Sport-Related Concussion: Neuroimaging, Biomarker, Vestibular and Neuropsychological Studies

Gard, Anna

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ANNA GARD
CLINICAL SCIENCES, LUND | FACULTY OF MEDICINE | LUND UNIVERSITY

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Anna Gard

LUND
UNIVERSITY

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Faculty opponent
Professor Grant Iverson
Harvard Medical School, Massachusetts General Hospital
Boston, Massachusetts, United States

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Abstract:

A sport-related concussion (SRC) is caused by a force transmitted to the brain during sports, and may lead to long-term disabilities and neurodegeneration. The underlying pathophysiological mechanisms causing persistent post-concussive symptoms (PPCS) lasting beyond the normal four-week period, have not been established. The aim of this thesis was to investigate mechanisms of persistent symptoms including vestibular dysfunction, white matter pathology and neuroinflammation in SRC athletes and PPCS. A retrospective cohort (*Paper I*) of ice hockey players retired due to SRC and prospective cohorts (*Paper II-IV*) of athletes with SRC and PPCS ≥ six months, were analysed. Athletes in *Paper II-IV* had severe PPCS and cognitive impairments.

Paper I: Seventy-six former ice hockey players were assessed at a mean of five years after their latest SRC and were found to have a high symptom burden and a reduced quality of life.

Paper II: Twenty-one athletes with PPCS and 21 matched controls were evaluated. The athletes had a peripheral vestibular dysfunction suggesting an injury to the inferior vestibular nerve.

Paper III: Twenty-four athletes with PPCS and 12 controls were included. The athletes had increased levels of eight cerebrospinal fluid (CSF inflammatory biomarkers (IL-2, TNF-α, IL-15, TNF-β, VEGF, Eotaxin, IP-10, and TARC), and decreased levels of Eotaxin-3.

Paper IV: Twenty-two athletes with PPCS, and 22 controls were included. On diffusion imaging PPCS athletes had diverging metrics in 28% of analysed white matter tracts, which correlated with the CSF axonal injury marker neurofilament light.

Athletes with SRC and PPCS suffer long-term disabilities and reduced quality of life. We found evidence of injury to the inferior vestibular nerve, a persistent CSF neuroinflammation, and widespread white matter alterations. These results emphasize that repeated concussions may trigger prolonged injury processes in the brain, which potentially contributes to the persistent symptoms observed in these athletes.

Key words: Sport-related concussion, persistent post-concussive symptoms, traumatic brain injury, ultra-high field strength MRI, white matter injury, neuroinflammation

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Anna Gard

LUND
UNIVERSITY

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Clinical Sciences Lund, Faculty of Medicine
Department of Neurosurgery
Lund University and Skåne University Hospital

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To David and Dagmar

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Popular scientific summary (populärvetenskaplig sammanfattning)

”Hjärnan, skapelsens krona, är nästan okänd för oss”, sade prästen och naturforskaren Nicolaus Steno år 1669. Sedan dess har hjärnans anatomi utforskats och klarlagts till den grad att vi nu åtminstone vet hur en nervtråd förgrenar sig och kommunicerar med andra nervceller. Klart är också att vi sedan Gilgamesheposet där hjärnans funktion förlades till hjärttrakten nått kunskap om var tanken har sin hemvist. Under antikens Grekland med sina många atleter författade Hippokrates den första beskrivningen av en hjärnskakning, som då inte kunde skiljas från något annat trauma mot huvudet. Denna beskrivning har sedan förfinats över århundraden, men forskningen om idrottshjärnskakningar har fortfarande många kunskapsluckor. Denna avhandling har därför i fyra studier undersökt hjärnskakningars inverkan på hjärnan och kroppens funktion.

En atlet kan under idrottsutövande träffas av ett slag mot kroppen eller huvudet, vilket kan ge upphov till en kraft som förs vidare till hjärnan och leder till en idrottsrelaterad hjärnskakning. Idrottaren kan förlora medvetandet, drabbas av huvudvärk, illamående, dålig balans och minnesluckor i anslutning till traumat. Det är viktigt att atleten omedelbart avslutar sin idrottsaktivitet efter hjärnskakning, för att minska risken för nya skador och påskynda återhämtningen. Återgång till skola, arbete och idrott sker sedan successivt och styrs av atletens besvär. I de flesta fall blir idrottaren helt återställd inom ett par veckor efter sin skada, men vissa utvecklar symptom som kvarstår i över fyra veckor, vilket är en onormalt långt tid för återhämtning. Hos de idrottare med långvariga symptom blir många bra inom det första året, men en liten andel får besvär som sträcker sig däröver och kan kvarstå resten av livet. Dessa besvär kan ha långtgående följder för idrottaren som i förtid tvingas sluta med sin sport, samt ge negativa ekonomiska såväl som sociala konsekvenser. Vidare har idrottaren många gånger utmaningar med arbete, skola, socialt liv och enklare aktiviteter i vardagslivet eftersom dessa situationer tenderar att förstärka och försämra idrottarens besvär.

Upprepade hjärnskakningar, symptombördan vid skadetillfället, kvinnligt kön och en för tidig återgång till sporten, är några av de faktorer som kopplats till förlängda besvär. Det har spekulerats i att en hjärnskakning kan utlösa en sjuklig process i hjärnan som inte läker ut, och leder till bestående besvär för vissa av idrottarna. Denna avhandling har därför haft som syfte att beskriva besvären och undersöka de underliggande biologiska förklaringarna till de långvariga besvär som vissa idrottare drabbas av efter idrottsrelaterade hjärnskakningar.

Artikel ett: Före detta ishockeyspelare som slutat spela på grund av hjärnskakningsproblematik svarade på enkäter rörande hjärnskakningssymptom, symptom på posttraumatisk stress och livskvalitet. Sjuttiosex tidigare idrottare medverkade, där 58% angav att de slutat spela på grund av kvarvarande besvär efter hjärnskakningar och 42% på grund av en rädsla att drabbas av ytterligare

hjärnskakningar. Idrottarna var i snitt 25 år när de slutade och hade då drabbats av i medeltal sex hjärnskakningar under sin karriär, varav den senaste för i snitt 5 år sedan. Ishockeyspelarna hade uttalade hjärnskakningssymptom och en sänkt livskvalitet, där fler och mer uttalade symptom var associerat med en lägre livskvalitet. De som slutat spela på grund av kvarvarande symptom hade även besvär med symptom på posttraumatisk stress, vilket avspeglades i bekymmer med humör och uppmärksamhetsförmåga.

Artikel två: Tjugoen idrottare med hjärnskakning och kvarvarande symptom över sex månader, och 21 kontroller, undersöktes med symptomskattning, balanstester och en extra stark magnetkameraundersökning. Idrottarna var i medeltal 26 år, hade i snitt fem tidigare hjärnskakningar där den senaste uppträdde ca 2,5 år innan deltagande i studien. Idrottarna angav uttalade besvär med hjärnskakningssymptom, depression, ångest och balansbesvär som påverkade deras livskvalitet negativt. Idrottarna hade inga avvikelser på hjärnvolymer eller vitsubstansen i lillhjärnan. På balanstesterna hade 13 idrottare en störning i balanssystemet. Denna balansstörning var i de flesta fall perifert lokaliserad utanför hjärnan, mer specifikt hade idrottarna tecken till skada på en av balansnerverna som löper mellan balansorganen i ytterörat och hjärnan.

Artikel tre: Tjugofyra idrottare med kvarvarande besvär efter senaste hjärnskakningen, och 12 idrottande kontroller undersöktes med symptomskattning, kognitivt test och provtagning för inflammatoriska markörer i ryggmärgsvätska. Idrottarna var i medeltal 26 år gamla och hade drabbats av i snitt fem hjärnskakningar, varav den senaste ca 17 månader tidigare. Idrottare med hjärnskakning hade nedsatt kognitiv funktion samt stegrade inflammationsvärde i åtta av 25 analyserade biomarkörerna, och en markör hade lägre koncentration bland de hjärnskakningsdrabbade.

Artikel fyra: Tjugotvå idrottare med hjärnskakningar och kvarvarande symptom och 22 friska kontroller undersöktes med symptomskattning, omfattande neuropsykologiska tester och extra stark magnetkameraundersökning. Idrottarna lämnade också hjärnvätska för analys av biomarkörer. Idrottarna var i medeltal 26 år och hade i snitt fem tidigare hjärnskakningar där den senaste hjärnskakningen skedde ca 2,6 år tidigare. Idrottare med hjärnskakningssymptom hade uttalade besvär med ångest, depression, mental trötthet, nedsatt initiativförmåga, sänkt livskvalitet och flera försämrade kognitiva förmågor. Idrottarna hade också tecken på vitsubstansskada på magnetkameraundersökning, och dessa fynd korrelerade med en biomarkör för skada på nervtrådar.

I denna avhandling har unga idrottare med kvarvarande besvär i månader till år efter sin senaste hjärnskakning undersökts i fyra studier. Långt efter skadetillfället har idrottarna besvär med uttalade hjärnskakningssymptom, yrsel, ångest, depression, trötthet och nedsatt initiativförmåga, samt nedsatt kognitiv förmåga med bland annat nedsatt minne, nedsatt uppmärksamhetsförmåga och mental förlångsamning. Dessa

besvär leder till en sänkt livskvalitet och en nedsatt förmåga att studera, arbeta och fortsätta med sportutövande.

Hos dessa idrottare har vi funnit tecken till skada på balansnerven i *artikel två*, pågående inflammation centralt i hjärnan i *artikel tre* och skada på den vita substansen och nervtrådar i hjärnan i *artikel fyra*. Detta talar för att hjärnskakningar kan utlösa en sjuklig process i hjärnan som kan fortsätta och eventuellt förvärras över tid. Det är möjligt att denna process börjar med en akut inflammatorisk reaktion som i vissa fall övergår i en kronisk inflammatorisk fas som kan leda till lokala skador på nervstrukturer och hjärnans vita vävnad. Denna kroniska inflammation med nervskador skulle kunna vara förstadiet till nedbrytning och gradvis förminskning (atrofi) av hjärnan, en konsekvens som påvisats i tidigare studier. I studierna i denna avhandling har vi undersökt idrottarna i ett tidsintervall där de ännu inte har förlorat volym av hjärnsubstans men har pågående skadliga processer i hjärnan. Resultaten från denna avhandling öppnar upp för fler studier rörande behandlingsmöjligheter med målet att på sikt kunna avstanna denna biologiska process som leder till permanenta skador och förhindra långdragna kvarvarande besvär efter hjärnskakningar inom idrotten.

