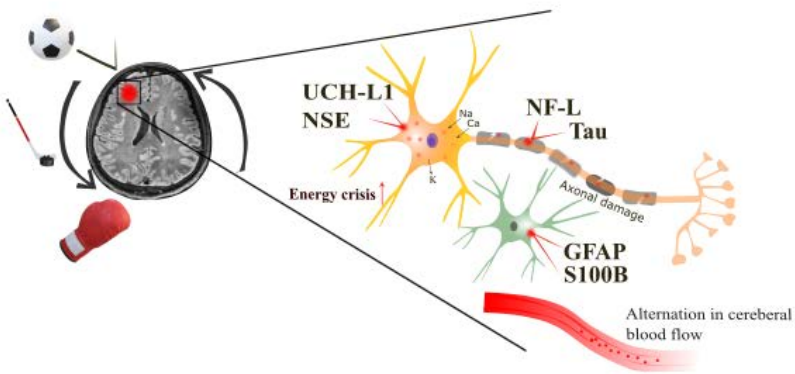


**Figure 2**. Sport-related concussion can be caused by rotational forces, which induce a cascade of injury-related processes. This results in the release of astrocytic biomarkers (S100B, GFAP) due to glial cell injury, and axonal damage is reflected by elevated levels of axonal injury markers (NF-L, Tau). These processes are also associated with increased energy demands and altered cerebral blood flow. A rise in neuronal soma-related injury biomarkers can also be observed, demonstrated by increased levels of e.g., UCH-L1 and NSE.

The impact energy at time of concussion is transmitted to the brain, and the primary injury results in tissue and vascular damage directly attributable to the applied force, occurring across multiple axes and planes. A cascade of events is then induced in response to the induced traumatic force, including neurotransmitter release, alterations in cerebral blood flow (CBF) and disruption of axonal integrity [49, 50]. As one of the earliest events, there is an efflux of potassium and an influx of sodium and calcium ions into neurons, leading to neuronal inhibition and the activation of glial cell-mediated injury processes. This leads to increased energy demands at time of reduced blood flow, whereby neurons attempt to re-establish homeostasis across their membranes using energy-intensive ionic pumps. Inadequate restoration of the energy balance may lead to mitochondrial dysfunction and an exacerbated cellular energy crisis [49].

In concussed athletes, CBF was decreased both at 24 h post-injury and 8 days post-injury when compared to athletic controls [51, 52]. This CBF decrease has been observed to extend along with delayed recovery post-concussion [53], while in longitudinal studies, some athletes showed delayed CBF restoration up to one-year post-concussion, or longer [54, 55].

In the early post-concussion phase, neurons enter a vulnerable window for additional injuries, making metabolic stressors more damaging [50, 51, 56, 57]. A destabilization of neurofilaments and microtubules within axons has also been documented, resulting in compromised axonal integrity and the formation of axonal varicosities due to disrupted axonal transport systems [58, 59].

*Short- and long-term metabolic changes following concussion*

The brain accounts for 20% of the total metabolic consumption of the body [60]. Sports-related concussions appear to cause a biphasic time-dependent change in metabolic cerebral demands, which can be evaluated by measuring brain perfusion and the cerebral metabolic rate (CMR). In the first hours-to-days after injury, metabolic demands seem to increase and are associated with higher symptom severity [61]. A second, delayed phase follows with suppressed metabolic demands and reduced cerebral perfusion, observed as early as 8 days [62] and persisting up to 180 days post-SRC [55, 56, 63, 64]. Together, these findings suggest that later hypoperfusion is unlikely to reflect a pure supply limitation and may instead indicate impaired or suppressed metabolic function [62, 65]. Moreover, and of importance for this thesis, exercise-induced brain hyperthermia (*vide infra*) increases the CMR that may exacerbate the brain injury through secondary mechanisms [66].

## Glymphatic system

The glymphatic system is a perivascular clearance pathway that mediates cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange in the brain. Astrocytic endfeet envelop cerebral arteries, capillaries and veins, lining perivascular spaces (PVS) that serve as low-resistance conduits for fluid flow. These endfeet are enriched with aquaporin-4 (AQP4) water channels on their perivascular membranes, facilitating rapid fluid movement between the perivascular spaces and the brain parenchyma (Figure 3). The PVS have received increased focus due to their sensitivity to aging and vascular pathology [67]. CSF enters the brain through periarterial spaces that are continuous with the subarachnoid space, with CSF mobility influenced by e.g., arterial pulsatility and respiration [68]. From there, it enters the parenchyma via AQP4-dependent transmembrane water flux, where it mixes with the ISF and carries solutes and metabolic waste products. It is subsequently cleared along perivenous pathways and ultimately drains via meningeal lymphatic vessels. With aging, glymphatic function declines, which could lead to reduced clearance of e.g., β-amyloid, tau, ions such as potassium, and metabolic by-products such as lactate. In human TBI, using MRI PVS changes have been associated with age, small-vessel impairment, cognitive decline and post-TBI sequelae [69, 70]. Most work has relied on volumetric approaches, which do not capture dynamic solute-transport capacity. Diffusion MRI models can be used to follow fluid motion along PVS pathways [71]. Although only a few studies have examined PVS morphology and perivascular diffusivity in concussed athletes, early findings suggest an enlarged PVS with reduced solute diffusivity, consistent with glymphatic dysfunction [72].

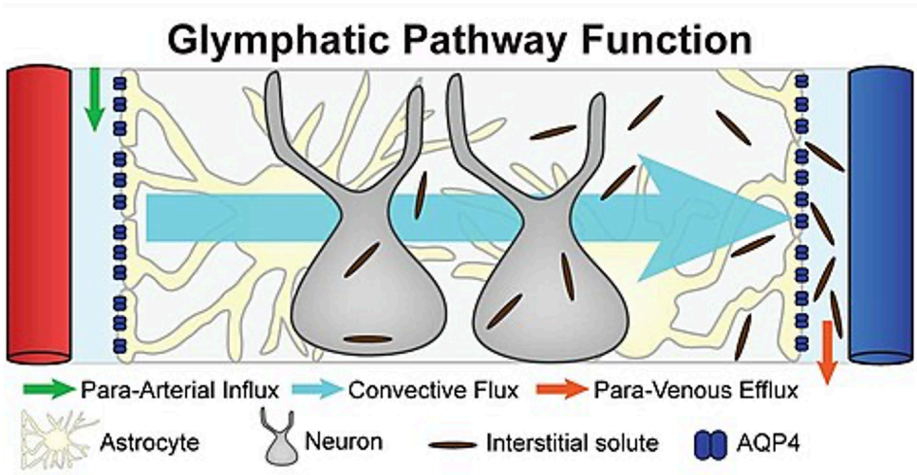


**Figure 3.** The image shows the glymphatic pathway, which is driven by arterial pulsations from penetrating arterioles. This process is supported by aquaporin-4 water channels located at the endfeet of astrocytes. CSF crosses into the interstitial space via convective flux, where it mixes with the interstitial fluid and facilitates the clearance of waste solutes and proteins. The waste-containing interstitial fluid is subsequently transported out of the brain along the perivenous system. Source Wiki Common.

## Temperature

Brain and core body temperature follow a daily circadian rhythm that is not static, reaching their lowest point during the night. This rhythm reflects well-regulated physiological temperature control, and when absent it is an adverse prognostic marker for outcomes following TBI [73]. Under normal conditions, brain temperature is slightly higher than core temperature, a difference driven by cerebral metabolic activity [74, 75].

Brain temperature is dynamically regulated by cerebral blood flow via the carotid arteries that are closely linked to cerebral metabolic rate of oxygen (CMRO2). Accordingly, cerebral metabolism increases by approximately 6–8% for each 1°C increase [76]. In athletes during exercise-induced hyperthermia, an increased cerebral metabolic demand is observed [77]. Modest elevations of brain temperature have been linked to a worse outcome following TBI and, in the experimental setting, worse histopathological damage [77-79].

This tightly regulated system of brain temperature becomes particularly challenged during strenuous physical activity and hot environments. Under these conditions both brain and core temperatures rise [80, 81] with brain temperatures slightly exceeding core temperatures [76]. Notably, even in cold environments, such as during ice hockey, exercise-induced hyperthermia has been observed [82]. This exercise-induced brain temperature elevation requires up to 1 hour to reach normothermic state by physiological cooling [80, 83]. Consequently, hyperthermia may increase the vulnerability of the brain. Elevated brain temperature has *per se* been shown to increase the release of brain injury biomarkers in healthy subjects, suggesting a compromised blood brain barrier (BBB) integrity [84]. This vulnerability is of particular concern for athletes, who are repeatedly exposed to head impacts during exercise- induced temperature elevation [51, 85, 86]. Increased brain temperature also affects neuronal activity and impair neuronal stability [87], since a large amount of energy is required to maintain plasma membrane stability and temperature elevations itself increase the energy demand [88]. In animal studies, elevated brain temperature (39°C) prior to mTBI resulted in significantly increased neuronal death in the cortex and hippocampus and worsened cognitive deficits [83]. This makes temperature a potential exacerbating factor for SRCs.

Importantly, these observations highlight brain temperature as a dynamic and clinically relevant factor linking hyperthermia in sports with cerebral metabolism and neurological vulnerability following a concussion.

# Diagnosis and acute management of sport-related concussion

Clinically, SRC is recognized by the appearance of transient neurological symptoms, observed in a sports setting. Symptoms may include loss of consciousness, dizziness, neck pain, headache, confusion, vertigo and speech disturbance. The threshold for recognizing symptoms should be low, and even the slightest suspicion of an SRC must prompt immediate removal from play. Confirmation of an SRC may occur later, or suspicion may be disproved, but early action is important. There are several reasons for maintaining a low threshold for immediate removal from play; the athlete requires assessment to rule out any red flags [16] (Table 2) that may indicate a more serious TBI warranting urgent transfer to nearest hospital; there is a potential risk of the rare second impact syndrome that may have devastating consequences, and perhaps most importantly the increased risk of additional subsequent concussive events in view of the heightened brain vulnerability of the initial SRC.

A definitive SRC diagnosis is based on symptoms and signs that are presents in the Sport Concussion Assessment Tool (SCAT)-6. The SCAT is commonly used immediately post-injury on the sideline to evaluate symptoms, and to monitor athletes during return-to-play rehabilitation [89]. In the SCAT-6 different symptom subscales are included such as physical (e.g., balance problems, headache), emotional (e.g., sadness), cognitive (e.g., difficulty remembering), and sleep (e.g., fatigue or low energy) [89]. The 22 symptoms in SCAT-6 are graded from 0, which means no symptoms, to 6 which is the worst imaginable which makes the maximum score 132.

Since the first step in the acute management of SRC is immediate recognition, early diagnosis is crucial [15]. Without recognizing an SRC, it is not possible to initiate any return-to-sport protocol. The Concussion Recognition Tool (CRT6) is the latest tool for SRC recognition, helping non-medically trained staff decide when to remove athletes from play [90, 91]. In fact, athletes experiencing SRC-related events or symptoms are often surrounded by non-medically trained individuals. Therefore, CRT is a valuable tool for parents, coaches and referees for identifying SRC. More specific tools to evaluate symptom burden and status include the SCAT6 [89] and immediate Post-Concussion Assessment and Cognitive Testing (ImPACT ®)[92, 93].

**Table 2. Red flags**
Red flags listed as mentiond in SCAT-6 [91]. If any of the red flags is noticed the athlete requires hospital management.

| Red flags |
| --- |
| • **Neck pain or tenderness**<br>• **Seizure or convulsion**<br>• **Double vision**<br>• **Loss of consciousness**<br>• **Weakness or tingling/burning in more than 1 arm or legs.**<br>• **Deteriorating level of consciousness**<br>• **Vomiting**<br>• **Increasing headache**<br>• **Increasingly restless, agitated or combative**<br>• **GCS<15**<br>• **Visible deformity of the skull** |

## Acute management of sport-related concussion

After diagnostic confirmation, a return-to-sport (RTP) protocol should be initiated in accordance with the Amsterdam Concussion Consensus from 2022 [15]. The RTP should be initiated immediately by a period of relative rest during the first 24-48 hours. During this initial "brain rest" low-intensity physical activity, such as walking, should be commenced with acceptance of mildly exacerbating symptoms. In addition, the screen time should be minimized during these initial 48 hours [94]. The six-step protocol (Table 3) describes all the relevant steps. Recovery guidelines in the RTP protocol suggest at least 24-hour interval between steps, which means the minimum RTP time for full recovery is 6 days. Importantly, to progress to step 4, where high-intensity training drills are the goal, all symptoms must be completely resolved both at rest and after physical exertion, to achieve the status of complete recovery and to allow competitive play again.

**Table 3. Return to sports/play protocol**
This proctol provides details in each step, and the threshold for the type of activity [15].

| Return to play steps | Exercise strategy | Type of activity | Goal of each step |
|---|---|---|---|
| **Step 1** | Back to regular daily life activity | Regular daily activity such as walking or going to school. | Gradual return to work/school. |
| **Step 2**<br>**2A- Light (up to 55% max HR)**<br>**2B- Moderate (up to 70% max HR)** | Aerobic activity | Stationary slow to medium paced exercise or walking.<br>Sub-symptom threshold light resistance training. | Increase the heart rate (HR). |
| **Step 3** | Sport-specific exercise without risk for head impact. | Running or exercise including body and head movement. Weight-lifting is also allowed here. | To add body and head movement during exercise. |
| **Step 4** | High intensity non-contact activity | More non-contact sports strenuous activity. Harder training drills with high intensity. Regular weight-lifting is accepted here. | Combine high-intensity exercise with coordination challenges. |
| **Step 5** | Practice and full contact | Participate in normal training activities including contact sports. | Regain confidence and perform at normal functional level. |
| **Step 6** | Competition | The athlete may return to competition. | |

# Short and long-term outcome in concussed athletes

## Prolonged recovery following concussion in sport

The typical physiological and psychological symptom relief duration after an SRC is 7–10 days [95], which is observed in ca 85-90% of athletes. However, normal symptom duration is defined as up to 4 weeks. The term post-concussive syndrome (PCS) was previously used to define a prolonged period of symptoms lasting 3 months or more following a TBI, and several classifications exist. When comparing two internationally established classifications, the ICD-10 criteria define PCS as three or more symptoms that last for more than four weeks, whereas the DSM-IV criteria defined PCS as three or more symptoms that last at least three months. In the more recent DSM-V, PCS has been reconsidered as a neurocognitive condition that is based on neuropsychological deficits [96]. The term PCS has recently experienced lower usage to describe long-term consequences following SRC, due to the various definitions, and that the symptoms criteria for PCS can be experienced by many individuals without ever being diagnosed with a concussion [97, 98] , thus making the term highly unspecific.

Instead, the term PPCS has gained popularity. In the last concussion consensus statements (in Amsterdam 2022), "persistent symptoms" are defined as symptoms lasting more than four weeks regardless of age category [15, 99]. Symptoms of PPCS can also be caused by other overlapping comorbidities, therefore the consensus statement recommended a multimodal clinical assessment [95, 100]. Although PCS and PPCS appear similar in context, they are not interchangeable. The difference is observed in the terms themselves. PCS includes the word "syndrome", which refers to chronic and, in most cases, irreversible symptoms with a lack of aetiology, whereas PPCS describes symptoms that follow an SRC- "a known cause"- with potential recovery, either through management or physiological resolution [101].

PPCS is thus based on self-reported symptoms and objective diagnostic criteria are missing. Of PPCS athletes, many recover within 1–3 years [102-104]. However, should symptoms extend beyond this three-year timeframe there a higher likelihood of permanent impairment [104]. The following factors have been suggested to be linked to a higher risk of delayed recovery of post-concussive symptoms: injury severity, LOC, PTA, seizures, premorbidity including learning disorder, low education level, anxiety and other mood disorders, migraines, sleep disorders and medication, young age, female sex and a history of previous concussion [15]. Immediate and early post-concussion symptoms severity is suggested as the strongest predictors for a prolonged recovery.

*Sex differences*

Many studies indicate that females have higher risk of sustaining an SRC, and of developing long-term symptoms. Female athletes across both contact and non-contact sports show a higher number of total post-concussive symptom score than male participants, particularly somatic, emotional and migraine-related symptoms [105]. Time to recovery has shown mixed results, although most reports argue for a delayed recovery in women [106, 107]. Beyond clinical recovery trajectories, biomechanical evidence shows that women have greater difficulty stabilizing their necks during head accelerations than men [108, 109]. This leads to greater head displacement relative to the body, potentially attributed to weaker neck muscle strength and a smaller neck girth [109, 110]. Further sex-related vulnerabilities have been shown in neurometabolic and cerebrovascular function. Specifically, a greater number of unmyelinated axons, a higher rate of cerebral blood flow and increased glucose metabolism may exacerbate the metabolic cascade in females [111-113]. These factors may aggravate the initial injury following SRC [50]. As previously described in this thesis, temperature may play a potential role in exacerbating injury in concussion. Importantly, gender differences in brain temperatures have also been observed across the menstrual cycle showing a difference in luteal and follicular phases, where women in the luteal phase have 0.36°C higher brain temperatures [73].

Despite these risks and observations, in our day and age, even though the number of females participating in sports is increasing, many studies have primarily focused

solely on men. Moreover, further studies are needed to firmly and evidently establish correlations between sex and SRC outcomes, differences in pathophysiology and potential treatments [108, 114].

## Neurodegeneration and chronic traumatic encephalopathy (CTE) in athletes

Neurodegeneration is strongly associated with accumulation of irregular proteins, leading to neuronal destruction and loss of neuronal network functionality [115]. Ongoing, cumulative injury mechanisms from a single TBIs and repeated SRCs can result in a gradually exacerbating brain injury [116, 117]. Previous studies showed that elite athletes exposed to multiple concussion are more likely to be diagnosed with Alzheimer's disease and other forms of neurodegenerative disorders [118]. While a single concussion does not necessarily lead to a chronic brain disorder, RHI significantly raise the risk. At long-term, this can cause an ongoing decline of brain function, along with neurodegeneration. For instance, signs of axonal injury, microstructural white-matter changes, and decreased brain volume have been observed in athletes in contact sport exposed to RHI although without any history of a previous SRC diagnosis [119, 120]. Taken together, these findings argue that the cumulative effects of RHI may act as a trigger for neurodegenerative processes [121, 122]. Evidence from cohort studies indicates that American football and rugby players have a higher mortality from neurodegenerative diseases such as Alzheimer's dementia compared to the general population [123, 124].

*CTE and traumatic encephalopathy syndrome*

In healthy neurons, the tau protein stabilizes neuronal microtubules and helps maintain axonal structure. However, in pathological states, tau can become abnormally phosphorylated, which promotes the formation of toxic oligomers and ultimately neurofibrillary tangles (NFTs). Neuronal function is disrupted and neurodegeneration ensues, disorders collectively termed tauopathies. Abnormal aggregation of amyloid-beta (Aβ) and phosphorylated tau (p-tau) are hallmark findings of Alzheimer´s disease. However, CTE – while it may have a degree of Aβ aggregation as well- is mainly a tauopathy.

Today, CTE is defined by histopathological post-mortem criteria that include: " *(i) perivascular foci of p-tau immunoreactive astrocytic tangles and neurofibrillary tangles; (ii) irregular cortical distribution of p-tau immunoreactive neurofibrillary tangles and astrocytic tangles with a predilection for the depth of cerebral sulci; (iii) clusters of subpial and periventricular astrocytic tangles in the cerebral cortex, diencephalon, basal ganglia and brainstem; and (iv) neurofibrillary tangles in the cerebral cortex located preferentially in the superficial layers*" [125].

A clinical correlate to CTE has also been suggested: The National Institute of Neurological Disorders and Stroke (NINDS) criteria defining Traumatic Encephalopathy Syndrome (TES) are, in brief; (1) exposure to RHIs from sports, military or

other causes, (2) main clinical features of cognitive impairment or neurobehavioral dysregulation, (3) a progressive course and, lastly, (4) the clinical features are not fully accounted by any other neurologic, psychiatric, or medical conditions [22, 23]. However, TES has been criticized for being unspecific with many of the included symptoms overlapping with, and described in, other disorders [126, 127].

In combat sports, when boxers and MMA fighters were compared, boxers tended to fulfil the criteria of TES more frequently than MMA fighters, potentially associated with the start of boxing practice at a young age [24]. Demographically, the TES-positive boxers were mostly retired professionals, with an average age of 47 and also demonstrated lower regional brain volumes on MRI and had lower scores on e.g. psychomotor speed assessments [24].

# Head- and-neck cooling intervention as a treatment option

Increased brain temperature may place neurons in a vulnerable state, disrupt BBB integrity and increase metabolic demands, creating a condition that can exacerbate brain injury after an SRC [83], as noted in previous paragraphs. Systemic cooling strategies using hypothermia aimed to provide neuroprotection in severe TBI patients and were attempted in a number of studies [128]. However, when reaching systematic hypothermia below 34°C many adverse events such as cardiac, hematological and metabolic side effects were observed. Not least, susceptibility to infectious complications, and impaired coagulation were important clinical problems [60, 128]. To date, hypothermia should only be used in severe TBI in the context of clinical trials.

In the experimental setting, reduction of brain temperature post-concussion has demonstrated a neuroprotective effect by reducing cerebral metabolic demand and preventing neuronal loss [129, 130]. In clinical cooling intervention studies, a shorter return-to-play outcome in concussed elite ice hockey player [131], and reduced symptom burden in adolescent athletes [86] have been observed.

Several brain cooling methods have aimed at selectively reducing regional temperatures while simultaneously minimizing systemic complications, and showed a decrease in brain temperatures maintaining a gradient between core and brain temperatures [132, 133]. Methods for brain cooling have shifted from intranasal techniques to other non-invasive approaches, mainly including cooling helmets targeting the head and neck regions [133, 134]. This transition is attributed to the higher tolerability and easier monitoring associated with cooling helmets [85, 133], as nasal cooling may cause mucosal injury, skin irritation, and systemic adverse events [134].

The efficacy of cooling helmet methods has been demonstrated in multiple studies. In patients with severe TBI equipped with an invasive monitor for intracranial

pressure and brain temperature, a 2°C reduction in cortical temperature was achieved after 15 minutes of applying the cooling [135]. Among healthy controls without prior exercise, selective head-and-neck cooling for 80 minutes resulted in an average temperature reduction of 0.9°C [136]. In comparison, when athletes were cooled post-exercise for 60 minutes an estimated reduction of brain temperature by 1.5°C was achieved [80].

Selective brain cooling should target also the carotid and vertebral arteries, as they comprise the main upstream blood supply of the brain. This makes cooling a strategic approach to reach sufficient brain cooling. Thus, there is a strong rationale for developing selective head-and-neck cooling methods rather than whole-body cooling, with the aim of enhancing recovery while minimizing adverse events and rapidly reaching brain normothermia. By applying head-and-neck cooling in concussed athletes, a significant increase in CBF was observed. Additionally, cooling for 30 minutes resulted in a relative reduction of 0.4-0.6°C in brain temperature as evaluated by MRI. This increase in CBF following cooling in concussed athletes suggests that cooling may be effective in restoring altered CBF and metabolic demands in the brain [137].

# Evaluation of PPCS and RHI athletes

## Vestibular apparatus and assessment

To achieve and maintain bipedal stance and movement, humans must continuously counteract the effect of gravitation as well as the inertia of one's own movements to maintain upright stance- a process named postural control [138]. To recognize any movement or external perturbation of the body, information from vision, the vestibular sense organs of the inner ear, proprioception and mechanoperception (e.g., touch) is required (Figure 4) [139]. The information is then conveyed to the central nervous system where it is integrated and analyzed on several levels, leading to an output of a motor command to achieve either the maintenance of stance or an adjusted smooth movement [140].

In the above context, the vestibular senses are of utmost importance. The vestibular end organ is situated in the temporal bone together with the cochlea and make up the inner ear. Each inner ear contains three semicircular canals and two so-called otolith organs, e.g. the utricule and the saccule. The semicircular canals act as mechanical transducers of angular movements of the head, while the utricle and saccule detect linear acceleration (Figure 5). Besides providing sensory information and recognition of movement, as well as gravity, the vestibular senses are hardwired into reflexes such as the vestibular-ocular reflex (VOR) and vestibular spinal reflexes. The VOR originates in the semicircular canal and projects to the ocular muscles with a three-neuron reflex (inner ear - vestibular nuclei - eye motor nuclei). This allows activation of eye muscles creating eye movements within 10 milliseconds of

semicircular canal detection of head movements which is the prerequisite of clear and acute vision during movements. Without the VOR, vision would be blurred- the so-called Dandy phenomenon- and the visual surround will bob up and down during movement. Similarly, activation of the otolith organs sends projections through the medial or lateral vestibular spinal tracts to the important paraspinal and limb muscles to counteract and compensate for postural movements, and keep the body in balance within the gravitational field [140].

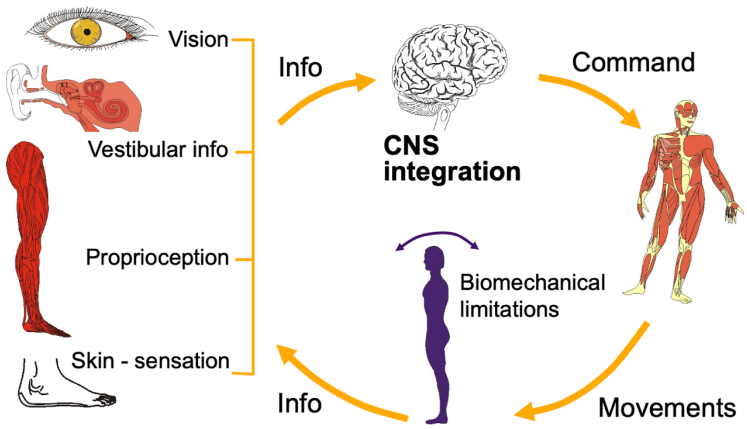


**Figure 4.** This figure demonstrates the integration between the components of the balance system. On the left are all four systems (vision, vestibular system, proprioception, and skin), which provide information to the central nervous system. The central nervous system subsequently sends commands that induce movement. Any impairment in these systems, at any level will be demonstrated as biomechanical limitations in maintaining balance [141]. *Courtsey of Måns Magnusson*

The semicircular canals, the utricle and the saccule project through the vestibular nerves to the brainstem and the vestibular nuclear complex; The anterior and lateral semicircular canals, and the utricle, are innervated by the superior vestibular nerve, whereas the posterior semicircular canal and the saccule are innervated by the inferior vestibular nerve.

The vestibular nuclei have a multitude of projections. Cranially they project through the medial longitudinal fasciculus and the Deiters tract to the eye motor nuclei, but there are also projections to the midbrain, the cerebellum (especially nodulus, uvula and flocculus), as well as cortical areas of the entire brain [140] -From the vestibular nuclei there is also a projection through the medial and lateral vestibulospinal tracts where the medial one mainly acts on cervical and upper limb motor neurons, while the lateral vestibular spinal tract has direct connections into the lower part of the body and the hind limbs. On a brainstem level the vestibular nuclei on both sides interact with each other and mirror the activity on the other side, so that excitation

on one side leads to a contralateral inhibition of nuclear neurons, and there is also interaction with the reticular formation. The vestibular neurons also receive projections from the cerebellum, which are considered of importance to calibrate reflexes and compensate for lesions [140].

In view of the complexity described in the previous paragraph, it is understandable why lesions within the vestibular system may lead to a number of effects not only on balance, but also on orientation [142, 143], cognition [144] and even alertness [145].

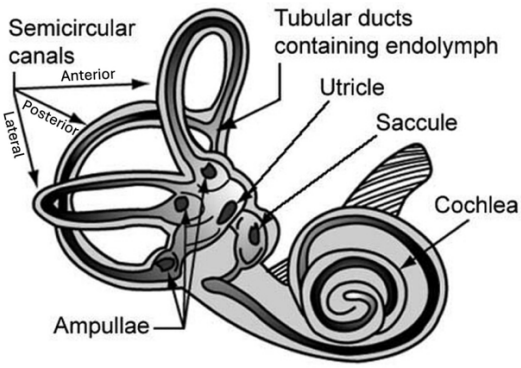


**Figure 5** The vestibular system is located within the inner ear and includes several components with the role to provide information about the head position both during movements, acceleration or resting state. Source: Image from Wikimedia Commons (Public Domain). The labels “anterior, posterior, lateral” were added by the author.

## Neuroimaging

As previously noted, neuroimaging is not needed for the diagnosis of SRCs. Moreover, in a vast majority of SRC athletes that do undergo conventional neuroimaging the investigation is normal. There is, however, increased interest in more refined imaging tools where SRC-induced alterations may be observed [146]. Unlike conventional imaging modalities that produce two-dimensional images primarily revealing structural abnormalities such as focal lesions, MRI's unique magnetic field properties enable the assessment of water molecule movement and other bodily fluids, facilitating the evaluation of metabolic changes and cerebral blood flow [147].

*Diffusion-weighted imaging*

Diffusion-weighted imaging (DWI) is an MRI technique that quantifies the microscopic diffusion of water molecules in tissue. Diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) are models for analysis of DWI data. DKI extends DTI by capturing non-Gaussian (non-homogeneous) diffusion and provides additional quantitative metrics that can be more sensitive to white-matter integrity [148].

In essence, DTI provides metrics reporting on the average properties of tissue, while DKI also provides metrics reporting on heterogeneity within the imaging voxel.
Regarding Gaussian and non-Gaussian diffusion, Gaussian diffusion assumes an obstacle-free medium, where molecular displacements are not disrupted by the surrounding environment. Non-Gaussian diffusion, by contrast, accounts for the restriction and hindrance of water molecules displacement caused by tissue microstructural barrier. However, biological tissues contain many barriers and compartments (membranes, organelles, myelin, crossing fibers), which means that diffusion deviates from Gaussian diffusion which is modelled by DKI [149].
During DWI, pairs of gradients are applied. Because diffusion occurs in 3D, gradients are applied along orthogonal X, Y and Z directions for each slice to fully measure the diffusion. Each image voxel represents a 3D volume, generated from the measured signals from the tissue, and appears as a single grey value in the image matrix. If diffusion is locally restricted (*i.e.* some signal loss in all three directions), the voxel appears brighter on the diffusion-weighted image [150].

*The diffusion tensor model (DTI) and diffusion kurtosis imaging (DKI)*

The tensor estimated by DTI can be illustrated by a 3D ellipsoid and be represented by for example the fractional anisotropy (FA), which reflects the degree of anisotropy [151]. Higher FA is typical of coherent, myelinated white-matter tracts and is sensitive to microstructural change but cannot determine its cause [151]. Another parameter is the MD (mean diffusivity), indicating greater overall diffusivity (more free water and less restrictions). The AD (axial diffusivity) is useful for assessing changes along axons and RD (radial diffusivity) increases – diffusion perpendicular to the principal axis –are often associated with demyelination [152].

Kurtosis reflects the variance of diffusivities across compartments within the voxel. Thus, kurtosis serves as an index of diffusion heterogeneity and provides information beyond the tensor. Since DKI retains sensitivity to tissue complexity (e.g. in crossing-fiber regions), kurtosis tensors can improve tissue characterization and aid tractography by better resolving complex white-matter architecture [148]. In diffusion kurtosis imaging (DKI), mean kurtosis (MK) reflects overall diffusional, axial kurtosis (AK) quantifies kurtosis along the principal (axial) diffusion direction, and radial kurtosis (RK) quantifies kurtosis perpendicular to that direction.

*MRI in sports-related concussion*

Neuroimaging in mTBI and concussion has traditionally relied on computed tomography (CT) scans to exclude severe injuries such as skull fractures and intracranial hemorrhages [153]. Conventional MRI has historically shown limited structural changes in concussion cases [15]. Arguably, mTBI, concussions and repetitive head impacts (RHI) may cause microstructural changes that are below the detection threshold of standard MRI sequences [154, 155]. However, non-specific conventional

MRI may still reveal macrostructural changes [156] such as microhemorrhages, enlarged cavum septum pellucidum, and subtle brain volume reductions [157, 158] in concussed athletes. Longitudinal studies have also revealed volume reductions in specific brain regions among athletes with an SRC history, including the corpus callosum, hippocampus, amygdala and thalamus [159, 160]. In addition, the cumulative effects of RHI have been associated with regional brain atrophy [161]. Thus, structural MRI remains valuable for detecting brain atrophy and for volumetric measurements in a research context [162, 163]. Since MRI is particularly sensitive for evaluating white-matter tracts DTI it has been increasingly used in concussion research over the past few decades [164, 165]. However, the limitations of routine neuroimaging have driven neuroimaging research toward higher-resolution MRI techniques capable of detecting pathology at a refined scale.

Ultra-high-field 7-Tesla MRI has emerged as a promising tool for detecting subtle concussion-related changes that remain undetectable with conventional imaging techniques [166]. While this technology offers enhanced sensitivity, concerns exist regarding potential over-diagnosis of clinically insignificant findings [167]. In sport-related concussion, reduced FA has been found in white matter tracts of rugby players and in boxers, where it correlated with the number of professional fights [168, 169]. When soccer players without a history of previous concussions were evaluated, widespread increased radial diffusivity suggesting demyelination was found [119]. Advanced diffusion imaging techniques, including DTI and newer models such as NODDI (Neurite Orientation Dispersion and Density Imaging), have shown superior sensitivity for detecting microstructural white-matter changes following concussion [170, 171], and are promising methods in SRC research.

## Biomarkers of brain injury

Neurons are the primary signalling cells in the brain and their cell bodies, which are unmyelinated and located in the grey matter, and axons extend through the partly myelinated white matter. In contrast, glial cells function as supportive elements that protect, myelinate, and maintain *e.g.,* the ion balance in neurons, and comprise up to half of the brain's volume [172]. Glial cells fulfil multiple additional functions, including immune defence by microglia, myelination by oligodendrocytes, and neuronal support and repair by astrocytes. Astrocytes also maintain the blood-brain barrier, regulate neurotransmitters and ion balance, and provide metabolic support to neurons. Oligodendrocytes produce the myelin sheath that insulates axons and facilitates rapid signal transmission, while microglia respond to injury as immune defence cells, and clear debris. Ependymal cells line the brain ventricles and are responsible for producing and circulating cerebrospinal fluid (CSF).

As a proxy for alterations or impairments in glial, vascular and neuronal cells, biomarkers of brain injury can be used to measure CNS-enriched proteins or other molecular markers from all cell types that are released from a brain injury- or by BBB disruption [173]. These biomarkers are most accurately quantified in CSF and

may enter the bloodstream by BBB disruption, passive leakage or active transport, with temporal dynamics varying according to the injury mechanism [174].

Key blood brain injury biomarkers in sports concussion and TBI research, and to some extent in clinical practice, are S100B, tau isoforms, GFAP and NF-L, all used in the present thesis and described in more details below [172] (Figure 6; Figure 7).