List of papers

Paper I

Gard A, Lehto N, Engström Å, Shahim P, Zetterberg H, Blennow K, Marklund N, Tegner Y. Quality of life of ice hockey players after retirement due to concussions. *Concussion*. 2020;Aug 4;5(3):CNC78. doi: 10.2217/cnc-2020-0007. PMID: 33005437; PMCID: PMC7506471.

Paper II

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;Mar 7. doi: 10.1089/neu.2021.0447.

Paper III

Gard A, Vedung F, Piehl F, Khademi M, Portonova-Wernersson M, Rorsman I, Tegner Y, Pessah-Rasmussen H, Ruscher K, Marklund N. Cerebrospinal fluid levels of neuroinflammatory biomarkers are increased in athletes with persistent post-concussive symptoms following sports-related concussion. *J Neuroinflammation.* 2023 Aug 17;20(1):189. doi: 10.1186/s12974-023-02864-0. PMID: 37592277; PMCID: PMC10433539.

Paper IV

Gard A, Kornaropoulos EN, Portonova-Wernersson M, Rorsman I, Blennow K, Zetterberg H, Tegner Y, De Maio A, Markenroth Bloch K, Björkman-Burtscher I, Pessah-Rasmussen H, Nilsson M, Marklund N. Widespread white matter abnormalities in concussed athletes detected by 7T diffusion MRI. *J Neurotrauma.* 2024 Jul;41(13-14):1533-1549. doi: 10.1089/neu.2023.0099. Epub 2024 May 3. PMID: 38481124.

Author's contribution to the papers

Paper I

Analysis and interpretation of data. Visualization, drafting, and redrafting the manuscript after comments from co-authors and reviewers. Final approval of the manuscript and responsible for the publishing process.

Paper II

Conceptualization and development of methodology. Project administration, inclusion of study subjects, and execution of selected examinations (medical history and MRI scanning). Analysis and interpretation of data. Visualization, drafting, and redrafting the manuscript after comments from co-authors and reviewers. Final approval of the manuscript and responsible for the publishing process.

Paper III

Conceptualization and development of methodology. Project administration, inclusion of study subjects, and execution of selected examinations (medical history, biomarker sampling and lab analysis). Analysis and interpretation of data. Visualization, drafting, and redrafting the manuscript after comments from co-authors and reviewers.

Paper IV

Conceptualization and development of methodology. Project administration, inclusion of study subjects, and execution of selected examinations (medical history, MRI scanning and biomarker sampling). Analysis and interpretation of data. Visualization, drafting, and redrafting the manuscript after comments from co-authors and reviewers. Final approval of the manuscript and responsible for the publishing process.

Other scientific contributions

Scientific work related to, but not included in this thesis.

Nilsson A, Uvelius E, Cederberg D, Kronvall E. Silver-Coated Ventriculostomy Catheters Do Not Reduce Rates of Clinically Diagnosed Ventriculitis. *World Neurosurgery*. 2018;117:e411-e6

Gard A. Hjärnskakning – dags att idrottare prioriterar hjärnan. *Vetenskap och Hälsa*. 2020; Okt.

Gard A, Tegner Y, Fazel Bakhsheshi M, Marklund N. Selective head-neck cooling after concussion shortens return-to-play in ice hockey players. *Concussion.* 2021 Apr 15;6(2):CNC90. doi: 10.2217/cnc-2021-0002. PMID: 34084556; PMCID: PMC8162197.

Tobieson L, **Gard A**, Ruscher K, Marklund N. Intracerebral Proinflammatory Cytokine Increase in Surgically Evacuated Intracerebral Hemorrhage: A Microdialysis study. *Neurocritical care.* 2022 Jun;36(3):876-887. doi: 10.1007/s12028-021-01389-9. Epub 2021 Nov 30. PMID: 34850333; PMCID: PMC9110446.

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. PMID: 36172026; PMCID: PMC9511028.

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. Epub 2022 Nov 11. PMID: 36222612.

Abbreviations

BRIEF-A	Behaviour Rating Inventory of Executive Function-Adult version
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
FA	Fractional anisotropy
GFAP	Glial fibrillary acidic protein
HADS	Hospital Anxiety Depression Scale
IES-R	Impact of Event Scale-Revised
IL	Interleukin
LiSat-11	11-item Life Satisfaction questionnaire
MFS	Mental fatigue scale
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
NfL	Neurofilament light
PET	Positron emission tomography
PPCS	Persistent post-concussive symptoms
QoL	Quality of life
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SCAT	Sport Concussion Assessment Tool
SF-36	Short Form Health Survey
SRC	Sport-related concussion
TBI	Traumatic brain injury
Tau	Tubulin-associated unit
vHIT	Video head impulse test
VNG	Videonystagmography

Introduction

Concussion in young healthy individuals and athletes are often trivialized due to its diverging clinical presentation, lack of structural abnormalities on routine neuroimaging, and a strong desire to return to normal life and sports participation. Elite athletes are expected to continue game play, to attend scheduled practices and deliver results, a self-expectation as much as an expectation from the teams and its supporters. A major part of this thesis is based on examination of young elite athletes, having to end their careers due to debilitating, persistent symptoms following concussions. Young and healthy individuals who often have devoted their childhood and early adulthood to their sport, and in the middle of a thriving career, they cannot continue their sport activities. Being unable to practice their sport, unable to resume their studies often postponed due to elite ambitions, unable to be social with their families, unable to go grocery shopping, unable to continue normal life. All these problems without a visible scar on their brain, nothing found, nothing to be done.

The aim of this thesis is to address the clinical presentation and underlying pathophysiological processes of concussion, in the hope of improving care of these patients. Proper information about the anticipated clinical course is of greatest importance to the athlete, to know how to act following a concussion and to be able to make an informed decision on whether to continue sport participation or to retire. This thesis has not addressed any medical treatment or other interventions following concussion, since the research has not come that far yet. The pathophysiology must first be thoroughly investigated to identify targets for treatment. This thesis provides novel data on several pathophysiological processes at long-term following concussion, hopefully encouraging further studies enabling results leading to new effective treatment options.

Traumatic brain injury

Traumatic brain injury (TBI) is a major health concern worldwide as a leading cause of death, disability and emergency department visits[1-4]. Each year 50-60 million people are afflicted by TBIs, and it is predicted to remain one of the top three causes of injury-related mortality and morbidity[5]. Worldwide the incidence is around 350 per 100 000 people per year[6]. In Europe the incidence varies considerably between countries and over time but can be roughly estimated to around 250 per 100 000 people per year, with a mortality ranging between 3.3 to 28 per 100 000 people per year[7]. It is estimated that 82 000 deaths and 2.1 million hospital discharges are TBI-related each year in Europe[3]. TBIs are substantially more common in low- and middle-income countries than in high-income countries due to a more chaotic traffic scene[8], although this is difficult to verify due to poorer accessibility to healthcare and hence lesser documentation and epidemiological data. The disease burden of TBI, measured as years lived with disability, is greater in countries with high sociodemographic development with higher survival rates and better long-term follow up[6].

Amongst the most common injury mechanisms are falls, motor vehicle accidents, violence, sport-related, accidents in the home or work, and suicides or suicide attempts, with the proportion of traffic collisions decreasing and the proportion of falls increasing during recent years[7]. TBIs are more common in men, though, with age this difference interchange with more elderly women afflicted than men[3, 7].

TBI is defined as a neurologic dysfunction or pathology in the brain arising from an external force[9]. Patients with TBI are vastly heterogeneous, with a large variation in how the trauma affects the brain and how it influences patient outcomes. Subclassifications of TBI patients are necessary to get better outcome prediction models, although these are still insufficiently accurate. TBIs can be classified by injury mechanism, by anatomical location, and by clinical presentation. Most commonly a patient with TBI is evaluated according to the Glasgow Coma Scale (GCS), and subdivided into mild, moderate, and severe TBI (Table 1)[10, 11].

Table 1. Glasgow Coma Scale
Sub-classification into three grades of traumatic brain injury (TBI) by clinical examination and scoring of eye opening, verbal response and motor response.

Domain	Response	Score
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	No response	1
Best motor response	Obeying	6
	Localizing pain	5
	Withdrawal to pain	4
	Flexion to pain	3
	Extension to pain	2
	No response	1
Severe TBI		**3-8**
Moderate TBI		**9-12**
Mild TBI		**13-15**

Sport-related concussion

A concussion is a form of mild TBI (mTBI), the terms are often used interchangeable in the literature even though the definitions are not the same[12]. Sport-related concussion (SRC) is a TBI caused by a transmitted force to the brain by a blow to the head, neck or body during sports or exercise-related activities. Symptoms and signs may arise immediately or evolve over minutes to hours, may or may not include loss of consciousness, and cannot exclusively be explained by other injuries, comorbidities, or substances. Conventional neuroimaging, computed tomography or T1- and T2-weighed magnetic resonance imaging (MRI), shows no structural abnormalities, however special modalities used in the research setting may detect abnormalities[13].

A somewhat controversial entity is subconcussion, a cranial impact that does not result in clinically observable deficits or a concussion diagnosis[14]. Subconcussions are believed to cause long-terms effects and worse outcomes[15]. Signs of axonal injury, microstructural white matter changes, and decreased brain volumes has been detected in athletes without a concussion diagnosis[16-19]. It is the cumulative effects of repeated, and not singular, subconcussions, or subconcussive head impacts that are speculated to trigger a neurodegenerative process in the brain.