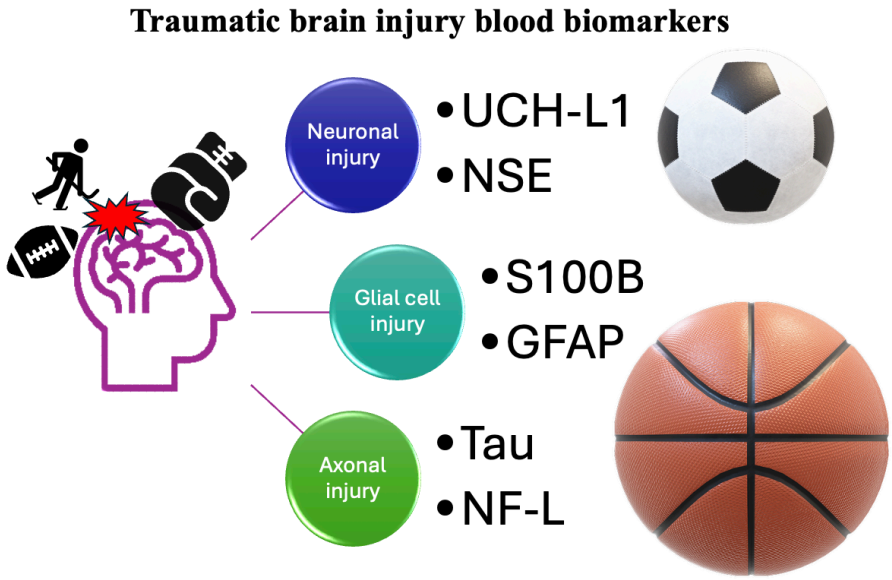


**Figure 6.** Brain injury biomarkers are released following sport-related concussions or successive events of repetitive head impacts. These biomarkers represent different mechanisms of injury within the central nervous system (CNS).

*S100B*

S100B is a calcium-binding protein, primarily localized in astrocytes, that serves as a brain injury biomarker [175]. It has a half-life in blood of approximately 2 hours [176] and its release from astrocytes is indicating intracerebral injury [175] and becomes detectable within one-hour post-injury. Elevated blood S100B levels are currently utilized to guide the need for brain imaging in the assessment of mTBI patients [177], included in the National Institute of Health and Care Excellence (NICE) Head Injury Guidelines [178], and the Scandinavian, Spanish and French guidelines [179-181]. In combat sports, S100B concentrations are increased within 5 minutes post-fight [182], and elevated levels have been observed in the CSF of Olympic boxers 1 to 6 days after competing [183]. However, S100B may also increase in response to physical exercise [184-186], potentially due to release from non-neural tissues such as muscle and adipose tissue.

*Glial fibrillary acidic protein*

GFAP is an astrocytic brain injury biomarker which, like S100B, indicates injury severity [175] and becomes detectable within hours after injury. In the acute phase, GFAP differentiates concussed athletes from both contact sport and non-contact sport control athletes and is markedly increased in athletes who experience loss of consciousness or post-traumatic amnesia compared to those without those symptoms [187]. GFAP levels are typically higher in the subacute phase post-injury than S100B [175] with reported hourly increase of 3.7% among CT-positive mTBI patients relative to CT-negative patients [188]. Given this profile, GFAP is a reliable marker for assessing the subacute period following brain injury. In boxing, for example, GFAP has been extensively studied, with significant elevations observed in blood 1–6 days post-fight in Olympic boxers [183], potentially indicating a delayed neuronal injury [189]. Similarly, research on collegiate level athletes and in the US military confirms the role of GFAP in the subacute post-concussion period, particularly within 24–48 hours after concussion. Furthermore, longitudinal studies have linked GFAP levels to DTI metrics, suggesting white-matter abnormalities, and to outcomes measured seven days after resolution of symptoms measured as return-to-play [190].

*Tubulin associated unit (tau)*

Tau is a neuron-derived biomarker of brain injury, enriched in cortical axons [175, 191]. It serves as a marker of axonal injury and is widely used in the diagnosis of tauopathies [175]. Tau concentrations increase acutely after high-acceleration impact events in high school football or in concussed hockey players; however, the duration of tau elevation varies across studies and assays [192-194]. Although plasma-tau is observed to increase first week post-fight in boxers [195], it is most frequently measured in CSF [189].

*Brain Derived -Tubulin associated unit (tau)*

BD-tau is derived from total tau (t-tau) and is intended to capture the fraction of tau in blood that originates specifically from the CNS [196]. This is important since the majority of t-tau in blood is peripheral and can dilute CNS-related signals. BD-tau has found its role primarily in diagnosis of Alzheimer's disease–type neurodegeneration [196]. As such, increased BD-tau levels could in the future enable early detection of neurodegenerative features in athletes experiencing RHI and/or several SRC during a career in contact sports.

*Neurofilament light*

Neurofilament light chain (NF-L) is a biomarker of brain injury localized within axons, and it reliably indicates large caliber axonal damage [175]. Unlike tau, NF-L becomes detectable several days to weeks after injury that may reflect ongoing axonal degeneration and impaired regeneration. NF-L is more sensitive for detecting

chronic injury than for acute diagnostic use [193, 197]. Moreover, NF-L concentrations are closely correlated with impact exposure in boxing and weakly associated with return-to-play in concussed hockey players [198]. NF-L has been observed to reflect the acute exposure of RHI in boxers, the clinical interpretation of which is uncertain [199]. Importantly, NF-L levels in CSF correlate well with those in peripheral blood [200].

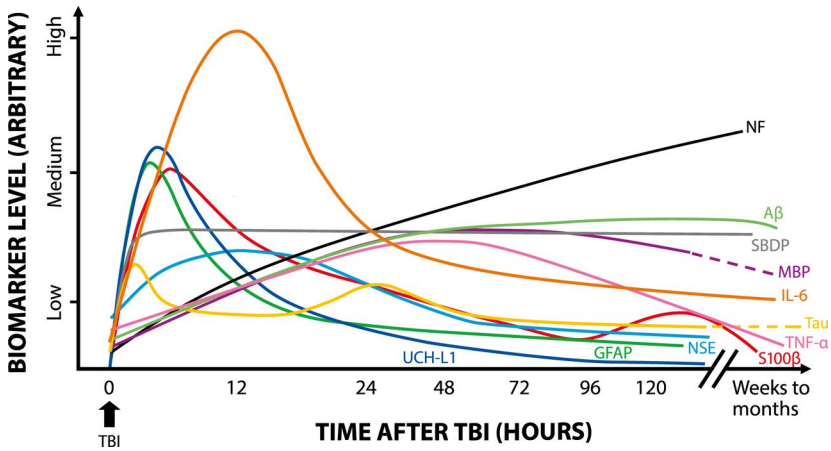


**Figure 7.** Biomarkers vary in their peak after injury, by their half-life, and by the duration before subsiding. These kinetics determine the ability to detect each biomarker and provide information about the timing of different types of injury (neuronal, glial, axonal). Source*: Adrian H, Kvist M, Nuutinen S, Välimaa L. Biomarkers of Traumatic Brain Injury: Temporal Changes in Body Fluids.* eNeuro. *2016;3(6):ENEURO.0294-16.2016* [201].

# 2 Aims

## General aims

- To diagnose the potential causes of vestibular symptoms in athletes with persistent post-concussion symptoms (PPCS) and assess their relationship to clinical symptoms.
- To evaluate fluid dynamics and perivascular spaces as indicators of glymphatic system function in the brains of active boxers, PPCS athletes and healthy controls.
- To evaluate whether attenuating brain temperature using selective head-and-neck cooling post-fight reduces blood brain injury biomarker levels and symptom rating in elite boxers.

# 3 Methods

## Patient cohorts

*Paper I*

Athletes aged 18 years or older with post-concussive symptoms for more than 6 months were included. Controls were age- and sex matched healthy individuals who exercised in a non-contact sport three or more times per week without any previous concussion. Inclusion criteria for symptomatic athletes: age ≥18 years; no comorbidities that could explain or contribute to the experienced symptoms or affect test measurements; no history of intracranial hemorrhage or lesions on neuroimaging.

Exclusion criteria for healthy participants: any comorbidity or previous concussions, or participation of contact sports.

*Paper II*

Twenty athletes with a history of PPCS lasting more than 6 months were included from Paper I to examine postural control. The symptoms should be sufficiently severe to impair participation in sports, studies and/or work. Inclusion criteria required; the symptoms required for inclusion must have developed in connection with the most recent sports-related concussion and persist without symptom-free intervals for more than 6 months. Exclusion criteria included any history of intracranial hemorrhage or other comorbidities that could explain the symptoms. Twelve healthy controls with no history of prior mTBI or neurological/musculoskeletal conditions were also included. All participants were instructed to abstain from alcohol for at least 48 hours before the vestibular examination.

*Paper III*

We aimed to include at least 20 boxers to undergo 7T MRI to enable analysis of the glymphatic system and perivascular spaces. The boxers were recruited from Paper V; those who agreed and provided informed consent to undergo MRI were included. The control and PPCS group were recruited from Paper I. In total, fifty-nine participants were enrolled from the groups, 20 controls, 18 PCCS athletes and 21 active boxers.

*Paper IV-V*

We aimed to include at least 40 boxers based on our sample-size calculation. All boxers were registered with the Swedish Boxing Association and had approved medical reports allowing competition prior to each tournament or boxing event.

Eligible boxers were 18–40 years old. This age range was approved by the ethics committee to include only adults (>18 years), and the upper limit of 40 years was set by the boxing association for active competitive boxers.

Boxers were recruited after study information to the tournament staff, who distributed it to all coaches. Coaches informed their boxers, and interested athletes contacted our research group. Full boxing histories were obtained after completion of the follow-up blood sample collection.

# Vestibular tests

The vestibular testing included a battery of tests for both vestibular function and voluntary eye movement. Tests included the video head impulse test (vHIT) in planes, the caloric test, cervical vestibular evoked myogenic potentials (cVEMPs), videonystagmography (VNG), posturography, pursuit eye movements (PEMs), and audiography. All participants were examined before undergoing testing to rule out obstruction of the ear canal, tympanic membrane perforations, or any other form of middle ear pathology. Earwax was removed as necessary, after which the participants were evaluated by audiography. All tests were administered by two experienced audiologists.

A blinded evaluation was performed by an otoneurologist, who classified the results as either normal or pathological. Based on the results of these tests, vestibular deficits were classified as peripheral, central, or a combination. Peripheral signs included abnormalities in the vHIT, caloric test, cVEMPs, and together with a peripheral pattern in the VNG. Central signs included a specific central pattern in the VNG (i.e., gaze-shifting nystagmus, continuous positional nystagmus) and findings from posturography. If both peripheral and central abnormalities were detected, the condition was classified as a combination lesion.

## vHIT

The vHIT was conducted according to the manufacturer's instructions (EyeSeeCam, Interacoustics, Middlefart, Denmark). Participants sat upright wearing goggles with an infrared camera to record eye movements and a motion sensor to record head movements. While focusing on a target 1 m away, head movements of 10-20 degrees over 150-200 deg/s were applied in the plane of each semicircular canal [202, 203]. To stimulate the left lateral semicircular canal (LLSC), the head was kept in a neutral position and moved to the left, whereas stimulation of the right lateral semicircular canal (RLSC) was achieved by moving the head to the right. Testing of the vertical canals involved turning the head 45 degrees to the right, followed by upward or downward movements to assess the left anterior-right posterior (LARP) canals, while turning the head to the left tested the right anterior-left posterior (RALP) canals [202]. Evaluation was based both on calculating vestibulo-ocular

reflex gains and, more importantly, on classifying responses as normal or abnormal due to potential inaccuracies in the gain calculations, particularly for the vertical canals [204].

## Caloric testing

In the caloric test, warm (44°C) and cold (30°C) water was flushed in the the ear for 25-30 seconds, and nystagmus was recorded using infrared goggles worn by the participant (VisualEyes 525, Interacoustics, Middlefart, Denmark). A pathological result was defined as a response differing by 25% or more compared with the opposite ear.

## cVEMP

The cVEMP test was conducted per the manufacturer's instructions (Eclipse, Interacoustics, Middelfart, Denmark). While seated, participant received a 500 Hz tone burst in one ear while turning the head to the opposite side. Surface electrodes were positioned on the contralateral sternocleidomastoid muscle, and myogenic responses were obtained. Evaluation consisted of both visual inspection of the recorded waveform and assessment of determined amplitudes, latencies, and asymmetries. Overall responses were categorized as normal or abnormal for one or both sides, as per standardized laboratory protocol.

## VNG

For examination with videonystagmografi (VNG) participants used goggles with embedded infrared cameras that tracked participants' eye movements (VisualEyes 525, Interacoustics, Middelfart, Denmark). Participants were asked to sit upright and look in various directions (left, right, up, down, and straight ahead) to try to identify spontaneous nystagmus. Further evaluation of horizontal and vertical nystagmus was conducted with the participant lying down and turning to either side or lying on their back with their head flexed 15 degrees. The head shaking test was then conducted by shaking the head side to side at a rate of 1-2 shakes per second for 10-15 seconds. After performed headshaking participants were asked to keep eyes in a central gaze position. A combined assessment of gaze direction, head shaking, and positional changes allowed us to categorize each nystagmus pattern as either normal, peripheral, or central. Peripheral pattern vestibular dysfunction typically demonstrates nystagmus to the contralateral lesion and paradoxically improves with gaze direction away from the lesion and is suppressed by visual fixation. Central pattern nystagmus is characterized by vertical or torsional nystagmus, that do not get suppressed by fixation and may switch directions [205].

## Posturography

In the posturography test, participants stood on a platform equipped with strain-gauge sensors and were instructed to look at a designated fixed point positioned 1.5

meters ahead. Alternatively, participants were blindfolded, and balancing responses were evaluated both with and without vibratory perturbation from the platform. The procedure includes four test conditions, with participants standing either with eyes open or closed for 30 or 230 seconds. Data from the first 30 seconds served as a baseline recording before pseudorandomized binary vibration sequences were applied to both calf muscles. The recorded body sway was then analyzed for frequency peaks, and the variance of the forces exerted by the feet the support surface during sway, reflecting the mechanical effort and energy to maintain posture, as described in previous studies [206].

### Pursuit eye movements

The PEM test assessed the ability to fixate on and smoothly follow a moving visual target. The visual signals travel from the retina to the middle temporal area and frontal eye fields, and then to the oculomotor regions of the brainstem. The signals then project to the striatum and cerebellum and then return to the brainstem [207]. Thus, the PEM test is a measure of integrated visual (sensory) and motor function involving several central brain structures, including the cerebellum. Abnormal results on a PEM test are defined as a marked reduction in pursuit velocity relative to the target, the presence of saccades, or the complete loss of pursuit.

## HADS and SCAT

The HADS is a self-reporting screening tool used to detect emotional distress in non-psychiatric settings. The tool has two subscales: HADS-A for anxiety and HADS-D for depression. Each subscale contains seven items scored from 0 to 3. A score of 0 indicates no difficulty/symptoms (i.e., the participant is at a non-pathological baseline level of anxiety/depression) while 3 indicates maximal severity. Total scores of 0–7 were considered within normal limits, while scores of 8–10 indicated a minor (borderline) pathology. Scores of 11–21 indicate significant pathology [208, 209].

The SCAT5 (the fifth edition of the SCAT) is a self-reported concussion assessment tool for adults and adolescents aged 13 years and older and includes a standardized symptom scale [210]. The symptom checklist includes 22 possible symptoms evaluated in a Likert scale. Each symptom was rated from 0 to 6, with a maximum total score of 132: 0 = within normal limits, 1–2 = mild, 3–4 = moderate, and 5–6 = severe. SCAT5 results were assessed at several time points: at baseline, immediately post-fight, 45 minutes post-fight, as well as on day 3 and day 6 post-fight.

# MRI

Imaging was performed on a Philips Achieva 7.0T ultra-high field whole-body magnetic resonance imaging (MRI) system (Figure 8). The MRI protocol included three sequences: a 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence (field of view [FOV]: 230 × 230 × 180 mm3, resolution 0.80 × 0.80 × 0.80 mm3, repetition time [TR]/echo time [TE]: 8.00/1.97 ms); a diffusion-weighed imaging (DWI) sequence for diffusion tensor imaging (DTI) (FOV: 224 × 224 ×110 mm3, resolution 2 × 2 × 2 mm3, and TR/TE: 9200/65 ms) in which the diffusion encoding was applied in six directions with a b-value of 100 s/mm2 and 30 directions with a b-value of 1000 s/mm2; and a DWI sequence for diffusion kurtosis imaging (DKI) (FOV: 224 × 224 × 120 mm3, resolution 2 × 2 × 2 mm3, and TR/TE: 9800/76 ms) in which the diffusion encoding was applied in six directions with a b-value of 100 s/mm2, six directions with a b-value of 500 s/mm2, 10 directions with a b-value of 1000 s/mm2, and 30 directions with a b-value of 2000 s/mm2. For both DWI protocols, two b-values of 0 s/mm2 volumes were acquired with phase-encode blips with opposing polarities for use in distortion correction.

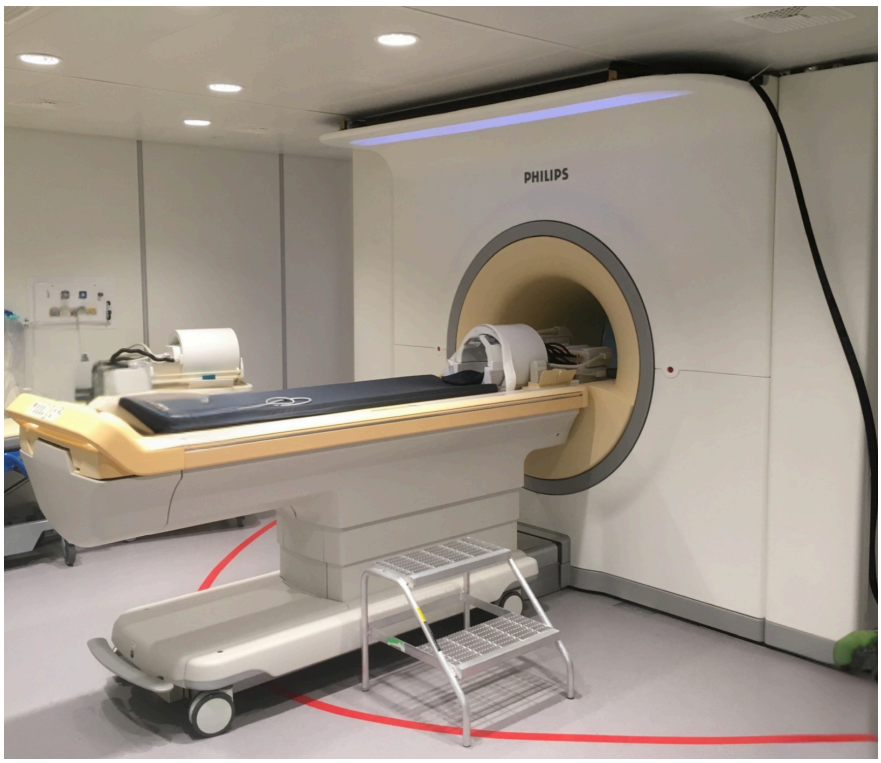


**Figure 8.** The 7T Philips Achieva at The National 7T facility at Skåne University Hospital in Lund. Courtesy of Karin Markenroth Bloch.