An SRC can result in numerous symptoms that can be subclassified into five domains: Cognitive (*e.g.* concentration difficulties, memory difficulties, amnesia), ocular-motor (*e.g.* blurred vision, sensitivity to light, double vision), headache-migraine (*e.g.* headache, neck-pain, nausea), vestibular (*e.g.* dizziness, balance problem, vomiting), and anxiety-mood (*e.g.* depression, irritability, confusion)[20]. The recovery and the resolution of physical and mental symptoms usually occurs gradually, with most adults recovering within 7-10 days[21-23]. Nonetheless, as many as 15-20% of athletes do not recover within the normal four-week timeframe[24-26] and some have symptoms persisting for month and years[23, 26]. The initial symptom severity, repeated concussions, female sex, previous treatment for psychiatric disease or substance/alcohol use, and an ignorance towards return-to-play recommendations are linked to a longer duration of post-concussive symptoms[26-31].

The term post-concussion syndrome (PCS) is used to describe persistent symptoms following a TBI and is generally defined as three or more post-concussive symptoms lasting three months or longer, but several classifications exist[32-34]. The International Classification of Diseases, 10th revision (ICD-10)[34] defines PCS as three or more symptoms lasting more than four weeks and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)[33] defines PCS as three or more symptoms lasting at least three months. In the latest edition of DSM, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V)[35], PCS is redefined as a neuro-cognitive condition and the diagnosis is based on neuropsychological deficits.

The various definitions of PCS are generous and the symptoms unspecific, and the criteria may be fulfilled by individuals without prior concussion[36]. Due to the lack of specificity, the absence of the diagnosis in DSM-V and the overall incoherence regarding the diagnosis of PCS, it has become more favorable to use the descriptive term Persistent post-concussive symptoms (PPCS). In the latest version of the Consensus statement on concussion in sport '*persistent symptoms'* are defined as persisting over four weeks in children, adolescents, and adults. The consensus statement recommends a multimodal clinical assessment, because of the commonly co-existing comorbidities existing in this group of patients that may interfere with diagnosis, preferable treatment options, and outcomes[13]. The diagnosis of PPCS is based on symptom rating with standardized symptom rating scales, and to date there are no other means in which to improve accuracy of the diagnostic process[37].

Concussions in history

It is maybe of no coincidence that the first description of a concussion is found in the Hippocratic corpus, from ancient Greek with its abundant athletic history. Hippocrates described the entity of a "cerebral commotion" but made no distinction between types of head injuries. Similarly, Galen of Pergamon, who in the Roman era treated neurotrauma in gladiator games and did pioneering studies of neuroanatomy, did not distinguish concussion from other types of brain injury. It was not until the end of the first millennium the distinction was done, when the Arabic physician Rhazes used the term concussion and defined it as transient loss of function without physical damage, a definition partly still prevailing[38]. At the Age of Enlightenment during the 18th century, the idea of concussion as a transient symptom were questioned when several hypothesis were formed about the underlying pathophysiology, and during the 19th and 20th century modern research concluded that concussions may lead to neurodegeneration and psychiatric disease[39, 40].

Following the civil war in America the game of American football became increasingly popular. The game was known for its brutality. During the season of 1905 with 18 deaths and 159 serious injuries amongst the athletes brought the attention of President Roosevelt, a big advocator of the game. Roosevelt invited a group of medical professionals to the White House and encouraged the formation of a national athletic medical association, with the goal of reducing injuries to enable the survival of the game[41]. At this time another popular sport was boxing, and in 1928 Martland described a complication of repetitive head trauma seen in the sport, a special type of post-traumatic encephalitis, the "punch drunk".

"*Many cases remain mild in nature and do not progress beyond this point. In others a very distinct dragging of the leg may develop and with this there is a general slowing down in muscular movements, a peculiar mental attitude characterized by hesitancy in speech, tremors of the hands and nodding movements of the head…in severe cases, there may develop a peculiar tilting of the head, a marked dragging of one or both legs, a staggering, propulsive gait with the facial characteristics of the parkinsonian syndrome, or a backward swaying of the body, tremors, vertigo and deafness. Finally, marked mental deterioration may set in necessitating commitment to an asylum…the occurrence of the symptoms in almost 50 per cent of fighters who develop this condition in mild or severe form, if they keep at the game long enough, seem to be good evidence that some special brain injury due to their occupation exists*."

Martland's hypothesis was that concussion caused multiple hemorrhages in the deep parts of the brain, leading to gliosis and neurodegeneration, in boxers with severe or repeated head trauma[42]. Punch drunk was 1937 replaced by "dementia pugilistica" which described the boxer to be increasingly vulnerable to concussive blows, suggesting an exponential increase in brain damage during this time of

vulnerability and emphasizing the importance of retiring early. Chronic traumatic encephalopathy (CTE), the name still used today, was suggested in 1957[43].
Besides the field of sports medicine, there are several other populations especially exposed to TBIs. During and after the time of World War II, an escalation of head injuries occurred in the military and in motor vehicle accidents, why several scientists took a special interest in TBI. Significant progress was made in the understanding of the biomechanics of concussions, with acceleration, deceleration and rotational forces[44, 45]. Despite these studies and a few case reports of dementia pugilistica in people who were not boxers, CTE was until the beginning of the 21st century believed to exist primarily in boxers. In 2005 Omalu published a case report of a retired National Football League player, showing neuropathological changes consistent with long-term exposure of repetitive concussive injury[46], a report that would trigger an upsurge of studies, a media storm concerning the consequences of concussions and a concussion movie starring Will Smith. Nevertheless, to date we still do not know the full pathophysiological process, its long-term consequences, or how to stop or treat concussions successfully.

Epidemiology

An estimated 90% of all TBIs are mild TBIs (mTBI), and this figure is probably highly underestimated[47]. In a European epidemiological study with country-level populations 8-9% of all TBIs were sport-related. Given the reported total mean incidence, these results suggest about 28 new cases of SRCs per 100 000 people per year[7]. In a statewide population-based study from the US of self-reported lifetime injuries, 36.4% reported having had an mTBI[48]. Many patients suffering an mTBI never seek medical care and are not recorded in medical charts. In the statewide study mentioned above, 27.5 % of the people suffering from a TBI of any severity, did not seek medical care and 9.8% were seen in a family physician's out-patient clinic[48].

Approximately 21% or 3.5 million US High school students reported having sustained one or more SRCs during 2017[49]. In a Swedish study of ice hockey players, a mean of 77 SRCs per 1000 games during 29 seasons was found, and during the most resent season 17% of all injuries were SRCs[50]. In a study of rugby players after an exposure of 25 matches, the athletes were more likely having sustained a concussion than not[51]. Sports with especially high rates of SRCs includes American football, soccer, ice hockey, rugby, wrestling, and lacrosse. SRC rates are higher during competitions than in practices and is more common amongst females than males[52]. During later years the number of SRCs have increased, across all sports and ages[52].

There are several difficulties with estimating the incidences of mTBIs and SRCs and there is probably not a prefect way of grasping the true burden. Most epidemiological data is based on emergency department visits and hospital

admissions. SRCs can be unobserved, unreported by the athlete, and undiagnosed by a physician or researcher, resulting in an undocumented injury. SRC history is most often measured by self-reporting. Athletes tend be inconsistent in reporting injuries, both overestimating and underestimating, especially in athletes with a greater number of SRCs[53]. Consequently, there is a high risk of reports being incomplete and misleading, but most probably the rates of SRCs are underestimated. About 15-20% of athletes develop PPCS beyond the 4 weeks post-SRC[24-26]. The majority of PPCS athletes recover within one year following SRC and most within three years, if PPCS extends beyond that timeframe, recovery is uncertain and some never recovers[26].

Sex differences

Females are at higher risk of sustaining an SRC and more often develop persistent symptoms with longer recovery times compared to men[54-57]. Concussed female athletes report a greater number of symptoms, with somatic, emotional and migraine related symptoms being more frequent as well as neurocognitive impairments[54].

During head acceleration, females have been found to have a poorer ability to stabilize their neck leading to a greater displacement of the head relatively to the body, which may be attributed to a weaker neck muscle strength and a smaller neck girth[58]. A greater number of unmyelinated neurons, higher rate of cerebral blood flow, and a higher demand in glucose metabolism, has also been proposed to exacerbate the metabolic cascade and aggravating the initial injury following SRC[54].

Female participation in sports is increasing, but still females are understudied with many SRC studies focusing on men. Further studies are needed to firmly establish correlations between sex and SRC outcomes, differences in pathophysiology, and eventual treatments.

Acute management

The most important factors to minimize the acute and long-term effects are to effectively recognize the SRC, to prevent additional injuries and hasten recovery. Loss of consciousness, confusion, disturbed speech, pain in the head or neck, difficulties moving, or distorted balance are some of the symptoms that should trigger further investigation and immediate remove the athlete from sports activity. Symptoms may be more subtle and in those cases the suspicion of an SRC is enough to remove the athlete from play, and a concussion diagnosis may or may not be established later. It is essential to remove the player from activity to eliminate the risk of sustaining additional SRCs and orthopaedic injuries, and to enable further diagnostic means to establish whether it is a concussion or not[13, 59]. It is then

possible to recognize ‘red flags’, symptoms and signs of more serious injuries requiring visits to the emergency department or hospital admission[60](Table 2).

Table 2. Red flags
Red flags as included in the The Sport Concussion Assessment Tool 6th edition[60] that shuld raise suspicion of more serious injury. GCS = Glasgow coma scale.

Red flags
• Neck pain or tenderness • Sezure or convulsion • Double vision • Loss of consciousness • Weaknes or tingling/burning in more than 1 arm or in the legs • Deteriorating concious state • Vomiting • Severe or increasing headache • Increasingly restless, agitated or combative • GCS <15 • Visible deformity of the skull

It is important that the clinical presentation of an SRC is well known, not only by health care providers, but by coaches, referees, parents, and by the athletes themselves, to improve the likelihood of early management, raised awareness and reduce stigma related to an athlete being removed from play. The Pocket Concussion Recognition Tool (CRT) can be used by the non-medically trained layperson to recognise a suspected SRC and aid in the decision to remove the athlete from activity[61]. The concussion diagnosis should then be established by a medical health care provider accustomed to the clinical presentation and available diagnostic tools, and the athlete should be re-evaluated several times during the first hours and days[62]. Depending on the presentation of symptoms the medical provider decides what tools are needed to establish a diagnosis and document initial symptoms, and whether the athlete needs specialized care. There are numerous clinical tests that can aid in the acute setting, such as the The Sport Concussion Assessment Tool (SCAT)[60, 63] and the Immediate Post-Concussion Assessment and Cognitive Test (imPACT)[64].