### MRI-volumetrics

For volumetric analysis, regions of interest were segmented from T1-weighted images using FreeSurfer software [211] (http://surfer.nmr.mgh.harvard.edu). In Paper I, cerebellar white matter (WM) and grey matter (GM) volumes were analyzed. Each three-dimensional segment was reviewed by an expert reader using three sequential editing procedures to identify any misclassification of WM, GM, or pial surface boundaries [211]. Images were initially screened for WM omissions, with control points inserted to extend segmentation boundaries and ensure complete inclusion. Residual meningeal tissue within the pial surface was then removed manually. Segmentations were systematically reviewed for misclassified WM or GM regions, and boundaries were corrected accordingly. All edited images were reviewed.

### DTI and DKI

The processing of DTI and DKI included denoising aimed to suppress local signal fluctuations with sources other than the source of anatomical detail, which can improve visual and statistical interpretations. Processing also included corrections for Gibbs-ringing artefacts [212] brain extraction and correction of distortions from head motion and eddy currents [211, 213] and median filtering (for DKI only). Tract segmentations were done by TractSeg. In Paper one, three cerebellar tracts were analyzed: the inferior (left and right merged), middle, and superior (left and right merged) cerebellar tracts. The fractional anisotropy (FA) and mean diffusivity (MD) were analyzed for DTI and mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK) for DKI.

### Perivascular spaces (PVS)

In the PVS processing for Paper III, white matter hyperintensities (WMHs) were segmented and excluded prior to detection to prevent false positives when applying morphology-based tubular-structure enhancement for PVS identification. Parasagittal dural space (PSD) regions were automatically segmented along the superior sagittal sinus for regional volumetric analysis. However, FA in PVS lacks a clear and stable biological interpretation. PVS is a fluid-filled space that may be isotropic or weakly constrained; anisotropy is mainly influenced by local geometry and orientation dispersion rather than by coherent microstructural organization.

## Head- and-Neck Cooling

Participants were allocated randomly to either a routine post-fight return-to-sport management (control) protocol or selective head-and-neck cooling by drawing paper slips (i.e., pieces of paper labelled “cool” or “control”). Cooling was delivered with a silicone-based cap with an insulating cover that incorporated circulating coolant maintained at 0 °C (Figure 9). Participants remained seated and relaxed during

the 45-minute procedure, which was initiated within 10 minutes after completion of the fight. The portable cooling system was set up at the tournament venue on the morning of a fight day. After cooling (or control), all participants followed routine return-to-fight guidance (Figure 9; Table 4) and could exercise freely while avoiding activities with the potential for head or body impact for six days.


**Figure 9.** A) The PolarCap unit is responsible for maintaining the coolant temperature throughout its cooling system. (B) The Polar coolant is transported through silicone, targeting the head and neck regions. (C) A neoprene cover is applied on top of the cap as an insulator against the cold.

# Biomarkers analysis

Venous blood (3.5 mL in serum tubes) was drawn from all study boxers at five time points: at baseline, immediately post-fight, 45 minutes post-fight, and day 3 and day 6 post-fight (Table 4). Tubes were stored in portable refrigerators at 5–8 °C and transported to Lund University Hospital for centrifugation at 3,000 revolutions per minute (rpm) for 10 minutes at 4 °C. Serum was then transferred to 1.5 mL tubes using a pipette (800 µL to 1200 µL). The 1.5 mL tubes were stored in a −80 °C freezer until transport to the laboratory in Gothenburg for analysis. S100B, GFAP, t-tau, BDtau and NF-L, were measured in coded samples using an established single-molecule array (for GFAP, tau isoforms, and NF-L) by Quanterix previously described in detail [214] and electrochemiluminescence immunoassays (for S100B) by Roche Diagnostics [215, 216]. During transport from Lund to Gothenburg, samples

were shipped with a temperature probe with logging capabilities. In all cases, the temperature profile recorded confirmed that the required conditions were maintained throughout transit.

**Table 4.** Demonstration of timeline of enrolment, intervention, and assessment during the study period. SCAT-5 scores and blood samples were collected at baseline, post-fight, 45 minutes post-fight, day 3 and at day 6. A[a]: intervention group. B[b] control group. SCAT-5[c] Sport Concussion Assessment tool-5.

| **Procedures** | **Study period** | | | **Post allocation** | | | | **Close-out** |
|---|---|---|---|---|---|---|---|---|
| **Time point** | **Enrolment -$t_1$** | **Preallocation Baseline** | **Allocation 0** | **Post-fight** | **45 min post-fight** | **Day 3** | **Day 6** | **1-week post-fight** |
| **Enrolment:** | | | | | | | | |
| **Eligibility screen** | ✓ | | | | | | | |
| **Informed consent** | ✓ | | | | | | | |
| **Basic medical examination** | ✓ | | | | | | | |
| **Allocation** | | | ✓ | | | | | |
| **Interventions:** | | | | | | | | |
| **Selective head and neck cooling (A[a])** | | | | ✓ | | | | |
| **Return to fight protocol (A[a] + B[b])** | | | | ✓ | ✓ | ✓ | ✓ | |
| **Collecting blood samples** | | ✓ | | ✓ | ✓ | ✓ | ✓ | |
| **Assessments (SCAT-5[c])** | | | | | | | | |
| **SCAT-5** | | ✓ | | | | | | |
| **SCAT-5 follow-up** | | | | ✓ | ✓ | ✓ | ✓ | |
| **Boxing history** | | | | | | | | ✓ |

# Statistics

## Paper I-V

Data collected for manuscripts were compiled in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and exported to Statistical Package for the Social Sciences (SPSS) 25 to 30 (SPSS Inc., Version 25-30, IBM Corporation, Armonk, NY, USA) for statistical analyses. The threshold for significance was set to 0.05 for all analyzed data except for multiple comparison of the three cerebellar tracts where Bonferroni corrections were applied (significance threshold 0.017) in paper I. No corrections were applied across diffusion metrics (MD, AD, RD, MK, AK, RK), as each metric reflects a distinct microstructural property [(217)]. In Paper II Bonferroni corrections were considered but as no dataset was included in the within subject or

between groups test more than once, no corrections for multiple comparison were required.

All data were evaluated for normality and skewness using Q-Q plots, Shapiro-Wilk tests, and histograms. Modell assumption for the General liner model was done by analyzing datasets residuals normal or close to a normal distribution, thus validating the appropriateness of the methods. Log transformation of the data was tested for skewed variables in Papers II and V, but normal distribution was not achieved. Analysis of normally distributed data was done by paired Welch t-tests for group comparisons for baseline characteristic and unadjusted endpoints measurements. These data are presented as means ± standard deviations (SD). Skewed or categorical data were evaluated using Mann-Whitney U-tests for pairwise comparisons and Chi-square tests for categorical and binomial values, respectively. This data presented as medians and interquartile ranges (IQRs). For repeated measures as in paper II generalized linear models (e.g., analysis of variance (ANOVA) was used for outcome measurements. In paper V, the effects of the cooling intervention on brain injury biomarkers (measured as change observed from baseline to day 6 post-fight) were analyzed using the general linear model (GLM) known as analysis of covariance (ANCOVA), while adjusting for the acute change (baseline to post-fight) as a covariate for normally distributed data. Spearman's or Pearson's coefficients were calculated for all correlations.

Non-parametric tests were used to analyze results emerging from experiments with small sample sizes ($n < 30$) as in Paper II. Results of vestibular tests were reported dichotomously in Paper I (i.e., assigned to one of two distinct, mutually exclusive categories). Self-reported symptom evaluation, Hospital Anxiety and Depression Scale (HADS), Dizziness Handicap Inventory (DHI), and Sport Concussion Assessment Tool (SCAT) 5 scores were presented as raw values.

In paper III statistical analyses were performed using Python (SciPy and statsmodels libraries). Given a non-gaussian distribution for several MRI derived metrics, non-parametric approach was used for robust inference. For global comparisons between the three groups Kruskal–Wallis H-test was used, and Mann- Witney U test was used for pairwise comparisons. For correction of multiple comparisons the level of significance was corrected by the Benjamini-Hochberg False Discovery Rate (FDR) where statistical significance is reported as q-values. Cliff's Delta was used as measurement of the effect size.

In Paper IV power calculations were done (*vide infra)* [218] after consultations with a statistician. The numbers were based on previous reports of increase in serum levels of critical brain injury biomarkers post-concussion in athletes. We assumed that data from the cooled and control groups exhibited equal variance, with the power set to 0.8.

## Language editing

This thesis was written entirely by the author, who is responsible for all content and interpretations. An AI-based language editing tool (ChatGPT) was used solely to refine and improve language clarity and readability, as the author is not a native English speaker. No AI tools were used in any part that could influence the scientific content, data analysis, interpretation of results, or the conclusions.

# 4 Results

## Paper I

### Study population

In this case-control study, 42 subjects were included: 21 athletes with persisting post-concussive symptoms (PPCS) and 21 healthy age- and sex-matched controls. Due to incomplete MRI protocol one patient was excluded and thus 41 subjects were analyzed by 7T MRI. Mean age was 26 (range 18–43) years, and 60% were males. The SRC athletes had previously participated in ice hockey, soccer, karate, handball, indoor hockey, wrestling, or endurance riding for a mean of 18 years of practice. Controls were only participating in non-contact sports.

### SCAT, DHI and HADS

The PPCS athletes reported a median of 20 symptoms (IQR 20–22) with a median symptom severity score of 64 (IQR 44.5–81.5). The most frequently reported symptom was fatigue (100%), while the least common were nausea and vomiting (60%). Vestibular symptoms were experienced by a vast majority (85%) (Figure 10). To assess more specific symptomatology related to everyday-life vestibular difficulties, the Dizziness handicap inventory (DHI) was used. The DHI showed higher scores in athletes with PPCS (median 40; IQR 27-55) compared to controls (median 0; IQR 0-0; $p<0.001$). Similarly, HADS scores were also higher in PPCS athletes than controls in both subscales, HADS-A (median 9; IQR 5.5-11.5 vs. median 3; IQR 2-4.5) and HADS-D (median 7; IQR 5-8.5 vs. median 1; IQR 0-2), further underscoring the broader impact of PPCS.

Covariate factors, including number of sport-related concussions (SRCs), age, and sex, did not demonstrate significant correlations with SCAT5 symptom severity, DHI, or HADS scores ($p >0.05$).

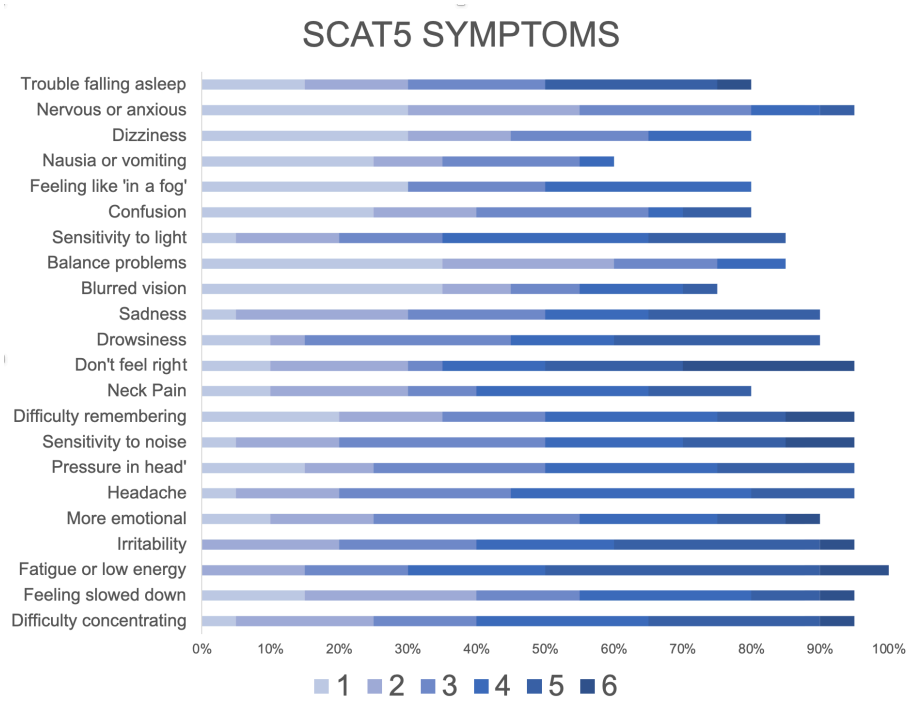


**Figure 10. SCAT-5 in PPCS athletes**
Sport concussion assessment tool-5 (SCAT-5) shows the proportion in percentage of PPCS athletes that reported symptoms and what symptoms they displayed. Symptom scale categorized as follows: 0 = no symptoms, 1-2 mild, 3-4 moderate and 5-6 severe experience of the symptom.

## 7T MRI: Cerebellar volumetrics, DTI, and DKI

Two PPCS athletes and three controls were excluded due to artefacts during volumetric segmentation, and one control from the DKI. Missing DTI data were reported in one athlete, and DKI from two athletes. Images were reviewed by an independent neuroradiologist, and no structural abnormalities were observed.

No significant differences were observed regarding volumetric data in Cerebellar white and grey matter volumes between PPCS athletes and controls ($p = 0.441$ and $p = 0.722$, respectively), with similar volumes between the groups. In addition, no volumetric correlations with vestibular dysfunction were observed ($p = 0.361$ and $p = 0.774$, respectively). The diffusion metrics revealed a decrease in DKI metrics in mean kurtosis in both superior and inferior cerebellar peduncle, and radial kurtosis in superior cerebellar peduncle of PPCS athletes when compared to controls. No metric did show any significant correlation with vestibular dysfunction in both DTI and DKI metric, $p>0.017$.

## Vestibular dysfunction

Primary comparisons showed a dominance of vestibular dysfunction in 13 of 21 PCCS athletes compared to 3 of 21 controls ($p = 0.001$). Vestibular dysfunction classified by origin in controls showed peripheral ($n = 1$), central ($n = 1$), or combined ($n = 1$) origin. In PPCS athletes peripheral ($n = 9$) or combined ($n = 4$) origin was diagnosed (Figure 11). All participants had a normal audiogram, except one athlete with SRC who had a left-sided peripheral vestibular dysfunction although a right-sided hearing impairment.

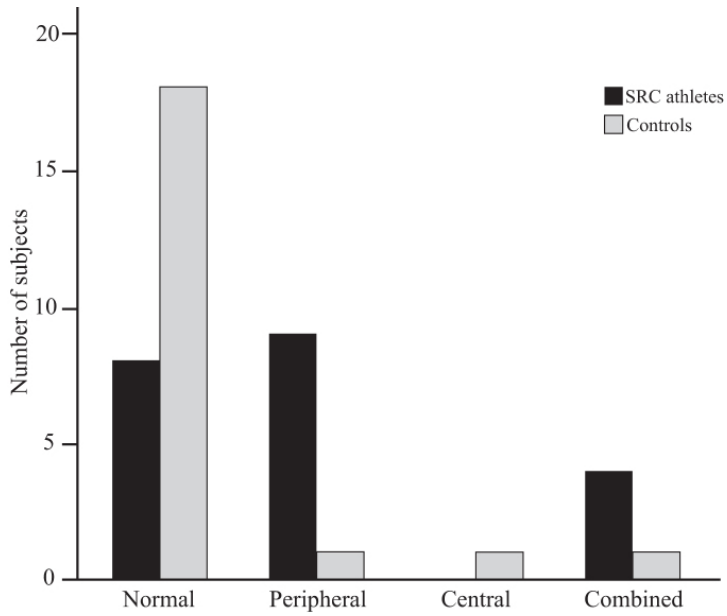


**Figure 11**. Graph illustrating the differences between athletes with SRC and controls in the origin of identified dizziness/vertigo.

Further vestibular assessment revealed that PPCS athletes showed worse results in vHIT and cVEMP; all test results are listed in Table 5. Abnormal test results on the posterior semicircular canal in vHIT and on the ipsilateral cVEMP indicated strongly for an injury to the inferior vestibular nerve (Figure 12), based on the fact that both semicircular canals (vHIT) or the saccule (cVEMP) are innervated by inferior vestibular nerve [(219)]. Vestibular dysfunction did not correlate with the number of previous SRCs as a covariate ($p = 0.971$), age ($p = 0.141$), sex ($p = 0.758$) or SCAT-5 symptom severity ($p = 0.418$). Subjects with vestibular dysfunction had higher scores on DHI (median 35, IQR 4.5–47 vs. median 0, IQR 0–20.5, $p = 0.019$) and HADS (median 15, IQR 9.25–19.75 vs. median 5, IQR 3–12.25, $p = 0.004$) when compared to subjects without vestibular dysfunction.