Following diagnosis, the athlete should be under supervision due to potential progression of symptoms and deterioration. The graduated return to play protocol as accepted during the latest Amsterdam consensus statement on concussion in sport 2022[13] (Table 3) should be initiated immediately. The relative rest should last 24-48 hours before step two. Advancement to the next step is dictated by symptoms, cognitive functions and clinical judgement, after typically 24 hours. It is accepted that symptoms can be mildly and temporarily aggravated if the athlete is to proceed to step three. Step four should not be initiated before full resolution of all symptoms

at rest and following physical exertion. The protocol is expected to last at least one week and is concurrent with return to school followed by return to work[13].

Table 3. Return to play protocol
The graduated return to play protocol as adapted by the latest Amsterdam consensus statement on concussion in sport 2022[13]. maxHR = maximum heart rate.

Step	Exercise strategy	Activity
1	Symptom-limited activity 'relative rest'	Daily activities that do not exacerbate symptoms
2	Aerobic exercise 2a – light, up to about 55% of maxHR 2b – moderate, up to about 70% of maxHR	Cykling, walking at mild pace Light resistance training that does not trigger more than mild and brief worsening of symptoms
3	Sport-specific exercise	Sport-specific training away from the team environment, no activities that risk additional SRC
4	Non-contact training drills	High intensity training drills, can be integrated in the team environment
5	Full contact practice	Normal training activities
6	Return to sport	Normal game play

Pathophysiology

By a blow to the head, neck, or elsewhere on the body, energy is transmitted causing acceleration and deceleration forces to the brain. These forces are predominantly rotational in SRC but can also be linear[65]. The concussion cause the brain to deform, leading to stretching of axons, neurons, glial cells, and blood vessels, and cortical areas are pressed against the inner surfaces of the skull, along the falx, or the tentorium[66]. The brain itself is highly organized with areas of white and grey matter, sulci and gyri, areas close to membranes, vessels, and bone. These tissues all have different densities. When a rotational force is spread throughout the brain, these junctions between different tissues are especially vulnerable to shear- and pressure-induced damage[65]. Rotational forces can be generated in different directions, in the coronal, axial or horizontal plane, where forces acting on the coronal plane cause most brain tissue damage[67]. The biomechanics is the same for all forms of TBIs, with higher forces causing more tissue damage, and hence, a more severe TBI.

As a response to the concussive forces, a series of pathophysiological events occur simultaneously with neuronal depolarization, changes in glucose metabolism, release of neurotransmitters, altered cerebral blood flow, and disrupted axonal integrity[68]. Potassium flows out of the neuron, sodium and calcium enters the cell, causing a widespread neuronal depression leading to barrier dysfunction and inability to clear debris, to resolve inflammation, or to repair neuronal connections.

The neuron aims to restore homeostasis via membrane ionic pumps requiring vast amounts of energy. Since there is a concurrent inability to deliver energy, due to altered cerebral blood flow and mitochondrial dysfunction, the cell suffers an energy crisis which may generate long-lasting impairments and increased vulnerability to repeated injury[69]. Furthermore, athletes have a higher metabolic rate and a raised body temperature at time of an SRC, increasing the vulnerability of the brain to secondary injury processes[70, 71]. As a consequence of the neurometabolic cascade and energy crisis, a neuro-inflammatory process can ensue[72].

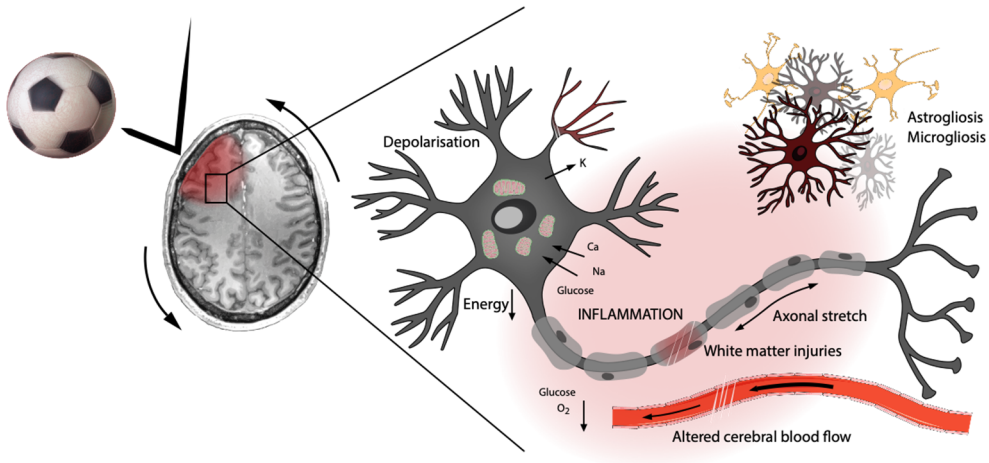

Figure 1. Concussion pathophysiology
A football hits the head resulting in a rotational force acting upon the brain. In magnification to the right a neuronal body with its axon, is portrayed. The axon stretches by the rotational force and calcium, potassium and glucose enters the cell, while sodium exits, leading to a neuronal depolarisation. Altered cerebral blood flow leads to a decrease in the glucose and ozygen delivered to the injury site, further exaberating the loss of energy. In the sports setting this happens during raised body temperature and higher metabolic rate, increasing brain voulnerability. Astrogliosis, microgliosis, inflammation, and white matter injuries may pursue.

Following concussion, a tension-driven destabilization of neurofilaments and microtubules in axons may lead to a disconnection of axonal integrity and the formation of varicosities along the axis of the axon, named axonal beading[73, 74]. Unmyelinated axons may be especially vulnerable to traumatic axonal injuries[75]. Following the acute phase of mTBI, serum cytokines are increased[76-78]. In mice, TBI induces an immunosuppressive state that gives rise to long-term exacerbation or dysregulation of cytokine signaling and *e.g.* disrupted antigen presentation, impaired phagocytic activity, and oxidative stress, with the consequence of a chronic immune impairment[79]. In other mouse models of TBIs, microglia have been found to be a critical mediator of chronic inflammation and neuronal dysfunction[80], one single mTBI has been found to elicit parenchymal

neuroinflammation with infiltrating macrophages, microgliosis and astrogliosis[81], and ongoing neuroinflammation found to be associated with a neurodegenerative processes[82]. Signs of astrogliosis found to increase acutely and persist several years following SRC[83-85] and a study of mTBI concluded that a low-level systemic inflammation persisted for one year following mTBI[86]. In long-term follow up studies of SRC athletes with positron emission tomography (PET) imaging, neuroinflammation with microglial activation was seen two years[87] and at seven years[88] following last SRC, and at 24-42 years following retirement from the National Football League[89].

These cascades are triggered within minutes, but can continue for several months to years, and contain maladaptive stages that may exacerbate the initial injury and lead to a chronic inflammatory stage with astrogliosis, microglial activation, DNA-damage, axonal beading, and neurodegeneration[73, 80, 90-93].

Neurodegeneration

Neurodegeneration is a symptom and consequence of an underlying pathology causing accumulation of abnormal proteins, leading to destruction of neuronal structures and loss of neuronal function[94]. The above-mentioned pathophysiological mechanisms of TBIs and SRCs may lead to progressive neurodegenerative processes. A singular SRC does not necessarily lead to a chronic neurodegenerative state, however repeated injury cumulatively increases the risk of brain injury with neurodegeneration as a long-term consequence[95]. The incidence of Alzheimer's disease, amyotrophic lateral sclerosis and neurodegenerative mortality is increased in elite athletes with repeated SRCs[96]. Football and rugby players have been found to have an increased risk of neurodegenerative disease[97-99]. Athletes had a decreased mortality up to the age of 70, with lower rates of ischemic heart disease, lung cancer and respiratory disease, followed by an increased overall mortality and mortality from neurodegenerative disease following the age of 70[98, 99]. Alzheimer's disease and other forms of dementia were more common, however motor neuron disease and Parkinson's disease was less common in football players[97, 98].

Tubulin-associated unit (Tau) is a protein with the main function of stabilizing neuronal microtubules and it is involved in several neurodegenerative diseases called tauopathies, and Amyloid-β is a hallmark protein of Alzheimer's disease[100]. Both Tau and Amyloid-β as blood and CSF biomarkers have promising diagnostic utility regarding prolonged symptoms and neurodegeneration following mTBI and SRC[101, 102]. Tau mainly stabilizes neuronal microtubules, and in pathological conditions it can undergo phosphorylation with the formation of toxic oligomers and neurofibrillary tangles (NFTs) leading to neurodegeneration[100]. Amyloid-β is derived from amyloid precursor protein which undergoes toxic transformation and can be deposited into the extracellular space of the brain as amyloid plaques[103].

Deposits of Tau has been observed in subcortical grey matter of young athletes with a mean age of 26 years and a history of repeated SRCs[87] and in frontal, temporal, and parietal regions of symptomatic former American football players aged 40 to 69 years[104]. The metabolism of Amyloid-β is altered following SRC[105], and brain deposits have been found in autopsy studies of athletes with previous SRCs[106]. However, Amyloid-β plaques, as measured by PET imaging, are in most studies not increased in SRC-athletes[107] and the diagnostic utility of Amyloid-β to detect neurodegeneration secondarily to SRC seems to be inferior to that of Tau.