**Table 5. Vestibular assesment**
Classification of vestibular dysfunction into peripheral, central or combined origin when analyzed by several tests that assess different parts of the vestibular system. Tests that indicate peripheral origin for the pathology are vHIT, cVEMP and Dix-Hallpikes, while Pursuit eye movement indicates central pathology.

| **Vestibular test** | **PPCS athletes (n)** | **Controls (n)** |
|---|---|---|
| Number of participants | 21 | 21 |
| vHIT<br>- Peripheral system test of vestibular nerve and semicircular canal | 10 | 0 |
| cVEMP<br>- Inferior vestibular nerve, Saccule | 8 | 0 |
| Dix-Hallpikes<br>- Benign paroxymal postional vertigo | 0 | 1 |
| Purusit eye movement<br>- Central system | 4 | 2 |
| Type of Dizziness | **PPCS athletes (n)** | **Controls (n)** |
| Isolated central dizziness | 0 | 1 |
| Peripheral dizziness | 9 | 1 |
| Combined dizziness | 4 | 1 |

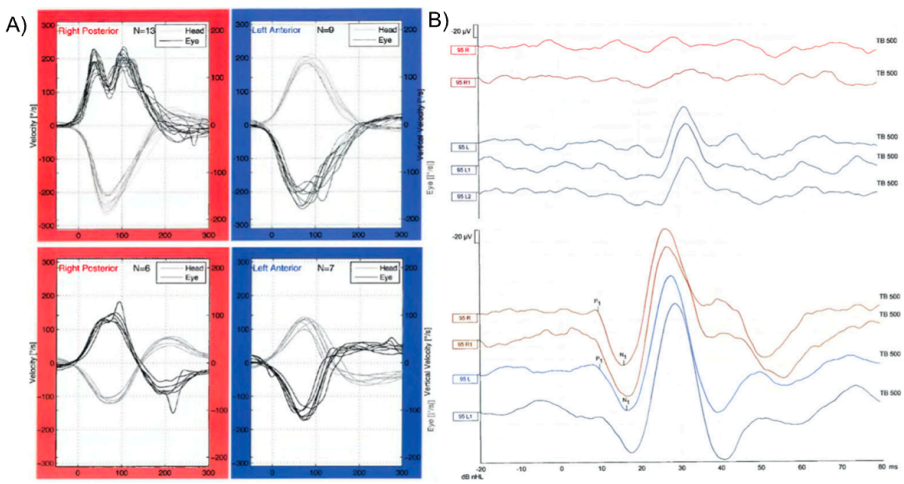


**Figure 12**. Graph illustrating to the left A) the video Head Impulse Test (vHIT), to the right B) cervical Vestibular Evoked Myogenic Potential (cVEMP). A) top left square shows biphasic waveform in a PPCS athletes indicating an abnormal response from the right posterior semicircular canal. All other squares representing normal responses from the semicircular canals from controls. B) The top panel shows low amplitudes mainly on the right side in cVEMP response from a PPCS athlete indicating impaired inferior vestibular nerve function on the right side. Bottom panel displays the characteristically high amplitudes observed in healthy controls.

# Paper II

## Study population

Thirty-two participants were included, 20 symptomatic athletes with persistent symptoms > 6 months following their most recent concussion, and 12 healthy controls.The PPCS group included 12 males with the mean age of 26.6 years (range 19–35 years), with a mean weight 73.7 kg (SEM 3.6 kg) and mean height of 178.6 cm (SEM 2.6 cm). The control group included nine males, mean age 26.4 years (SD 1.6 years, range 20–38 years), mean weight of 71.3 kg (SEM 3.8 kg), and a mean height of 183.2 cm (SEM 2.6 cm).

## Postural control

Results are reported for three frequency spectra (total, <0.1 Hz, and >0.1 Hz) across 200 s of perturbations, which include all registered movement regardless of frequency. The <0.1 Hz band reflects low-frequency movements, such as smooth, corrective postural adjustments, for example leaning forward to absorb perturbations. The >0.1 Hz band represents faster corrective movements used to maintain postural balance.

There is a rationale for analyzing the energy required for maintaining postural control during perturbations in spectral bands. While low frequency movements <0.1Hz represents change of posture, the high frequency >0.1Hz represents the movements one does to continuously correct for body deviations with small induced movements responding to afferent vestibular and proprioceptive information. An increased amount of energy consumption here reflects lesser effective postural control and hence, are more important for testing our hypothesis.

Group comparison showed that mTBI athletes used more energy to maintain postural control in all spectral bands when compared to controls: total ($p = 0.004$), low frequency (<0.1 Hz; $p = 0.007$), and high frequency (>0.1 Hz; $p = 0.004$) (Fig 13 A-F). Adaptation was assessed over the 200s of perturbation, where both groups showed an adaptation over time in all frequencies of movements reflected by reduced use of energy over time for adaptation. Importantly, PPCS athletes did not adapt to the perturbations as did the controls, and hence used more energy compared to controls in all spectral bands with the biggest difference in High frequency: 28% vs. 6% ($p = 0.040$).

Vision (i.e. standing with open eyes allowing visual reference of sway and orientation) had a clear impact in both groups where eyes closed required more energy compared to eyes open in both total and high frequency ($p < 0.001$; Fig 13 A-B, E-F). The within group comparisons showed: PPCS: higher energy in eyes closed (EC) than eyes open (EO) for total (+63%, $p < 0.001$) and high frequency (+93%, $p <$

0.001), and controls: higher energy in EC than EO for high frequency (+116%, $p < 0.001$).

*Quiet stance*

During quiet stance, PPCS athletes used more energy than controls across all spectral categories: total (+128%, $p = 0.034$), low frequency (+136%, $p = 0.048$), and high frequency (+109%, $p = 0.015$). In the eyes-closed quiet stance condition, between-group differences were pronounced, with PPCS athletes using more energy than controls in all bands: total (+222%, $p = 0.003$), low frequency (+290%, $p = 0.014$), and high frequency (+124%, $p = 0.002$).

Within groups, closing the eyes increased energy use, mainly in the high-frequency domain: PPCS: EC increased total (+103%, $p = 0.008$), low frequency (+116%, $p = 0.015$), and high frequency (+75%, $p = 0.019$), and in controls: EC increased total (+98%, $p = 0.009$) and high frequency (+54%, $p = 0.003$), while low frequency decreased (−18%, $p = 0.048$), indicating a spectral shift ) (Figure 13 A, C, E).

*Post-hoc tests*

During perturbation with eyes open, mTBI athletes used more energy than in controls at all periods 1-4, in high frequency.

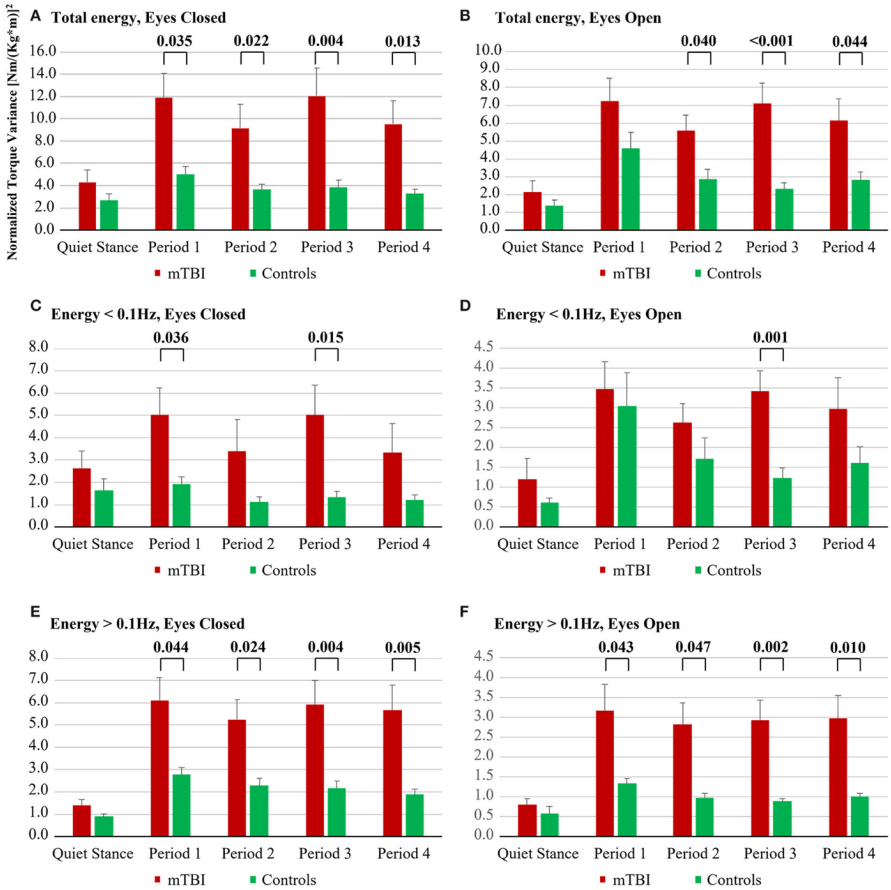


**Figure 13 A-F**. Energy used by mTBI subjects and controls during five balance perturbation periods: (A) total energy, eyes closed; (B) total energy, eyes open; (C) energy < 0.1 Hz, eyes closed; (D) energy < 0.1 Hz, eyes open; (E) energy > 0.1 Hz, eyes closed; (F) energy > 0.1 Hz, eyes open. An initial 30 seconds of quiet stance was followed by 200 seconds of perturbation sequences.

# Paper III

## Study population

In total, 59 participants were enrolled; 20 controls, 18 PPCS athletes and 21 active boxers (Table 6). No difference was seen regarding mean age across the groups; ($p= 0.43$). However, differences were seen between PPCS athletes and boxers in years of sports practice ($p < 0.0001$) and number of concussions ($p= 0.0002$), despite that the mean number of boxing bouts in boxers was 27, with a maximum number of 100 bouts. Demographic and SRC characteristics for the groups are presented in (Table 6).

**Table 6. Baseline characteristics**
Baseline characteristics for controls, PPCS athletes and active boxers.

| Demographics and baseline characteristics | Controls (n) | PPCS athletes (n) | Boxers (n) | P-value |
|---|---|---|---|---|
| Number of participants | 20 | 18 | 21 | NS |
| Sex:<br>Male<br>Female | <br>12<br>8 | <br>15<br>5 | <br>18<br>3 | |
| Age mean ± SD (years) | 25.8 ±1.1 | 27.4 ± 1.5 | 24.7±1.5 | P = 0.43 |
| Years of practice | | 18.7 ±1.1 | 6.4 ± 0.8 | P < 0.0001 |
| SRCs | 0 | 5.2 | 1.2 | P = 0.0002 |
| Number of boxing bouts | 0 | 0 | 27±6.5 | - |

In this paper, the centrum semiovale, basal ganglia, and midbrain were analyzed as the main regions of interest (ROIs) for analyzing PVS in the brain. These three ROIs are reported to be the brain locations where PVS are most commonly found [220, 221]. Across the three ROIs, the most robust and consistent results were captured by diffusion parameters within the segmented perivascular space. Diffusivity metrics (MD, AD, RD) and diffusion kurtosis metrics (MK, AK, RK) within perivascular spaces (PVS) were collectively analyzed under the term PVS-Dex. For each metric, a corresponding PVS-weighted Dex was additionally calculated. Each PVS metric was weighted by the relative volume of the PVS within the region of interest. This weighted measure was included to determine whether the PVS-Dex results were driven by the volume of PVS rather than by true changes in diffusivity. In case of significant changes in diffusivity, the role of diffusivity within the PVS is superior to changes in PVS volume *per se*.

*PVS volume*

In the analysis of the PVS volume no significant differences were observed across groups regarding all three ROI, Centrum Semiovale (CSO), Basal ganglia (BG) or midbrain (MB). Notably, a slight trend for the volume of CSO were observed (q= 0.068)

## PVS diffusivity

The centrum semiovale (CSO) showed the strongest statistical significance of the ROIs and remained significant after FDR correction for multiple comparisons. This was demonstrated by highly significant alterations in all three diffusivity metrics mean diffusivity (q = 0.002, H = 21.5), axial diffusivity (q = 0.001, H = 22.7), radial diffusivity (q = 0.002, H = 21.2), and the axial kurtosis (q = 0.035, H = 12.8) within the perivascular space (Figure 14).

Notably, regional variation in sensitivity between the three ROI were noticed with significant results in mean diffusivity in the basal ganglia (q = 0.040, H = 11.8) and radial diffusivity in the midbrain (q = 0.039, H = 12.3) (Figure 14).

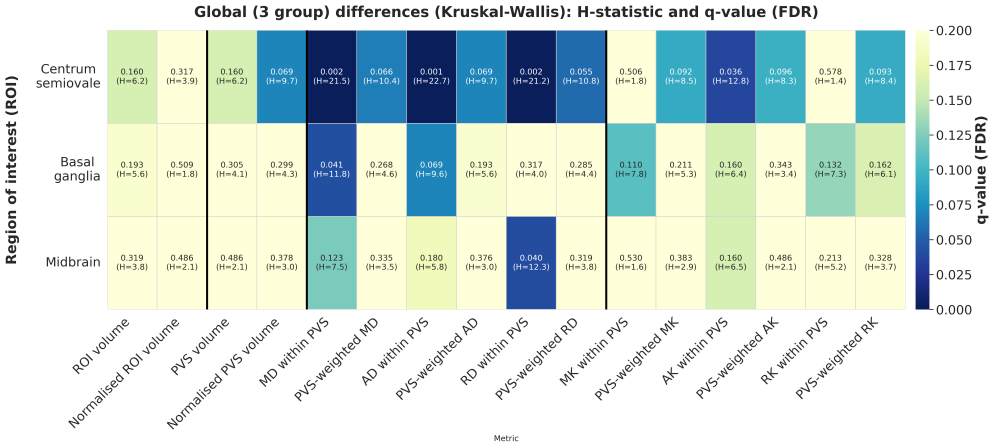


**Figure 14.** Heatmap summarizing global three-group comparisons (healthy controls, athletes with persistent post-concussion symptoms, and elite boxers exposed to repetitive head impacts) using the non-parametric Kruskal–Wallis H-test across regions of interest (rows) and imaging-derived metrics (columns). Color scale represents false-discovery-rate–corrected q-values (Benjamini–Hochberg), with darker colors indicating stronger group effects. For each cell, the q-value is shown together with the corresponding H-statistic in parentheses.

## Regional volumetric group differences of PVS

A systemically consistent pattern of enlargement in PVS volumes in elite boxers exposed to RHI were seen across all three ROIs (centrum semiovale, basal ganglia, and midbrain), compared to both healthy controls (HC) and PPCS athletes. Pairwise comparisons quantified by Cliff's Delta indicated moderate effect size when comparing RHI group vs HC in the centrum semiovale (Δ = +0.37), basal ganglia (Δ = +0.30), and midbrain (Δ = +0.21). Same patterns were seen when comparing RHI group vs PPCS athletes, with effect sizes of Δ = +0.42 in the centrum semiovale, Δ = +0.34 in the basal ganglia, and Δ = +0.24 in the midbrain. No effect size was noticed between HC and PPCS athletes indicating largely comparable PVS volumes within all three examined ROIs.

## Elevated diffusion metrics in PVS compartments in boxers

Diffusion metrics within the PVS revealed most prominent changes in boxers exposed to RHI when compared to both healthy controls and PPCS athletes. These results were mainly demonstrated in the PVS of Centrum Semiovale (CSO), where mean diffusivity (MD) was significantly elevated in the boxers with RHI compared to both HC (q = 0.002, Δ = +0.59) and PPCS athletes (q = 0.002, Δ = +0.83) (Figure

15 D). Similarly to the elevated MD in the RHI cohort relative to controls, significant elevations in both axial diffusivity (AD; $q = 0.001$, $\Delta = +0.64$) and radial diffusivity (RD; $q = 0.002$, $\Delta = +0.62$) were observed in the RHI cohort (Figure 15 E–F). Moreover, complementary pattern was observed in axial kurtosis (AK) showing a significant decrease in the RHI group when compared to the PPCS group ($q = 0.035$, $\Delta = -0.66$) (Figure 15 H).

Analysis of basal ganglia and midbrain did corroborate the findings in CSO by highlighting consistent alteration in the RHI cohort. Significant differences were observed in the basal ganglia measured in increased mean diffusivity in RHI cohort when compared to the PPCS athletes ($q=0.040$, $\Delta = +0.63$). Similarly, the comparison between RHI cohort and healthy controls revealed a trend of increased mean diffusivity ($\Delta = +0.43$).

In the midbrain PVS-Dex pairwise comparisons showed significant difference in boxers exposed to RHI, with higher radial diffusivity when compared to healthy controls ($q=0.039$ $\Delta = +0.62$).

These results suggest that the centrum semiovale (CSO) is the primary region for evaluating microstructural glymphatic disruption in boxers exposed to repetitive head impacts (RHI), while effects also extend into subcortical grey matter structures associated with perivascular fluid transport.

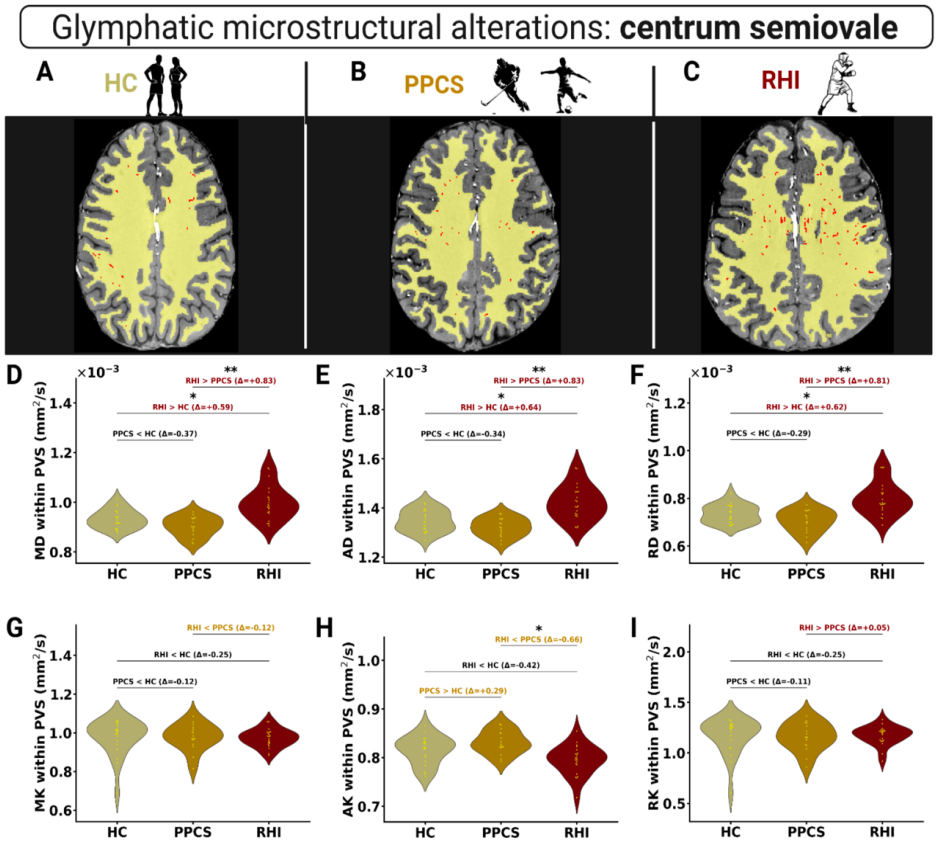


**Figure 15.** Representative axial T1-weighted images illustrate perivascular space (PVS) segmentation within the centrum semiovale in (A) healthy controls, (B) athletes with persistent post-concussion symptoms (PPCS), and (C) elite boxers exposed to repetitive head impacts (RHI), with PVS voxels overlaid in red on the white matter mask (yellow). Panels (D–I) show group-wise distributions of diffusion and diffusion kurtosis metrics restricted to the segmented PVS compartments: mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK).