Neurodegeneration in the form of brain volume loss has been observed in several cohorts of athletes with SRC. Athletes with SRC have a higher prevalence of enlarged cavum septum pellucidum and cavum vergae, and reduced brain volumes[18, 108-110]. The presence of cavum septum pellucidum and cavum vergae is a finding associated with brain atrophy[109]. Cortical thinning has been reported in soccer players and American football players with a history of SRC[111, 112]. Reduced volume of the hippocampus, a key structure of the human memory and essential for normal cognition, has also been observed in SRC athletes[17, 113].

Athletes subjected to repeated head injuries, such as in American football[17] and ice hockey[18], had decreased brain volumes when compared to controls, regardless of the presence of concussions. Such findings argue that multiple non-symptomatic subconcussive events may be enough to lead to neurodegeneration.

Chronic traumatic encephalopathy

Historically, a clinical neurological condition affecting athletes with multiple head injuries which resulted in mental deterioration and dementia was named “punch-drunk”, “traumatic encephalopathy”, “dementia pugilistica”, and currently “chronic traumatic encephalopathy (CTE)”[43]. Increased recognition of this clinical entity led to several case reports of diseased athletes with repeated SRCs describing neuronal loss, cortical and corpus callosum atrophy, ventricular enlargement, cavum and fenestrated septum pellucidum, depigmentation of substantia nigra, cerebellar scarring, gliosis, and deposits of Amyloid-β[114-117].

Today CTE strictly refers to a post-mortem tissue-based neuropathological diagnosis and the clinical syndrome associated with CTE is known as traumatic encephalopathy syndrome[118]. The diagnosis is made by tissue sectioning of 11 brain structures with a minimum of one cortical pathognomonic lesion or CTE foci present. A CTE foci consists of phosphorylated tau aggregates in neurons at the depth of a cortical sulcus around a small blood vessel, in deeper cortical layers not restricted to subpial and superficial region of the sulcus[119]. Dependent on the amount of CTE foci the disease can be classified as “low CTE” for milder and more focal cases, and high CTE for more advanced, widespread, and diffuse disease[119].

Figure 2. CTE pathology
Three cases of Chronic traumatic encefalopathy (CTE) pathology stained for phosphorylated tau, revealing irregular patches at the depths of cerebral sulci. *McKee AC, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathogica. 2016 Jan;131(1):75-86* [120].

Signs of CTE has been found in the brains of athletes involved in several sports including boxing, American football, soccer, rugby, and ice hockey, as well as in military personnel, a singular case of interpersonal violence, and in patients with poorly regulated grand mal seizures[121]. It is likely that repetitive head injury, or multiple SRCs, lead to an increased risk of developing CTE-pathology[121].

The entity of CTE has been debated during the last two centuries, and still there are some controversies surrounding the diagnosis. Before the consensus statements in diagnosing CTE in 2016[120] and 2021[121] the disease was not well defined and had overlapping pathology with Alzheimer's disease, other neurodegenerative diseases, and normal aging. Still there are some concerns that the pathology may not be specific to repetitive neurotrauma, and that the disease is not always progressive[122]. It also remains an issue that the clinical features of symptomatic athletes have not been securely linked to CTE and that we cannot diagnose this disorder in the living patient[123].

Persistent post-concussive symptoms (PPCS)

Attempts to find diagnostic means to identify athletes with SRC who are especially prone to develop PPCS or neuropathology have been made for a long time without much success. The final aim is to early on be able to pinpoint which athletes are at risk and to treat the underlying pathophysiology to stop or delay the process of axonal injury, neuroinflammation, and neurodegeneration.

In this thesis we have conducted neuroimaging, biomarker, vestibular and neuropsychological studies to explore symptoms, diagnostic tools, and underlying pathology explaining these long-term problems in athletes with PPCS.

Neuropsychological evaluation

It is well known that cognitive and behavioral changes can be a devastating consequence of concussions and especially at long-term. Concussed subjects in the general population have higher levels of anxiety and depression in addition to difficulties with concentration, and impaired inhibitory control[124]. In military personnel, repeated concussions have been shown to lead to a higher risk of depression, emotional distress and decreased cognitive efficiency, independent of any coexisting post-traumatic stress disorder (PTSD)[28]. Impaired executive function, information processing, memory and learning difficulties, as well as anxiety and depression, have been observed in the short- and long-term following mTBI[125]. Furthermore, patients with mTBI and persistent symptoms experience more anxiety and depression compared to patients with previous mTBI but without PPCS[56]. Similarly, following SRC athletes suffer executive dysfunction including impaired inhibitory control and reduced cognitive flexibility[124, 126-128]. The risk of a clinical depression diagnosis is higher in football players with previous SRCs compared to those without, and the risk increases with number of concussions[129].

To properly study these behavioral and cognitive aspects there are several methods, of which self-report measures and psychometric tests that can be either self-administered, computerized or conducted by a neuropsychologist, are common choices in the clinical and research settings.

Self-report measures, or patient reported outcome measures (PROM), are regularly used for the evaluation of several symptoms and diseases but are known to be easily influenced by the responder's recollection and experiences of general health, resulting in large variations between responders[130]. One can argue that these are still important, since the individual experience is what we want to evaluate. Common symptoms evaluated with self-report measures are *e.g.* pain, anxiety, and fatigue. In contrast, psychometric tests provide exact figures of how well a patient performs on a test, that can be used to determine if the individual performs within normal limits or not. Common cognitive domains evaluated with psychometric tests include *e.g.* processing speed, memory, and attention.

Today it is becoming more frequent to use computerized tools, since it increases efficiency in the administration and interpretation of tests if using a stable software and a suitable digital device[131]. With digitalized tools there is a higher risk of patients not understanding the task or responding with suboptimal effort, leading to invalid results[132]. The traditional method of a face-to-face interview and testing by a neuropsychologist provide the opportunity to monitor and correct the patient's eventual misperceptions, demotivation, and distractions to improve test accuracy[133]. Cognitive performance can be affected by several non-cognitive factors such as the emotional condition of the person being tested[134]. Therefore, face-to-face assessment can be of special importance in patient populations that may be prone to underachievement. Depressive symptoms have been shown to be

associated with lower cognitive performances that, at least partially, are believed to be secondary to a negative attitude towards testing and lower motivational effort[135, 136]. Anxiety can have both negative and positive effects on cognitive performance[137, 138]. Moreover, although subjective cognitive deficits are common complaints in patients with brain injury and mental fatigue, the relationship between mental fatigue and actual cognitive impairments on tests has often been inconsistent or weak[139].

The superiority of one testing modality over the other remains unproven, and hybrid test batteries compromised of the top-performing tests might be the best choice[140]. Combining self-report measures and psychometric tests, in both a digitalized and face-to-face manner remains as standard procedure in most clinical settings.

Neuroimaging - MRI

Magnetic resonance imaging yields an image made up of grey scale intensities that reflect the tissue property to which the imaging sequence is sensitized. The experienced radiologist or physician will rapidly recognize how different types of tissue appear on different sequences to be able to describe pathological changes in terms of anatomical location. Conventional scans generating a two-dimensional picture are not sensitive to metabolic changes, microstructural architecture and do not account for tissue orientation, but specified sequences can account for this and allow for pathological alterations to be detected before visible changes appear.

Concussion, mTBI and repetitive asymptomatic subconcussions are thought to cause injury to cortical and subcortical microstructures of the brain, despite visible gross findings on conventional MRI being rare[108]. The latest consensus statement for concussion in sports, states that no abnormalities are found with structural neuroimaging but can be seen with specialized methods in the research setting[13]. Acute imaging is generally acquired to rule out severe brain injuries requiring neurosurgical care and structural abnormalities are not expected in milder trauma. However, it has been argued that this lack of pathology is due to low sensitivity and that modern MRI techniques at higher field strengths may increase the chance of detecting discrete pathologies.

The high signal-to-noise ratio of 7T MRI scanners allows for high-resolution structural imaging in clinically feasible scan times. The high image contrast can aid detection of milder pathology[141].

Structural imaging

Structural MRI is routinely performed in the clinical setting to rule out causes of neurological deterioration, such as haemorrhage, diffuse axonal injury, mass lesion and stroke. It also provides a topographic representation that can be used to calculate multiple brain volumes and examine patterns of atrophy. Athletes with SRC have a

higher prevalence of non-specific MRI findings, white matter changes, cerebral microhaemorrhages, enlarged cavum septum pellucidum and cavum vergae, and reduced brain volumes[18, 108-110]. The possibility of sub-segmentation has revealed more specific declines in several distinct volumes with the hippocampus being the most frequently and consistently reported[17, 113], but also the corpus callosum, amygdala, cingulate gyrus, thalamus, fronto-insular region, temporal region and cerebellum[109, 142, 143]. The cumulative effect of multiple subcuncussions has also been suggested to cause atrophy[17, 18].

Diffusion weighted imaging

Diffusion weighted imaging (DWI) is an MRI method using diffusion of water molecules to create contrast and allowing mapping of specific tracts of diffusion.

Albert Einstein described diffusion as a random transport of one material from one location to another, over time and in three dimensions[144]. As time and temperature increase, so does diffusion. Diffusion of water molecules in biological tissues are restricted by cellular membranes, macromolecules, and organelles, constraining the water into alternative pathways, and resulting in greater movability in the direction with the least obstacles. If diffusion is equal in all dimensions, it is considered isotropic and if it is significantly greater in one or several dimensions, it is considered anisotropic. In the brain, diffusion is considered isotropic in grey matter and cerebrospinal fluid (CSF) and more anisotropic in white matter. In the white matter of the brain, the diffusion is relatively unrestricted in the direction parallel to the fiber orientation, along the axis of neuronal axons. Conversely, diffusion is highly restricted in the direction perpendicular to the axons[145]. By measuring changes in the MRI signal along different diffusion directions it is possible to learn something about the underlying tissue architecture and to create estimates of white matter trajectories with tractography[146]. Diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) are DWI sequences.