# Paper IV

## Protocol for a randomized control trial (Paper IV)

This protocol describes a plan to examine whether selective head-and-neck cooling after a boxing bout alters blood levels of brain injury-related biomarkers as primary endpoint, and self-reported symptoms as secondary endpoint during the first week post-fight. In Paper IV, we presented the protocol, including the study design and power calculation for the randomized trial presented in Paper V (Figure 16). The

power calculation was conducted using the formula presented in Figure 17 [218]. Consequently, the target sample size was set at 40-50 boxers to account for potential dropouts.

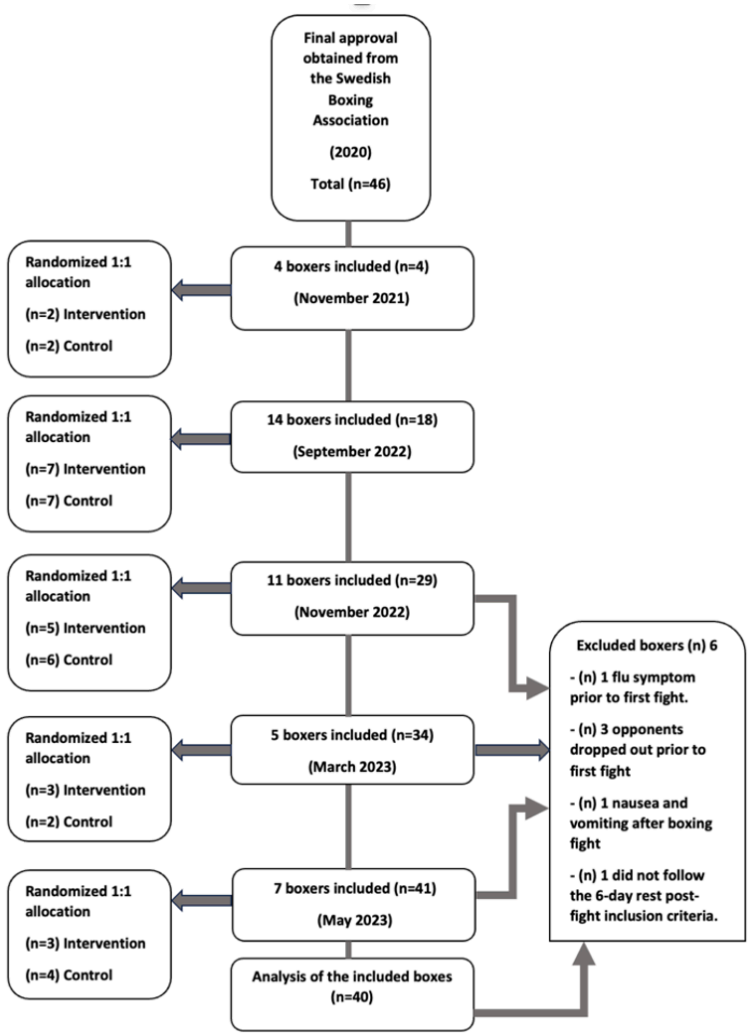


**Figure 16.** Over a two-year period, 46 boxers were recruited; six were excluded, resulting in a final sample of 40 participants. Allocation and randomization in a 1:1 ratio were conducted after obtaining signed informed consent and prior to baseline testing.

$$n = \frac{2 \cdot \left(Z_{power} + Z_{alpha}\right)^2 \cdot SD^2}{effect\ size^2}$$

**Figure 17.** Power calculation formula as previously suggested [218].

# Paper V

## Study population

Here, 46 boxers were enrolled over a two-year period, of whom 6 were subsequently excluded (Figure 16). Forty boxers were then available for analysis and included in the final analysis (21 controls; 19 intervention). Of these, there were 36 males (18 in each group), and 4 female boxers (one in intervention, three in control group); p= 0.851. There were no statistically significant differences between the intervention and control groups in baseline characteristics, including number of head strikes, body strikes, total strikes, sex, age, SCAT5 baseline scores (all p > .05).

## Correlations - Head strikes, SCAT- 5 symptom rating and biomarker levels

Spearman's rank correlation analyses were conducted to assess the association between strike exposure and biomarker changes. In combined group analysis, NF-L level changes from baseline to day six post-fight correlated with cumulative head strike exposure ($\rho = 0.422$, p =0.018). In group-specific analyses, the control group demonstrated a significant correlation between head strikes and the increase in GFAP from baseline to post-fight ($\rho = 0.457$, p =0.049). These correlations suggest a potential association between greater head impact exposure and elevated brain biomarker release. No correlations were observed between symptom severity changes from baseline to post-fight, as measured by SCAT5, with either strike exposure or biomarker increases (all p > .05).

## Symptom scores in intervention and control groups

There were no significant differences in SCAT-5 symptom scores between the control and cooling intervention groups at baseline (p = .784; Table 1) or immediately post-fight (18 [7–27] vs. 14.5 [1.25–23], p = .609). However, at later time points, a trend toward lower symptom scores was observed in the intervention group. At 45 minutes post-fight, median scores were 8 [3–15] for controls and 4.5 [0–8] for the intervention group (p = .096); at three days, 4 [0–12] vs. 0 [0–7] (p = .085); and at six days, 3 [0–9] vs. 0 [0–3] (p = .084) (Figure 18).

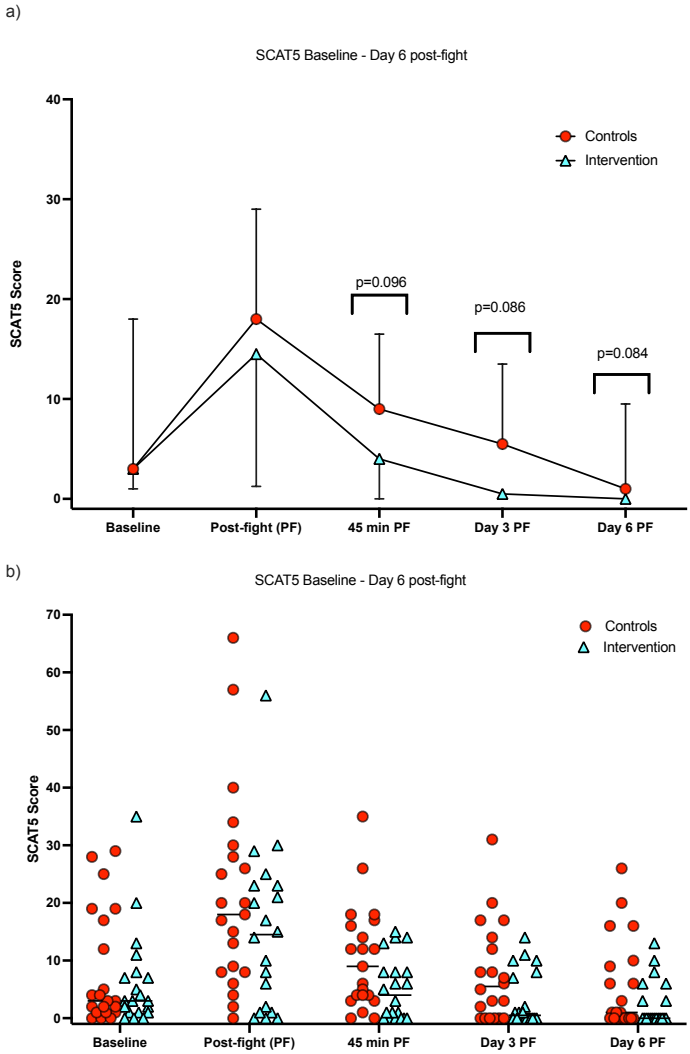


Figure 18. SCAT-5 scores for each group—selective head-neck cooling (intervention) and controls—were analyzed. a) A line diagram presents the SCAT5 scores with medians and interquartile ranges (IQRs). b) A scatter plot displays individual symptom severity scores for each participant (y-axis) at each timepoint (x-axis). Each dot represents a boxer.

## Head-neck cooling accelerates normalization of elevated post-fight brain injury biomarkers.

Immediately post-fight, blood samples were analyzed for GFAP, NF-L, S100B, BD-tau, and t-tau levels. This post-fight levels showed increasing values in all brain

injury biomarkers compared to baseline (Table 7). At the later time point (45 minutes post-fight), all biomarker levels were slightly lower in both groups.

**Table 7. Early elevation of blood brain injury biomarkers**

Observed levels of brain injury biomarkers from baseline to post-fight, measured in % and pg/ml.

| Blood Brain Injury biomarker | Baseline to post-fight changes in % | Baseline to post-fight changes in pg/mL |
|---|---|---|
| GFAP mean ± SD | 21% ± 36 | 16.4 ± 35 |
| NF-L mean ± SD | 17% ± 30.8 | 2.4 ± 5.1 |
| S100B median (upper range) | 68% (176%) | 0.068 (0.12) |
| t-tau median (upper range) | 47% (73%) | 0.77 (2.24) |
| BD-tau median (upper range) | 73% (112%) | 0.49 (0.79) |

The effect of the cooling intervention was assessed by analyzing changes from baseline to day 6 using a general linear model ANCOVA, with baseline-to–post-fight changes included as a covariate for both GFAP and NF-L. The control group exhibited increasing levels of GFAP and NF-L, whereas the intervention group showed reduced levels. A significant effect of the cooling intervention was observed for GFAP, both in absolute terms (23.8 pg/mL, $p = .019$ [$p = .012$ for unadjusted data]) and in percentage terms (28.3% difference, $p = .005 \pm 9.45\%$, 95% CI [9.06%, 47.50%]) when compared to controls (Figure 19). For NF-L, a trend toward between-group differences were observed, with a difference of 2.71 pg/mL ($p = .092$ [$p = .07$ for unadjusted data]; Figure 20).

S100B, BD-tau and total tau levels were not altered by the cooling intervention.

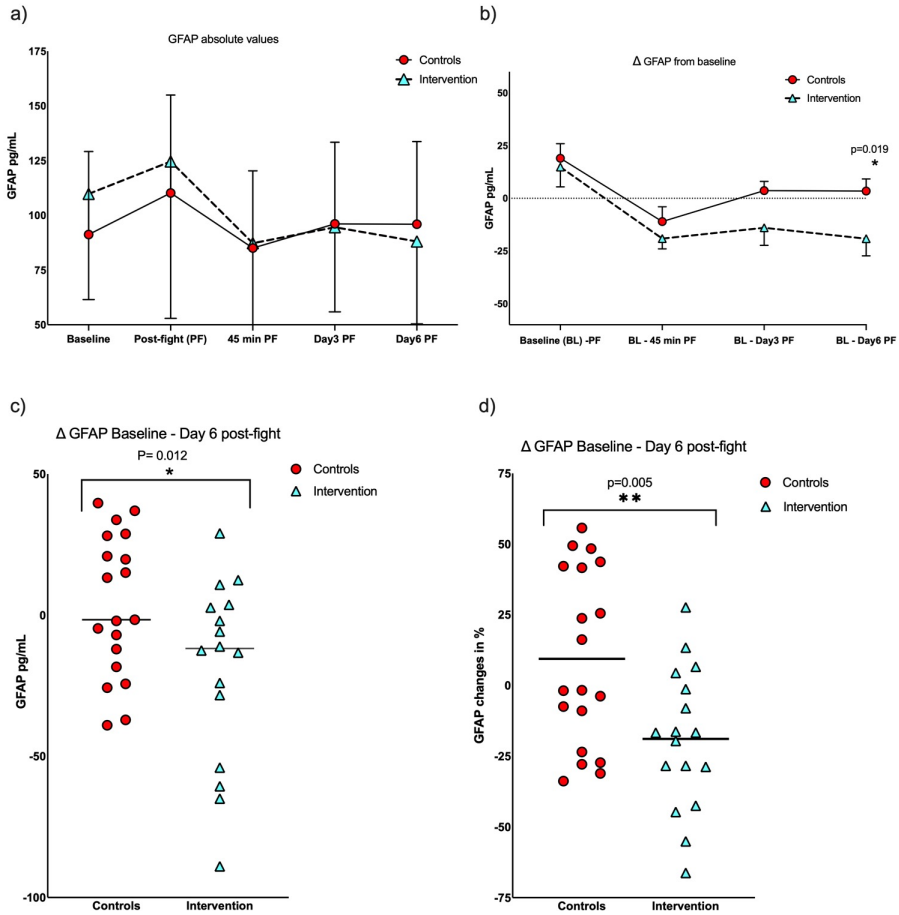


**Figure 19.** Blood levels of the brain injury biomarker GFAP in boxers receiving the selective head-neck cooling (intervention), and in the control group, measured in pg/mL or % change. a) Line diagrams for GFAP in pg/mL b) Difference (Δ) from baseline adjusted for baseline to post-fight changes. c-d) Baseline to day 6 post-fight changes without adjustment for baseline to post-fight changes expressed in pg/mL and in %. * = p < .05; ** = p < 0.01.

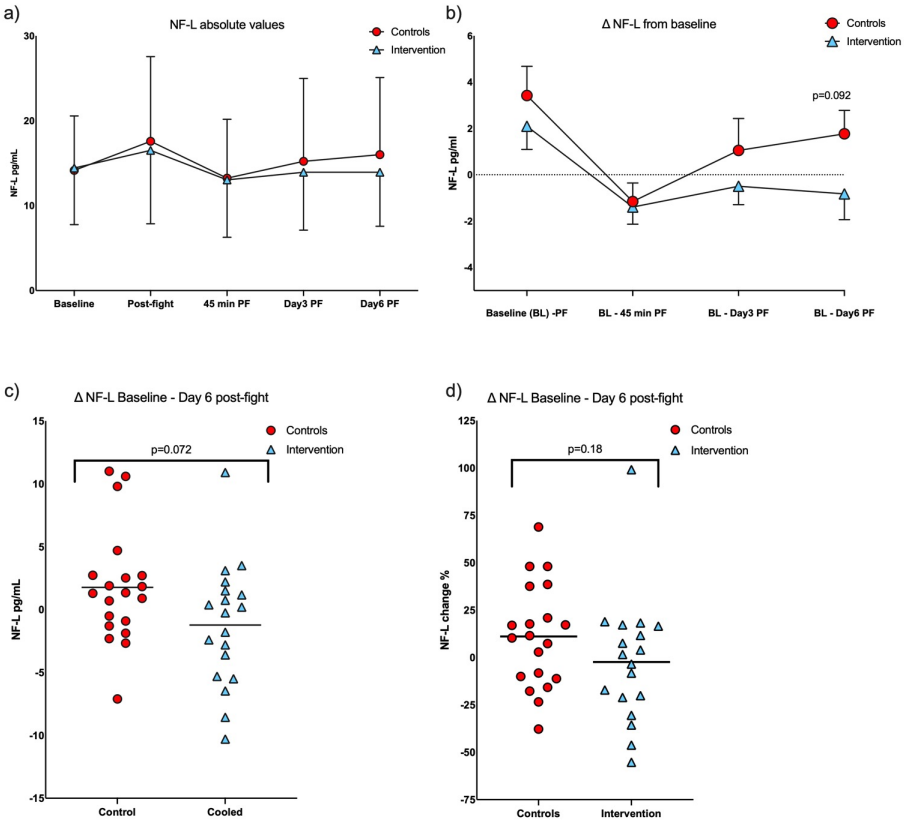


**Figure 20.** Blood levels of the axonal injury biomarker NF-L in boxers receiving selective head-neck cooling (intervention), and in control groups measured in pg/mL or % change. a) Line diagrams for NF-L in pg/mL b) Difference (Δ) from baseline adjusted for baseline to post-fight changes. c-d) Baseline to day 6 post-fight changes without adjustment for baseline to post-fight changes expressed in pg/mL and in %.

# 5 Discussion

## Clinical Findings – Papers I, II, & V

### Symptom presentation in athletes with persistent post-concussion symptoms

In Paper I, a high symptom burden that was both debilitating and prolonged was observed in the PPCS cohort. PPCS athletes also reported substantially higher scores across several self-reported symptom scales when compared to healthy controls. These tools were employed to characterize the nature and distribution of these symptoms.

In the SCAT-5 (22 symptoms; total severity score range 0–132), all athletes who had suffered concussions reported fatigue (100%). In addition, 80% and 85% of the PPCS athletes reported dizziness and imbalance, respectively. Self-perceived impairments related to dizziness were assessed using the Dizziness Handicap Inventory (DHI; 0–100), the scale used most widely to evaluate dizziness-related burden across three domains: physical; functional, and emotional. The PPCS athletes reported high scores in all DHI domains, while no symptoms were reported in controls. The DHI results indicate a substantial presence of dizziness and reduced orientation affecting daily life activities and hence, reduced quality of life in athletes with PPCS. Similarly, hospital anxiety and depression scale (HADS), which reflects the psychological consequences of the symptoms, indicated a higher symptom burden for both depression and anxiety in the PPCS group when compared to controls.

Taken together, these findings suggest that dizziness and balance-related problems are common in PPCS and interfere substantially with daily functioning and well-being.

### Interpretation of persistent post-concussive symptoms (PPCS)

The findings discussed above suggest that SRC athletes report increased symptoms of depression and anxiety, and that PPCS can contribute to a lower quality of life, consistent with previous publications [222, 223]. Further, symptom load (headaches, dizziness, concentration/memory problems, irritability, fatigue) has been associated with decreased quality of life for several months post- concussion [224]. Importantly, initial symptom severity acts as a predictor of PPCS [225] in addition to a history of repeated concussions in contact sports. These two indicators appear to exacerbate clinical outcome in concussed athletes [226].

## Interpretation of symptoms in repetitive head impacts (RHI) cohorts

Prolonged recovery is a substantial problem in SRC, although it has been debated whether symptoms should be assessed according to domains (physical, emotional, cognitive) or if only overall symptom burden should be considered [15, 227]. Consistently, the PPCS athletes in *Paper I* exhibited very high SCAT-5 scores with a median of 64 (of a maximum of 132), reflecting a substantial symptom load. In contrast, the cohort of active boxers exposed to repetitive head impacts (RHI) in *Paper V* exhibited considerably lower symptom scores at baseline and post-fight, indicating a comparatively milder clinical presentation. The symptomatology of the 40 boxers exposed to RHI were evaluated at baseline using SCAT-5 and showed rather mild symptoms, with a median symptom score of 4. As expected, it was followed by a marked increase in symptoms post-fight with a median of 18 on SCAT-5, which subsided to baseline in both controls and cooled boxers over a period of 6 days without sparring or bouts. Our data underscore the importance of the initial symptom burden post-SRC, where boxers resumed sparring or competition by day 6, and showed a difference in the course of symptoms between non-concussive RHI and SRC. Despite the absence of persistent clinical symptoms in boxers, elevated NF-L levels as a sign of axonal injury have been observed in boxers after 14 days of rest post-fight [228]. Although boxers may not exhibit clinical symptoms in the early stages, the cumulative burden of RHI has been associated with a slow progress of neurological disorders such as chronic traumatic encephalopathy (CTE) [229].

## Symptoms attributable to RHI in boxing

In boxing, the symptom burden has been examined more often by neuropsychological methods than self-reported symptom scales. These tests have frequently revealed deficits in memory, information-processing speed, finger-tapping speed, complex attentional tasks, and frontal-executive functions [230, 231]. Further, when former and active professional boxers were examined, neuropsychological deficits were frequently noticed. In contrast to professional boxers, amateur boxers did not show long-term changes in cognitive function or psychometric results [232] when studied longitudinally over 9 years [233]. This may indicate a role of cumulative RHIs since professional boxers have more active years of boxing compared to amateurs, and professional boxing includes more rounds per bout compared to amateurs [39],[40, 234]. The cumulative number of RHI in boxing has been previously documented showing that a majority of punches during fights are directed at the head. In 3 × 3-minute fights, approximately 40–50 head strikes occur per bout [235, 236]. These findings are highly comparable to our results (*Paper V*), in which the primary exposure also was to the head, with a median of 47 strikes. This similarity supports the representativeness of our cohort when examining cumulative RHIs.

Finally, the current return-to-competition policy in Swedish boxing requires only a 6-day interval between competitions, and in many European countries there is no

established interval between bouts. As based on our knowledge of SRCs in other sports, this timeframe between allowed bouts may be too short.

# Diagnostic and Pathophysiology – Papers I, II, III

## Vestibular dysfunction and impaired postural control

In *paper I* we identified inferior vestibular nerve dysfunction in athletes with PPCS. This was established by combining pathological outcomes in cVEMP and vHIT that showed impairment in the posterior semicircular canals (SCCs), both of which project through the inferior vestibular nerve. Other origins of pathology, such as isolated central vestibular pathology, were seen in only one control and none of the PPCS athletes. Combined central and peripheral types of pathology were seen in four athletes with PPCS and one control. Dix-Hall pikes test was positive only in a small number of controls, in contrast to being totally absent in PPCS athletes. This was unexpected because of the evident risk of benign paroxysmal positional vertigo (BPPV) [237], the most frequent cause of vestibular pathology after a head impact. However, the most frequent type of BPPV arises from the posterior semicircular canal (SCC), and with a lesion to the inferior vestibular nerve, symptoms and signs of BPPV may not be detected. Although there may be a dislocation of otoconias in the posterior SCC, as is assumed in traumatic BPPV, a lesion to the inferior vestibular nerve would prevent the erroneous vestibular signalling from reaching the vestibular nuclei and hence, symptoms and signs of BPPV will not occur. Similar to our study, a peripheral origin of vestibular dysfunction was observed in 26% of post-concussed children and adolescents in sports but without an established origin of pathology [238]. Vestibular nerve lesions following TBI have also been demonstrated in *post-mortem* studies, and in support of our findings, lesions of the superior and inferior vestibular nerves have been observed [239, 240].

Our results are consistent with those in previous studies where vestibular dysfunction was observed post-SRC in clinical tests [241, 242]. Importantly, vestibular dysfunction has been associated with prolonged recovery before returning to play [243, 244]. These data and ours argue why vestibular rehabilitation that focuses on e.g., improving gait performance may contribute to a reduced overall symptom burden [245], and similar results were observed also in cervico-vestibular rehabilitation [242]. Despite the clinical features of vestibular dysfunction following SRC, previous studies did not provide a clear diagnosis or pathophysiological explanation for the pathological findings and a multimodal assessment for diagnostic or prognostic tools following SRC is required [246, 247]. Accordingly, the reliability and validity of vestibular tests following SRC has not been sufficiently assessed [248]. Our results, as well as those of other reports, highlight the importance of comprehensive vestibular testing and of selecting a chronic time point when evaluating balance dysfunction post-SRC [249].

## Neuroimaging examination of infratentorial regions involved in balance

From a neuroimaging perspective, there were no significant changes in infratentorial brain volumes, while some significant results were found when DKI was used. In DKI metrics, lower kurtosis was observed on MK (in superior and inferior cerebellar peduncle) and on RK (superior cerebellar peduncle). These subtle changes may not be associated with, or the cause of, the symptoms experienced from the vestibular system. Previous studies that incorporated diffusivity measurements post-concussion included a very heterogeneous cohort compared to our PPCS cohort [250, 251]. Nevertheless, decreased cerebellar FA and increased MD were correlated with vestibular dysfunction in mTBI patients 22 days post-injury [252]. Different inclusion criteria may explain this discrepancy.

The chronicity of symptoms following SRC has been suggested to relate to white matter abnormalities [253]. However, in *paper I*, significant balance problems were reported without marked changes to the posterior fossa structures when high-resolution 7T MRI was used. This strengthens the findings of lesions in the inferior vestibular nerve as a main pathology in our PPCS cohort.

## Interpretation of impaired postural stability in PPCS athletes

Paper II investigated postural control by quantifying the amount of sway energy required for PPCS athletes and healthy controls to maintain postural stability, both during perturbation and quiet stance. These were quantified in three spectral categories: total energy used; energy used during high frequency components >0.1 Hz, and low frequency components ≤ 0.1 Hz. Adequate postural control was maintained by corrective movements. In our cohorts, higher frequency corrections >0.1 Hz reflect the corrective movements required during exercise, while a corrective movement ≤0.1 Hz represents low energy movements used in normal daily life activities. These spectral categories capture detailed information about the energy used for corrective movement to maintain balance [254]. PPCS athletes used significantly more energy across all three spectral band categories during adaptation over the 200s perturbation time and quiet stance. The increased use of energy to maintain postural control even in an unperturbed environment may contribute to the fatigue that PPCS athletes experienced.

These findings also suggest that SRCs may impair both postural control and motor learning through alterations in sensorimotor adaptation. This is consistent with prior research that demonstrated impaired postural control following concussion regardless of time post-injury, characterized by an increased reliance on visual and vestibular inputs to regulate balance [246].

The vestibular symptoms showed an association with exercise intolerance post-SRC [255, 256], which reduced the effectiveness of rehabilitation and prolonged the time to recovery [15]. Such patterns were observed in our PPCS cohort. This could be

interpreted as an extensive demand for energy in PPCS athletes to maintain postural stability during activity, which is demonstrated by exacerbated symptoms during exercise. Reduced fine tuning of movements caused by vestibular lesions will inevitably compromise motor skills, both in sports and in daily life.

The significant increase in use of energy both with eyes open or closed might be explained by underlying sensorimotor mechanisms. For instance, fast corrective movements increase when visual input is reduced in patients with obesity, or fatigue [257]. In contrast, low frequency movements increase during somatosensory stability challenges, e.g., standing on unstable surfaces such as foam [139, 258, 259].

The PPCS athletes demonstrated significantly greater use of fast corrective movements. This implies an alteration in fast subconscious movement control, suggesting a less efficient central sensorimotor process [260]. The increased energy demand to maintain postural control in PPCS athletes was greater during perturbations when compared to during quiet stance. During the perturbation sequences, PPCS athletes used more energy with both eyes open and closed, while in quiet stance, increased energy demand was observed only with eyes closed. This clinical pattern of integrity disruption in the sensory domain has been observed previously [246].

From a neurophysiological perspective, predictive muscle response occurs to reduce perturbation-induced imbalance [261, 262]. Sensorimotor adaptation ability is crucial in sport performance, and reduced capacity to adapt to balance perturbation in athletes will result in decreased performance and increased exercise intolerance [256, 263]. Moreover, a psychological aetiology of impaired postural control in PPCS athletes was not supported by our results. Fear of falling or persistent postural perceptual dizziness (PPPD) is reported to have a negative effect on postural stability [264-266], although such patterns were not observed in our PPCS cohort. This suggests that symptoms observed and experienced in psychological domains do not indicate any major psychosomatic basis for the imbalance observed. Thus, the psychological symptom burden appears to be distinct from somatic domains [15, 249].

The role of vision in maintaining postural control was found to be crucial in PPCS athletes, with increased differences when eyes were closed during perturbation compared to controls. This implies that when visual feedback or orientation was available, the PPCS group benefitted from it, suggesting that the high dependency on the visual system to maintain balance was a sign of vestibular dysfunction, consistent with previous findings [249]. Moreover, the visual dependency at several time points may extend up to years post-concussion [246, 267]. By changing visual state from eyes open to eyes closed, a shift of reference in sensory balance information changes from the primary source of information at eye level, to the mechanoreceptive and proprioceptive systems. This changes the reference for the postural control strategy and is a common observation after any vestibular lesion [254].

When interpretated in isolation, focusing solely on the role of vision in PPCS athletes without considering dysfunction in the vestibular nerve as in paper I could be

misleading and suggest a central origin for the postural impairment. Therefore, an active central compensation attributable to the impaired vestibular nerve function is the most likely origin of the PPCS athletes' impaired balance (Figure 21).

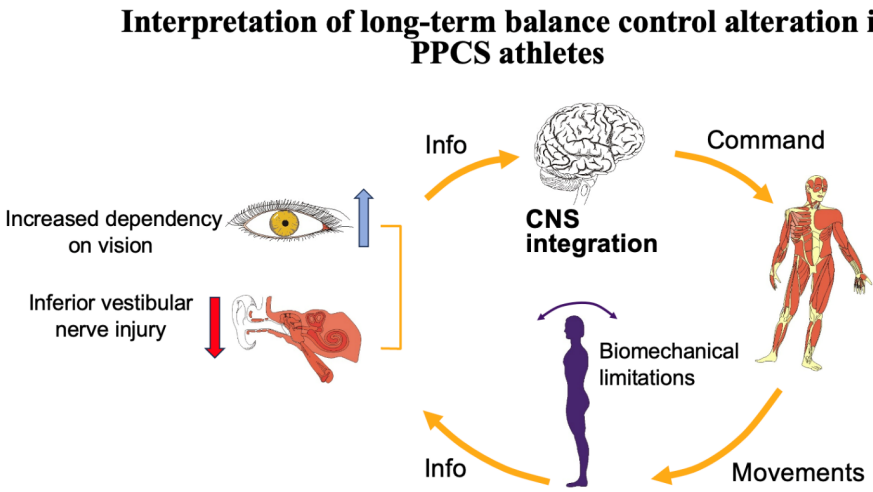


**Figure 21:** This figure demonstrates the integrity of the balance system, where Paper I demonstrate dysfunction of the inferior vestibular nerve (red arrow) and Paper II demonstrated increased demand on vision to maintain postural stability (blue), resulting in biomechanical limitations in maintaining postural control. Source: Courtesy of Måns Magnusson

## Perivascular spaces and the glymphatic system in the brain

In this paper ultra-high field strength 7T MRI was used to demonstrate novel alterations in perivascular spaces (PVS) as an estimate of the glymphatic system structure and function in active boxers exposed to RHI, in PPCS athletes and in athletic controls (HC). The primary findings were a consistent enlargement of the PVS in the RHI group, accompanied by significantly elevated diffusion metrics (MD, AD, RD). These significant changes were observed primarily across the centrum semiovale, as well as in the basal ganglia (increases in PVS-MD), and in the midbrain (increases in PVS-RD). These results suggest that PVS diffusivity is a highly sensitive marker, outperforming conventional volumetric measures in discriminating RHI-exposed athletes from the HC and PPCS groups. Overall, these findings indicate persistent alterations in the perivascular microstructure of active boxers, with potential implications for glymphatic clearance and long-term brain health.

*PVS expansion and microstructural remodeling post-concussion*

PVS is defined as the fluid-filled spaces surrounding small vessels such as penetrating arterioles and venules. They therefore form an interface between the vascular compartment and the brain parenchyma. Physiologically, PVS function as conduits

to facilitate CSF influx and interstitial fluid clearance via the glymphatic system (Figure 22). This perivascular transport system is regulated by aquaporin-4 located at the astrocytic endfeet [268, 269]. This system provides an essential clearance function for removing metabolic waste including amyloid-β, tau, and pro-inflammatory cytokines [270]. The consistent pattern of increased PVS volume in our RHI cohort in ROIs centrum semiovale (subcortical white matter) and basal ganglia (grey matter) underscores that RHI impacts may cause disruption in perivascular integrity and CSF-ISF exchange. Whether PVS dilation reflects impaired glymphatic outflow, compensatory fluid accumulation, vascular stiffness, astrocytic remodeling, or BBB disruption is debated, and the underlying mechanisms remain incompletely understood [67].

The enlarged PVS volumes in active boxers underscores the burden of cumulative RHI compared to PPCS athletes who did sustain several SRCs but presumably less subconcussive impacts to the head. This is further confirmed by the absence of differences in PVS volumes between PPCS athletes and HC. This may indicate a natural resolution of PVS enlargement over time, while simultaneously strengthening the association between PVS enlargement and active boxers who continuously are exposed to RHIs.

Observed abnormalities in mainly diffusion, but also kurtosis, within PVS are consistent with results from pre-clinical models where evidence of dysfunctional clearance within the glymphatic system by stasis and glial remodeling was found post-mTBI [271]. Our data indicate that a combined elevation of PVS burden and altered diffusivity may reflect disrupted solute clearance, reduced vascular pulsatility, or inflammatory processes that compromise the structural integrity of the glymphatic system.

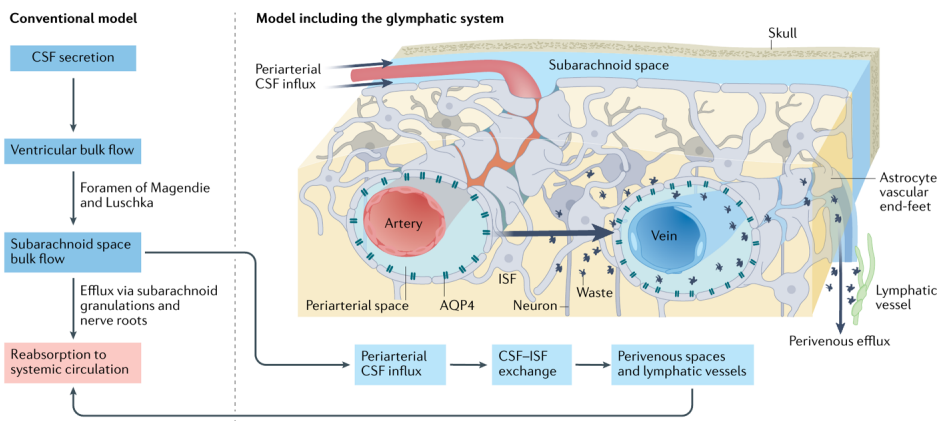


**Figure 22**. This figure demonstrates the integrity of the glymphatic system by showing CSF flow in the conventional model on the left, and the glymphatic system on the right. The conventional model illustrates the flow of CSF from the ventricles, then into the subarachnoid space, followed by reabsorption into the

bloodstream. The modern model, however, demonstrates that part of the CSF flows along the perivascular spaces surrounding the arteries. The presence of aquaporin-4 (AQP4) channels is essential during periods of high glymphatic flow. For instance during sleep, CSF enters the brain tissue, supported by AQP4, where it mixes with interstitial fluid (ISF) and subsequently drains along the perivenous spaces. *Adapted from: Lohela TJ, Lilius TO, Nedergaard M. The glymphatic system: implications for drugs for central nervous system diseases. Nat Rev Drug Discov. 2022;21:763–779. doi:10.1038/s41573-022-00500-9. Reprinted with permission from Springer Nature* [272].