DTI can be illustrated as an ellipsoid with several axis of vectors, called tensors, representing the principal direction of diffusion. Mathematically, this will generate useful measures describing the amount and direction of diffusion in a given voxel. The most common DTI metrics are the mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD). MD describes the total amount of diffusion irrespective of the direction[147], and is inversely correlated with the density of cell membranes and is hence sensitive to cellularity, oedema and necrosis[148]. FA describes the degree of anisotropy[147], and is considered to be a measure of the main direction of diffusion, presuming that degeneration can change the diffusion ellipsoid, making it highly sensitive for microstructural integrity of white matter fibers and axonal injury[149]. AD describes the diffusion in the axonal direction and RD the diffusion perpendicular to the axonal direction[150]. FA is the variance of AD and RD, and MD is the mean of AD and RD.

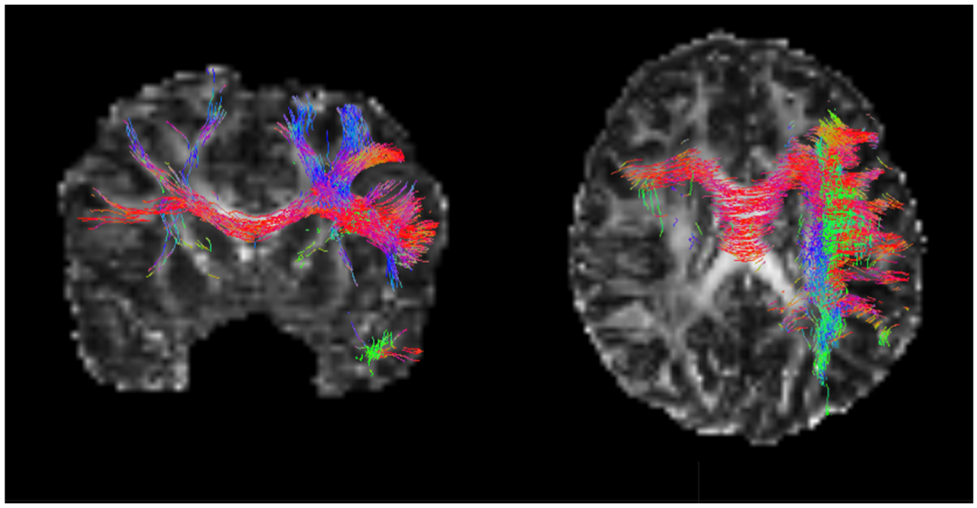

Figure 3. Diffusion directions
Coronal (right) and axial (left) slices of a diffusion tensor imaging (DTI) sequence, portraying diffusion in white matter tracts in three different directions, left to right (red), anterior to posterior (green), and superior to inferior (blue). *Courtesy of Evgenios Kornaropoulos.*

Although these tensors are highly sensitive to change and differences in diffusion, they are not specific to the type of change, why the use of multiple DTI measures and a well specified hypothesis is important[145]. Furthermore, the DTI technique assumes that water diffusion is undiversified and following a Gaussian form, which is appropriate in regions of homogenous tissue such as in CSF and uniform white matter. However, in tissues with more complex microstructure, such as the cerebral cortex and areas of substantial fiber crossings in the white matter, DTI fails to capture these inhomogeneous tissue properties[150]. The limited ability to capture complex microstructure with DTI can partially be overcome by the implementation of DKI. DKI is an extension of DTI, giving a more accurate estimation of the tensors produced by regular DTI[151], in addition to the kurtosis parameters mean kurtosis (MK) measuring the overall kurtosis, and the directional axial kurtosis (AK) and radial kurtosis (RK)[152]. The kurtosis is a measure of the diffusion's deviation from the Gaussian diffusion, the non-Gaussian diffusion of water molecules[153]. The kurtosis can be regarded as a measure of the degree of structure within a tissue, generating higher values within tissues with complex and restricted microstructure[153]. DKI is hence a suitable complement to DTI, and is possible a more sensitive tool to detect microstructural changes in the brain[152]. Both modalities are affected by temperature change, with rising temperature causing increased diffusion and a less restrictive environment and therefore an increase in DTI metrics and a decrease in DKI metrics[152].

There has been a large interest in DTI and DKI both in clinical and research settings as these methods enable evaluation of changes in brain tissue caused by disease, disease progression and treatment response[154]. DTI and DKI provide good results in detecting signs of microstructural alterations, and can be implemented as part of the clinical MRI protocol in patients with neurological disorders such as Parkinson's disease, mild cognitive impairment, Alzheimer disease, gliomas, epilepsy, cerebrovascular disease and mTBI[154, 155]. In SRC where an absence of structural pathology on conventional neuroimaging is expected, but nevertheless is thought to cause white matter dysfunction, it is especially interesting to implement these imaging modalities. DTI and DKI have in multiple studies shown the ability to detect signs of microstructural alterations in mTBI[57, 125, 156], SRC[157-160], sub-concussive repetitive head trauma[161-163] and in PPCS[56, 156]. Several of the metrics have been related to a poorer prognosis[164], prolonged symptoms[57], and impaired results on neuropsychology tests[125, 157, 161, 162, 165, 166]. Furthermore, the alterations seen in DWI-studies have shown to extend beyond symptom resolution in concussed athletes[158, 160, 167].

DKI has been indicated to be more sensitive to alterations in tissue microstructure following mTBI[57], repetitive head impacts[161, 163] and SRC[160], compared with DTI. However, the modalities have been shown to detect different alterations at different time points[125, 156], why the combined use may be the preferable option to be able to detect microstructural damage with the highest sensitivity.

Functional MRI

'Seeing the brain thinking' is the goal of functional MRI (fMRI) and is utilized by the blood oxygenation level dependent (BOLD) contrast. Oxygenated blood has a lower magnetic field compared with deoxygenated blood, and hence different MR signals. Increased consumption of oxygen during neuronal activation is accomplished by a decrease in oxygenation downstream from the site of neuronal activity, yielding an increased MR signal and making the activated area light up[168]. The BOLD effect is influenced by physiological parameters of cerebral oxygenation, such as the cerebral blood flow, cerebral blood volume and cerebral oxygen metabolism[169]. The imaging can be performed as a task-based fMRI, examining self-controlled functions such as specific movements, language, and vision, or as a resting state functional MRI (rs-fMRI) where the mind of the subject is supposed to be completely relaxed, and the intrinsic activity of the brain is evaluated.

There are several resting state networks in the brain. The salience network consisting of the dorsal anterior cingulate cortex, bilateral insula and presupplementary motor area. The network has a key role in regulating other networks, recognition of behaviourally relevant stimuli and coordination of neuronal resources. Hence, it is vital for the proper functioning of cognition processes and decision making[170]. The default mode network consisting of bilateral

symmetric cortical structures in the medial parietal, prefrontal and temporal cortex, and lateral parietal and temporal cortex. The network is active when there is no focused task being executed or prepared to be executed, the brain is in an active awake rest or involved in detailed abstract thoughts as when "*losing one's self in one's work*", it has been found to be central in attention and focus[171]. The central executive network is left-lateralized and oriented to the insula, frontal, and parietal regions. It is involved in control of the sympathetic nervous system and key for goal-oriented behaviour[172]. Activation changes in these resting state networks have been found following mTBI, especially in symptomatic patients[173].

Vestibular laboratory tests

The vestibular system is an intricate sensorimotor system responsible for detection of self-motion, head and body positioning, motor responses and multisensory integration with the main purposes of gaze stability and maintaining balance[174, 175]. It includes the inner ear or peripheral structures; vestibular nerve, utricle, saccule and semicircular canals (SSCs), and central structures; vestibular nuclei, flocculus and vermis of the cerebellum, midbrain, thalamus, parietoinsular vestibular cortex, visual cortex and projections between these structures[176]. The otolith organs located at the base of the SSCs register linear acceleration, the utricle senses horizontal movement and the saccule vertical. The SSCs are oriented orthogonally and register angular acceleration in three planes.

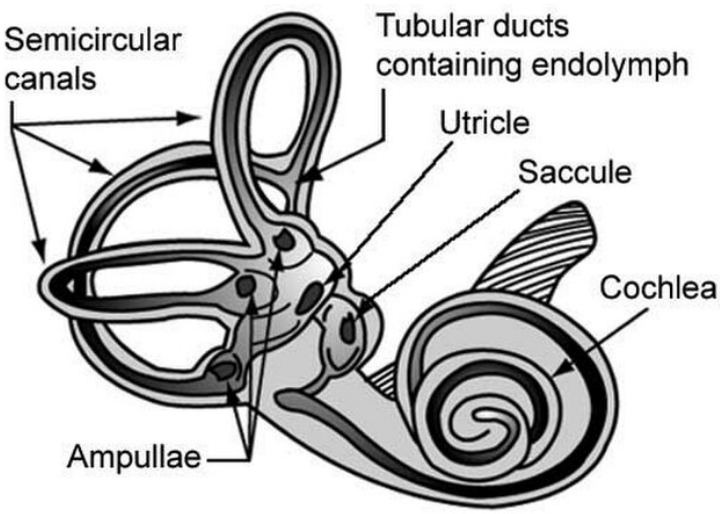

Figure 4. Peripheral vestibular organ
One of the two peripheral vestibular organs with its the three semicircular canals, tubular ducts, ampullae, utricle, saccule, and cochlea. *Source: Wikimedia Commons.*

Afferent fibers of the VIII nerve/vestibular nerve transmit signals from these sensory organs to the vestibular nuclei at the floor of the fourth ventricle. Signals are transferred to the vestibular nuclei as part of the vestibular-ocular reflex transmitting visual information to maintain gaze stability and visual focus during head movements[177] and the vestibular-spinal reflex transmitting peripheral somatosensory information to maintain postural stability[178].

Balance dysfunction following SRC can be due to a dysfunction of the vestibular, proprioceptive or central systems of the vestibular apparatus, and may act as a target for specific vestibular rehabilitation[179]. A study of healthy young adults found that headshake activity and postural training recalibrated the vestibular system resulting in better postural control and a more stable gaze[180], a potential future rehabilitation strategy for SRC athletes with vestibular dysfunction. Signs of vestibular dysfunction usually subsides by day three to five post-injury[181]. In those with persistent symptoms of vestibular disturbances there are a multitude of possible explanations, like permanent peripheral or central vestibular lesions, or combinations of central and peripheral lesions, but the knowledge of possible causes are scarce.

Biomarkers

At time of a concussion tension and stretching of brain structures causes a neurometabolic cascade and energy crisis that may lead to neuroinflammation and disrupted axonal integrity[66-69, 72]. These acute events may in rare cases progress with the detrimental effects of long-lasting neuroinflammation with astrogliosis and microglial activation, DNA-damage and neurodegeneration[73, 80, 90-93]. The regular mTBI patient seldom seek care and if so, they are often rapidly discharged from the emergency department if neurologically intact and do not have findings on routine imaging[5]. Similarly, the SRC athlete rarely seeks hospital care and are seldom followed to long-term if not embraced by a well-established medical team of their sports club. It would therefore be of great benefit if biomarkers could offer the ability to aid the diagnostics in the acute and chronic phase of SRC, avoid unnecessary computed tomography (CT) scans, follow the natural course of recovery, monitor eventual treatment, and help sort out those patients who are at greatest risk of chronic consequences. In the sports setting it could also help in determining when it is safe to return to play to avoid exposure to a new injury during a time of extra vulnerability.

A biomarker is a substance that can be objectively measured and assessed to indicate a biological or pathologic process, or the pharmacologic response to a therapeutic intervention[182]. Biomarkers can be measured from almost all bodily fluids, in SRC it is most common to analyse blood, saliva, and CSF. These are amongst the most studied biomarkers:

S100B

S100B is a calcium binding protein found primarily in astrocytes, but also in skeletal muscles, adipocytes and melanocytes[183, 184]. Historically it is one of the most studied biomarkers of TBI and was the first to be proposed for use in clinical practice by the Scandinavian Neurotrauma Committee. In the latest Scandinavian Guidelines, sampling is recommended to rule out the necessity of a neuroimaging in the acute phase following milder forms of head injuries without risk factors for a more severe TBI[185]. Blood levels of S100B in the acute phase following TBI peak within one hour and have a half-life of only 30 minutes to two hours. Similarly following SRC, S100B peaks one hour after injury whereafter it rapidly decreases[186]. Due to its low specificity to injury to the central nervous system it may also increase during strenuous physical activity, concomitant musculoskeletal injuries, and in several other neurological diseases[183, 187]. Elevated levels in the CSF does not necessary result in elevated levels in blood samples unless the blood brain barrier is disrupted causing leakage of the protein, hence the correlation between CSF and blood concentrations is relatively poor[188]. Due to its high sensitivity to brain damage, it can still be applied in the clinical setting to rule out injury and avoid unnecessary neuroimaging[188].

Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is a biomarker of astrogliosis[83], also located outside the brain in Schwann cells, chondrocytes, enteric glia, and cells in the testis, liver and pancreas[188]. GFAP increases with age, why its diagnostic utility might be insufficient in the elderly patients, although better four younger[189]. Concentrations of serum GFAP have been found to increase acutely following TBI and SRC, being able to discriminate patients with mTBI from controls[84, 187]. Elevations in GFAP correlates well with findings on CT and MRI, with its high sensitivity and specificity for predicting lesions it has outperformed S100B, Neurofilament light (NfL), Tau, and UCH-L1[187].

Neurofilament light

Neurofilament light (NfL) is a component of the axonal cytoskeleton in large-caliber myelinated axons and a sensitive biomarker of neuroaxonal injury[190]. It can be measured in CSF and blood serum, with close correlation between these compartments [191]. NfL increases acutely during the first 30 days after TBI and SRC whereafter it stabilizes and eventually decreases, but it can stay elevated for several years following injury[85, 191]. NfL had the ability to distinguish SRC athletes who could return to play within 10 days from those who could not, and to separate SRC athletes with PPCS from recovered SRC athletes at one year post injury[191].

Tubulin-Associated Unit

As described earlier Tubulin-Associated Unit (Tau) is a protein with the main function of stabilizing neuronal microtubules. During pathological processes it can undergo phosphorylation and form toxic oligomers and neurofibrillary tangles (NFTs) involved in neurodegeneration[100]. Tau is mainly expressed in axons in the CNS and peripheral nerves, but also in smaller amounts in the kidney, lung, and testis. Plasma Tau has been found to increase in a biphasic manner with elevated concentrations at one hour, decreasing at 12 hours, and again rising at six days following SRC[186]. In a study of Olympic boxers CSF Tau was found to increase acutely at one to six days following a bout and normalizing at ≥14 days of rest[192]. Outside the biomarker-setting, Tau aggregation on PET imaging has been observed in a cohort of athletes with repeated SRCs and PPCS at two years following last SRC[87].

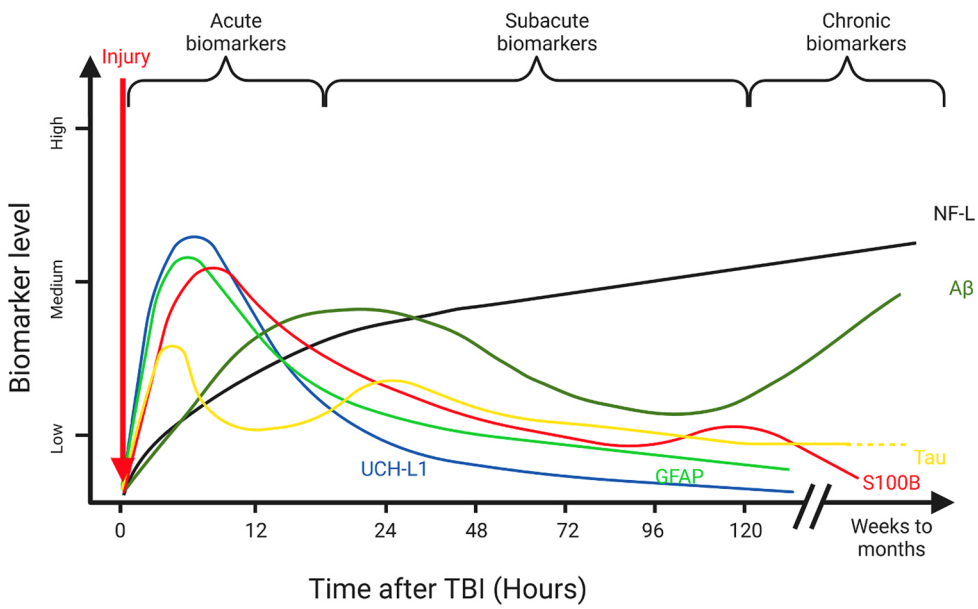

Figure 5. Temporal profile of TBI biomarkers

The temporal profile of biomarkers following traumatic brain injury (TBI). Ubiquitin C-terminal hydrolase-L1 (UCH-L1), Glial fibrillary acidic protein (GFAP), and S100B peaks fast and decreases over time. Tubulin-Associated Unit (Tau) have biphasic elevations. Neurofilament light (NfL) and Amyloid-β (Aβ) have acute, subacute and chronic profiles. *Hossain I, et al. Blood biomarkers for traumatic brain injury: A narrative review of current evidence. Brain and Spine. 2024 March; 4:102735*[187].

Ubiquitin C-terminal hydrolase-L1

Ubiquitin C-terminal hydrolase-L1 (UCH-L1) regulates protein metabolism mainly in the brain, composing about 5% of all neuronal proteins, and in much smaller

amounts in the gonads, fibroblasts and in cancerous cells. It is essential for the preservation of axonal integrity and dysfunction has been associated with neurodegenerative disease[193]. Serum UCH-L1 rises quickly after mTBI, peaking at eight hours and decreasing over 48 hours, having the greatest utility of separating mTBI from controls within the first 16 hours[194]. At seven months following TBI, UCH-L1 can distinguish patients with severe and moderate TBI, however not patients with mTBI, from controls[85].

Inflammatory proteins

A TBI elicits an acute local neuroinflammatory and peripheral systemic inflammatory cascade, which may lead to a chronic inflammatory stage. Severe TBI elicits a more profound inflammatory response than milder injuries, and the inflammatory profile following SRC is not as well established[90].

In studies of patients with mTBI, both increases and decreases of several inflammatory proteins have been observed in the acute phase and at follow up at two weeks, three months, six months, and 12 months post-injury. Amongst the elevated proteins were interleukin (IL) -2, IL-6, IL-8, IL-9, IL-17A, interferon gamma (IFN-γ), tumor necrosis factor (TNF), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β), and amongst the decreased proteins were IL-12, ICAM (intracellular adhesion molecule), VCAM (vascular cellular adhesion molecule) and Eotaxin[77, 78, 86].

In addition to the lack of clinical data there are several difficulties with interpreting inflammatory proteins as biomarkers of TBIs and SRCs. Cytokines may act both pro- and/or anti-inflammatory, as determined by the activation signal, the target cell and the timing[195]. The temporal aspect of sampling is very important, since levels of inflammatory proteins varies over time following TBI[76, 78, 86, 196].

Aims

The general aim of this work is to evaluate the manifestations, diagnostic tools, and the pathophysiology of long-term persistent symptoms following SRC.

Specific aims in populations of athletes with SRC and PPCS are

- To assess the symptom burden and quality of life in retired ice hockey players.
- To establish the origin of vestibular dysfunction and investigate if vestibular dysfunction correlates with symptom burden.
- To investigate if an inflammatory process is ongoing several months to years after the last SRC using CSF biomarkers, and if this is associated with cognitive function.
- To evaluate neurocognitive and mental health outcomes, explore measures of atrophy and white matter microstructure using 7T DTI and DKI, and evaluate evidence of astrogliosis or axonal injury using CSF biomarkers.

Material and methods

Study populations

The study subjects of this thesis are athletes with previous SRCs.

Paper I

We aimed to include players who retired from Swedish elite ice hockey after suffering from SRCs. Information about the study was sent to all ice hockey clubs in Sweden, the medical staff of the teams in the male and female elite leagues and all members of The Swedish Ice Hockey Medical Association. We asked to identify ice hockey players who retired from ice hockey as a consequence of SRC. The identified players gave consent to being contacted by, or were encouraged to contact, one of the authors (YT) if they were interested to partake in the study. In addition, all included players were asked if they were aware of other players who had had to end their ice hockey careers due to SRC. The internet was also searched for players who had stopped playing ice hockey due to SRC. If such players were identified the ice hockey club where the player had last been playing at was contacted, and recruitment was made using the same method as for the other participants. Athletes were recruited between 2014 and 2019.