### *PVS Dex: a novel metric of Glymphatic capacity*

To understand the role of PVS function, we aimed to develop a novel metric for the assessment of the glymphatic system. In contrast to previous studies evaluating the burden of PVS or water diffusion in isolation, and mostly focusing on enlargement of PVS based on volumetrics [273-276], our metric accounts for both available space for transport and the efficacy of the transport. Therefore, we consider it an improved indicator of glymphatic health in the brain. The significantly higher diffusivity observed in the brainstem and subcortical structures of boxers may reflect an initially increased activity of perivascular transport capacity, which may be explained by increased demand for clearance of solute and waste. In contrast to boxers, PPCS athletes did not show any alteration in diffusivity within the PVS, despite their chronic symptoms. This may underscore the potential of diffusivity to be a sensitive biomarker of the burden of cumulative RHIs, rather than reflecting the symptomology of the investigated athlete.

Importantly, our study shows the first *in vivo* application of these 7TMRI methods to assess neurofluid transport not only in concussion research, but also in other glymphatics-related pathologies such as neurodegeneration.

## Clinical Implications of Early head and neck Cooling After Repetitive Head Impacts in Boxing – Papers IV & V

This randomized single-center clinical trial provided novel insight into early selective head-and neck cooling in athletes exposed to RHI, with blood brain injury biomarkers measured as the objective outcome *(Paper V)*. Sample size calculation was made and presented in the protocol published in *Paper IV*. The cooling intervention, initiated within 10 minutes post-fight in competitive boxers, normalized glial fibrillary acidic protein (GFAP) levels to baseline levels when assessed 6 days post-fight. In addition, slightly reduced neurofilament-light (NF-L) levels and symptom rating scores ($p=0.07$ and $p=0.09$, respectively) were also observed. As in our previous studies, the cooling intervention was well tolerated and no adverse events related to it were reported [80, 131] . All biomarkers increased from baseline to immediately post-fight, indicating that the boxing match had a measurable effect on blood brain injury biomarker profiles.

## Symptom burden following repetitive head impacts in boxers

The boxers received a large number of head impacts during the -6-minute boxing match, a median of > 40, ranging up to 70 hits to the head per bout, as evaluated from streamed recordings. Although none of these head strikes resulted in a knock-out or other signs that mandated terminating the bout, many subconcussive events may have occurred. Immediately after the fight, boxers reported an increased number of symptoms on the SCAT-5, followed by gradual symptom resolution to baseline levels as evaluated over the 6-day observation period.

## Interpretation of brain injury biomarkers in a sports context

Consistent with the literature our findings showed an immediate post-fight increase in brain injury biomarkers [187, 277] . Despite considerable research on brain injury biomarkers, the detailed progression after repeated mild TBIs or in a sports setting remains insufficiently characterized. The early blood brain injury biomarker levels may also be influenced by the strenuous exercise *per se*, although this elevation appears lower than in concussion events. The brain injury biomarkers examined in SRC or RHI need to be brain-specific to minimize Type I errors, and elevated levels of e.g. S100B can be explained by its presence in adipose tissue and skeletal muscles [278] (Table 8). Further, exercise-related elevation of the biomarker UCH-L1, often used in combination with GFAP, has been found 45 minutes post-exercise [279]. A similar well-established pattern has been confirmed for S100B, which usually normalizes to baseline within hours [187, 277, 280]. More specific brain injury biomarkers, such as GFAP, NF-L, and t-tau, have been shown to distinguish between controls, SRC, and RHI [187, 281], and accurately distinguished cohorts of concussed athletes from uninjured athletes [281]. Similar patterns have been observed in the elevation of NF-L levels in other contact sports, such as after a football game [282-284], as well as following SRC in ice hockey games [194, 285]. Moreover, NF-L levels were associated with symptom burden post-concussion [281], and GFAP levels were associated with acute signs of SRC, such as loss of consciousness and amnesia [277].

**Table 8. Brain injury blood biomarkers**
Classification of brain injury biomarkers with considerations of peak time post-injury, limitations of specificity indicated by their extracranial localization [285, 286].

| Brain Injury biomarker | TIme fo peak post-injury | Intracranial localization | Extracranial localization |
|---|---|---|---|
| S100B | 0-4 hours | Astrocytes | Adipose tissue, chondrocytes, skeleteal muscles, melanocytes |
| T-tau | 4-12 hours | Neurons-axons | Peripheral nerves |
| BD-Tau | 4--12 hours | Neurons (brain specific iso-form) | None |
| GFAP | 12-36 hours | Astrocytes | Perpiheral nerves |
| NF-L | 4-12 days | Neurons-axons | Peripheral nerves |

S100B, an indicator of astrocytic damage, appears in mTBI guidelines where levels elevated within 6 hours (Scandinavian guidelines) [179] or 3 hours (French guidelines) [282] post-injury argue that neuroimaging is warranted. Importantly, S100B is not brain specific, as it is also expressed in extracerebral tissues such as melanocytes and adipocytes [287]. Moreover, the evaluated biomarkers may not be elevated exclusively by SRCs because in contact sports that include repetitive subconcussive impacts (e.g., football or ice hockey), GFAP elevations have been observed albeit at levels below those observed in concussed athletes [76]. These data argue that very early peaks in biomarker levels, which were similar between the two study groups in Paper V, should be interpreted with caution after boxing bouts.

Blood-brain barrier (BBB) disruption has also been associated with SRCs or RHIs [288, 289]. Although football players were not diagnosed with a concussion, S100B elevations predicted DTI abnormalities on MRI, which then correlated with cognitive changes [288]. Repeated exposure to head impacts may also contribute to a disturbed BBB, as shown by dynamic contrast-enhanced MRI within one-week post-SRC [289]. These findings might help explaining why brain injury biomarkers were elevated in our boxing cohort immediately after a fight.

## Biomarker normalization as a potential measure of neuroprotective efficacy

In Paper V, we considered the normalization of biomarker levels to baseline levels to be the most relevant outcome measure. In previous studies on boxers, immediate post-fight increases of e.g., IL-6 and cortisol have been found [290]. NFL, GFAP, and t-tau were among the biomarkers elevated, with NFL and GFAP levels persisting beyond the 14-day post-bout period [183]. In our study, boxers who received the cooling intervention had GFAP levels normalizing to baseline levels by day 6 post-bout,

in contrast to those who received standard post-fight management. In addition, a strong trend was observed for NF-L, which normalized faster with the cooling intervention. While CSF analysis may be more appropriate than blood when studying cerebral changes of many biomarkers, blood NF-L levels correlate closely with CSF levels [200, 291]. Because of the invasiveness of lumbar puncture to obtain CSF, blood sampling is preferrable, not least in a sport setting.

## Physiological rationale for selective head-and neck cooling

Strenuous exercise often leads to core temperatures of 39–40 °C, with prolonged normalization despite resting the first hours post-exercise [292-294]. There is a 6-10% increase in brain energy metabolism for each degree of increased temperature, which could contribute detrimentally to post-injury pathophysiology, as supported by experimental findings [76, 295].

Despite growing knowledge of the pathophysiology and diagnostics in SRC, treatment options are currently limited to standardized subsymptom-threshold exercise and return-to-play management [15, 296]. Thus, refined treatments are urgently needed. We chose the head-neck cooling intervention based upon our previous report on elite male ice hockey players, where cooling was initiated at a median of 11 minutes post-concussion and maintained for 45 minutes [131]. In that study, cooling resulted in faster post-concussion recovery with a higher proportion of cooled players returning to play at all time points from 14 days to > 100 days post-concussion [131]. Notably, this previous study on ice hockey players was not randomized, and a potential selection bias could not be excluded. In contrast, the boxing study presented in Paper V was designed as a randomized clinical trial, where competitive elite boxers were assigned randomly to either the cooling intervention or routine management, with objective brain injury biomarkers as the primary endpoint. Our study was based on the hypothesis that elevated brain temperature contributes to an unfavorable outcome in mTBI [83, 297]. This is explained by an exacerbation of the pre-existing damage induced from SRC or RHI, which is expressed as a cascade of neurological changes—including symptoms, biomarker alterations, and white matter abnormalities [17, 50, 298].

It is important to emphasize that the purpose of Paper V was to more rapidly reach post-fight normothermia- not hypothermia- by the intervention, with the goal of attenuating the potential metabolic impairment occurring following numerous head impacts [85, 299, 300]. A rapid normalization of brain temperature post-injury could thus potentially attenuate the secondary injury processes and improve outcomes. Because of the complications associated with invasive cooling, focal cooling methods are arguably preferrable [60]. Using a head cap, the temperature in the superficial cortical regions could be reduced, although cooling of the neck is also needed to target deep brain structures [301]. The efficacy of brain cooling using cooling helmets similar to the one used in Paper V targeting the head and neck regions has been evaluated by measurement of cortical temperature monitored by an invasive sensor

in neurocritical care of severely brain-injured patients. Here, head-neck cooling reduced brain cortical temperature by up to 2.0 °C within 15 minutes after the cooling helmet was applied [132, 135, 301]. Supportive results have also been observed in athletes where selective head-and neck cooling resulted in a greater post-exercise cooling with a difference of 1.5°C in brain temperature using the Zero Heat flux method [80]. Thus, although direct confirmation of the cooling intervention's reduction in brain temperature could not be obtained in Paper V, these background data support its plausibility. The beneficial effects of head-and-neck cooling have been demonstrated in multiple domains. Cooling interventions have been shown to enhance recovery time following concussion, even when initiated up to eight days after injury [86, 302]. In addition, cooling during exercise has been associated with reduced central neuromuscular fatigue [303] and neck cooling following post-exercise hyperthermia was associated with improved cognitive functions [304]. However, all previous studies lack objective measurements such as brain injury biomarkers.

Finally, our findings demonstrate significantly faster normalization of GFAP and a trend toward reduced NF-L levels following an early selective head-and-neck cooling intervention post-fight in elite boxers, indicating a potential tool for improved recovery. In support of our data, the sensitive brain injury biomarkers GFAP and NF-L have been investigated in several studies to identify potential trajectories for return to play and prolonged recovery [305, 306].

# 6 Strengths and weaknesses

In the present thesis, we describe rather small but highly characterized cohorts of elite athletes. Several limitations can, however, be identified in our studies.

In the PPCS cohort, the history of concussion was self-reported and objective measures were missing. This aligns with established patterns of under-reported history of previous concussions in athletes [307]. From an inclusion perspective, athletes with high symptom burden are more motivated to participate, which can lead to cohorts not representative of a majority of concussed athletes. A cohort of concussed but completely recovered athletes would also ideally have been recruited. The athletes with PPCS underwent a large battery of testing that was divided over two days. It included a vestibular test, audiogram, lumbar puncture, neuropsychological test interview and an almost 2-hour neuroimaging protocol. The order of the testing is crucial since it can affect the results in the vestibular test due to tiredness and previous MRI [308] and obviously the same pattern can be seen in neuropsychological tests. We kept the order of investigation identical among participants to avoid such sources of error. Thus, the PPCS athletes were extensively examined resulting in a detailed presentation of long-term SRC pathology.

In Paper III, four primary limitations were identified: the cross-sectional design prevented causal inference regarding the progression of perivascular and neurofluidic changes. Second, the PVS-Dex metric remains an indirect measure. Third, despite using a segmentation process to isolate artefacts, potential contamination from adjacent tissues cannot be entirely excluded. Fourth, the sample size could not capture the full spectrum of variability in individual history, genetic susceptibility, or resilience factors.

In the boxing RHI study in Paper V, blinding the participants for the cooling intervention is not feasible. Thus, an increase in Type II errors cannot be excluded regarding symptoms-related results. Moreover, the sample size of included boxers was based on pre-study power analysis. To increase the study's power, an even larger number of included boxers would have been preferable. However, to include additional boxers was a difficult task in view of the complexity of the study, willingness of the boxers to participate at all time points during the study and adherence to the study protocol. In addition, the number of eligible boxers was limited. A later time point for GFAP and NF-L measurements would also have been desirable, but the study had to be terminated at 6 days post-bout. This was due to the prohibition of extending the 6-day rest period between competitive fights, mandated by the Swedish Boxing Association. Additionally, the boxers were themselves generally unwilling to refrain from boxing for longer than 6 days. Notably, the number of

female elite boxers is lower than that of male elite boxers, as reflected by the fact that only 4 female elite boxers were included. Thus, we refrained from making sex-based comparisons of biomarker levels and we cannot exclude that the injury response and efficacy of the cooling intervention differ between sexes. Finally, we did not include athletic but non-RHI controls, which should be considered in future studies.

The primary strength of our studies lies in the novel findings generated across the included investigations. In Papers I and II we used extensive examination of PPCS athletes, with a high symptom burden, that included a detailed interpretation of the test results, where we could provide a plausible origin of deficits in the vestibular system. In Paper III, the glymphatic system has not previously been evaluated in RHI or SRC cohorts by 7T MRI. By examining brain injury biomarkers at baseline, post-fight, 45 minutes post-fight, day 3, and day 6, using different biomarkers and analyzing their changes from hours to one week post-fight, we were able to distinguish between the natural course of biomarker resolution and the effects of the cooling intervention in Paper V.

# 7 Conclusions

Athletes with persistent post-concussion symptoms suffer from a high symptom burden dominated by fatigue and balance problems. A major contributor to these symptoms could be a lesion to the inferior vestibular nerve caused by rotational force at time of SRC. The PPCS athletes also use more energy to maintain postural control with high demand on vision, suggesting a central compensation. Surprisingly, when using 7TMRI to visualize perivascular spaces as a measure of the glymphatic system in the brain, only active boxers- not PPCS athletes- showed a consistent pattern of enlargement and increased diffusivity suggesting an RHI-associated deficit with a pattern of an overstrained system.

When we used a head-neck cooling intervention (Paper V, protocol described in Paper IV) in active boxers, the marked difference in GFAP levels between the groups suggests a potentially beneficial effect of early cooling, highlighting its promise as a neuroprotective intervention in contact sports given the limited treatment options and diagnostic tools currently available.

**Paper I**

- Athletes with persistent post-concussion symptoms for over 6 months suffer from anxiety and depression related to dizziness, which resulted in a reduced quality of life.
- Examining the infratentorial balance-related regions with 7TMRI did not reveal marked changes in volumetrics and diffusivity.
- Vestibular dysfunction in athletes with persistent post-concussion symptoms for over 6 months was related to a lesion of the vestibular nerve, explained by the ipsilateral combined pathology of the vHIT and cVEMP tests.

**Paper II**

- Impaired postural control was found in athletes with persistent post-concussion symptoms for more than 6 months, expressed by increased demand for energy to maintain postural stability.
- The PPCS athletes showed a high demand for vision to maintain postural control.

**Paper III**

- Enlargement of perivascular space was observed in active boxers when compared to both PPCS athletes and healthy controls.
- Increased diffusivity in active boxers within the perivascular space indicates alteration of the glymphatic system, which can be explained by strain to the glymphatic system.

**Paper IV**

- The required sample size to establish a sufficient effect - a 20% reduction in brain injury biomarkers- from the cooling intervention in boxers estimated a total number of 20 participants per group with a power of 0.8.

**Paper V**

- Boxing bouts of 6 minutes resulted in significant increases in brain injury biomarkers post-fight and an increase in self-reported symptoms.
- In a 6-minute boxing bout, the boxers received a median of 47 head strikes.
- Early selective head-and-neck cooling post-fight in boxers reduced the levels of the astrocyte-associated biomarker GFAP at day 6 post-fight, measured in pg/mL and percentage, when compared to boxers receiving standardized post-fight management.
- A trend of reduction in NF-L levels and symptom scores was observed in boxers who received selective head- and-neck cooling.

# 8 Future directions

It has been established that SRCs cause long-term persistent symptoms resulting in a reduced quality of life. The balance-related symptoms demonstrated here appear to have a key importance in the recovery process and contribute to the overall prognosis. This may argue for physiotherapy targeting vestibular rehabilitation early post-concussion to enhance recovery. Currently, the lack of validated diagnostic biomarkers for SRC and RHI makes it challenging to accurately evaluate the true extent of injury and predict prognosis. Future studies focusing on a targeted panel of brain injury biomarkers, including GFAP and NF-L, are motivated to follow the trajectory of recovery, and to be used when evaluating treatment interventions.

Additionally, early head-and-neck cooling as used in our study suggested a potential neuroprotective effect, shown by faster normalization of GFAP levels. A multi-center approach would be needed to increase the number of participants, not least to recruit a higher number of female boxers. Since the levels of GFAP and NF-L were increased in boxers not receiving the cooling intervention, biomarker levels may be used to guide return to match sparring or competitive fighting. From a future perspective, the long-term effects of the cooling interventions could be evaluated as a therapeutic tool to prevent prolonged recovery. Furthermore, the impact of cooling on structural changes should also be investigated using refined neuroimaging, such as white matter abnormalities, in PPCS athletes and boxers. The current finding of a dysregulated glymphatic system in active boxers compared to PPCS athletes, suggests a promising area for future studies that should include athletes who currently report low or absent symptoms following SRCs.

On a personal level, I would like to conduct a longitudinal study to assess the cooling intervention using a multimodal assessment, including brain injury biomarkers, MRI, SCAT-6, and adding end points at 2 months (free from contact sports) and 1-year post-fight with no restrictions. Such study would aim to examine the natural course of sub-concussive repetitive head impacts over time, in addition to the suggested neuroprotective effects of cooling. Additionally, tau-PET using second generation tau tracers in PPCS athletes and boxers, as well as using novel tau biomarkers (e.g., p-tau 217 and -181), could add relevant information related to the development of chronic symptoms and potentially neurodegenerative processes.

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# About the author

This thesis is written by me, a former competitive kickboxer and current medical doctor, driven by a long-standing ambition to contribute to the field of traumatic brain injury in athletes. It explores key aspects of clinical neuroscience and represents a deeply personal journey, uniting two domains close to my heart: the world of sports and the complex challenges of traumatic brain injury in athletes.

"The knowledge of anything, since all things have causes, is not acquired or complete unless it is known by its causes."
— Ibn Sina (Avicenna)

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