Paper II and IV

Professional athletes over the age of 18 years with a history of at least one sports related concussion, symptoms debuting within a day after the concussions and exceeding six months, were included into the patient group. Athletes with a history of neurological or psychological disease prior to the concussion were excluded, as were the patients with any magnetic metal in their body making them unable to complete an MRI. Healthy athletes, exercising three times or more per week, over the age of 18 years were recruited into the control group. Controls with a prior and current neurological or psychological disease, who practiced a sport with a high risk of SRCs and magnetic material in their body were excluded. Patients were mainly recruited via physiotherapists, team physicians or study participants, who identified athletes with post-concussive symptoms and sent a request of participation to the research team or encouraged the athletes to contact any of the authors directly. The PhD candidate contacted the patients by phone and included all whom fit the inclusion criteria and gave oral consent. Controls were recruited via advertisement.

Interested controls contacted the author (AG) who included all whom fit the inclusion criteria and matched the patients concerning sex and age. Information about the study was sent to all participants, and written consent was obtained.

Paper III

Adult athletes with a history of one or more SRCs and PPCS duration for at least six months were recruited from two locations - the University Hospital in Lund (same cohort as in *Paper II* and *IV*) and the University Hospital in Uppsala. Uppsala had a similar recruiting process as in Lund. As controls, CSF samples obtained from healthy individuals participating in a study at the Karolinska Institute, Stockholm, Sweden of the acute effects of aerobic exercise on biomarkers levels in plasma and CSF, were used[197].

Symptom rating and neuropsychological evaluation

For *Paper I* the questionnaires was sent by post or electronically and answered independently by the ice hockey players. Medical and sports history, and The Sport Concussion Assessment Tool 5th edition (SCAT5) for *Paper II-IV* was completed after an interview with each athlete, by the PhD candidate. The Dizziness Handicap Inventory (DHI) was administered together with the vestibular laboratory tests. Neuropsychological assessment was conducted during the midmorning on the same day that the subjects underwent other clinical investigations and lasted for around 1.5 hours. Assessment was administered by a neuropsychologist blinded to the results of other investigations in a form of clinical consultation with semi-structured interviews, psychometric tests and self-report measures. The subjects were informed of the results of the assessment and received recommendations during a follow up.

Self-report measures

SCAT5

The Sport Concussion Assessment Tool 5th edition (SCAT5)[63] contains a graded symptom checklist that has been a part of The Sport Concussion Assessment Tool (SCAT) since the first version[63, 198-200]. The symptom checklist is self-administrated. It evaluates 22 different symptoms in seven rankings on a Likert scale, where zero is unaffected and six is affected to the highest degree by the symptom. The scores are summarized as number of symptoms (maximum 22) and symptom severity (maximum 122).

IES-R

The Impact of Event Scale-Revised (IES-R) was developed for self-reporting of PTSD[201, 202], and has now been validated for several different types of physically and psychologically traumatic events. It is widely used to measure subjective distress in relation to a traumatic event[203]. The Swedish version has been implemented and validated for mTBI, whiplash injury and other traumatic events[204-208]. We classified the traumatic event as the realization that they had to give up ice hockey pre-maturely due to the effects of SRCs.

The scale consists of 22 questions in five different scores, zero is unaffected and four is extremely distressed. The scores are separated into three subscales: intrusion (eight items), avoidance (eight items), and hyperarousal (six items). The maximum mean score on each of the three subscales is four, the highest total mean IES score is 12 and the highest total sum is 88. Total scores of 24-32 are considered subclinical[209] and scores >32 considered clinical[210] for PTSD.

SF-36

The Short Form Health Survey (SF-36) has 36 questions measuring different health domains, low scores infer a poorer health-related quality of life (HRQOL). Scores are recorded between 0 and 100. The SF-36 is suitable for self-administration and can be completed in 5-10 minutes. For comparison, there are sex- and age-normative control groups [211]. The Swedish version of the instrument has been validated[211], and SF-36 has previously been used in the evaluation of mTBI[212, 213]. The SF-36 uses eight subscales with four scales relating to functional outcomes, three scales relating to well-being and one overall health scale. Functional scales: physical functional (PF) indicating limitations in physical activity, role physical (RP) indicating problems with work and daily activities due to physical health, social functioning (SF) indicating interference with normal social activities due to physical or emotional issues and role-emotional (RE) indicating problems with work or daily activities due to emotional problems. Scales relating to well-being: bodily pain (BP) indicating limiting pain, vitality (VT) indicating fatigue and mental health (MH) indicating feelings of nervousness or depression. The overall measure of health is the scale of general health (GH)[214].

DHI

The Dizziness Handicap Inventory (DHI) is a self-reported questionnaire assessing the physical, functional and emotional components of vestibular dysfunction. The total score is 0-100, where a high score indicates a high level of self-perceived handicap of vestibular dysfunction[215]. DHI is one of the most widely used scales for measuring the impact of dizziness on quality of life[216].

HADS

The Hospital Anxiety Depression Scale (HADS) is a self-reported measure of anxiety (HADS-A) and depression (HADS-D). Scores are graded in four rankings on a Likert scale. High scores imply a high level of self-perceived symptoms. Scores of eight or more, for HADS-A and HADS-D respectively, indicate clinically significant levels of anxiety and depression[217].

MFS

Mental fatigue scale (MFS)[218] is a self-report measure of typical and associated symptoms of mental fatigue following acquired brain injuries, including mTBI. Typical symptoms of mental fatigue include acute loss of energy, difficulties with maintaining concentration, prolonged recovery time and time-dependent access of mental energy. Associated symptoms include mood swings, irritability, sensitivity to stress, impaired memory, sleep disturbances and sensitivity to noise and/or light. Symptoms are rated upon intensity, frequency, and duration, and graded in seven rankings on a Likert scale. High scores indicate high level of self-perceived mental fatigue. A cut-off of 10.5 points is indicative of mild mental fatigue and predicts a decline in cognitive processing speed[219].

LiSat-11

The 11-item Life Satisfaction questionnaire (LiSat-11) contains a self-report assessment of global satisfaction ("Life as a whole") and four domain-specific satisfaction levels of social relations, health, leisure time and work/economy[220]. Every question has six alternatives, ranked on an ordinal scale, high rating indicates high level of satisfaction. Life satisfaction is an individual's contentment with life, and usually reflects a feeling of achievement regarding expected goals, ambitions, and performances.

BRIEF-A

The Behaviour Rating Inventory of Executive Function-Adult version (BRIEF-A)[221] is a standardised self-report measure that captures participants' views of their everyday executive functioning and self-regulation. The form has 75 questions with nine subscales: Inhibit, Self-monitor, Plan/organize, Shift, Initiate, Task monitor, Emotional control, Working memory, and Organization of materials. The scales form two indexes: behaviour regulation index (BRI) and metacognition index (MI), as well as the summarizing global executive composite (GEC). BRIEF-A also includes three scales of self-report validations, which estimates the ability to answer the form correctly. Scores are graded in three rankings on a Likert scale with high scores indicating worse executive function. BRIEF-A has previously been shown to indicate the extent of executive dysfunction in retired contact sport athletes[222].

Psychometric neuropsychology

RBANS

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a psychometric test consisting of 12 subtests organised into five index scores and a total global score[223]. It measures several cognitive domains of interest in mTBI - immediate memory, attention, language, visuospatial/constructional ability, and delayed memory. RBANS was designed for the evaluation of cognitive deficits in neurodegenerative diseases[224] and has been validated for TBI patients[225].

d2

The d2 test of attention (d2) test is a timed psychometric measure of selective and sustained attention and processing speed[226]. Subjects are asked to overstrike the letter d with a specified arrangement of dots, on a sheet containing 14 rows with 47 letters of p and d with different arrangements of dots. The test has been used to identify residual cognitive deficits in young adults with a history of concussions[227].

SDMT

Symbol Digit Modalities Test (SDMT) is a psychometric test that taps into many cognitive functions including working memory, attention, and especially, information processing speed[228]. In the test, subjects are asked to translate geometric symbols into numbers, as many as possible during a restricted amount of time. SDMT is a widely used, reliable and valid measure for detecting cognitive impairment and decline in a number of neurological disorders and bran injuries, including TBI[229].

Digit span – WAIS-IV

Digit span from the Wechsler Adult Intelligence Scale (Digit span - WAIS-IV) is a subtest composed of three tasks: Forward Digit span, Backward Digit span and Sequencing[230]. In the Forward Digit span task, participants are read a sequence of numbers and asked to repeat these in order whereas in the Backward Digit span task the numbers are to be repeated in reverse order. In the Sequencing task, the random numbers are to be repeated in ascending order. The Digit Span subtest measures auditory attention, short-term retention, and working memory and has been shown to differentiate patients with TBI from matched controls[231].

Vestibular tests

The battery of vestibular tests comprised both test of vestibular function and voluntary eye movement tests. These included video head impulse test (vHIT) in 3

planes, the caloric test, cervical vestibular evoked myogenic potentials (cVEMP), videonystagmography (VNG), posturography, pursuit eye movements (PEM) and an audiogram. Prior to testing the subjects were examined to exclude obstruction, tympanic membrane perforations or any middle ear pathology. If needed ear wax was removed after which an audiogram was obtained. Tests were performed by two experienced audiologists.

A blinded assessment of a physician specialized in neurotology (MM) was made. The tests were graded as normal or pathological. Vestibular deficits were classified as peripheral, central or of combined origin, depending on an overall assessment of test results. Peripheral signs included impairments of vHIT, caloric test, cVEMP and a peripheral pattern of the VNG. Central signs included a central pattern of the VNG (*i.e.* Gaze shifting nystagmus, continuous positional nystagmus) and posturography. If a subject was found to have pathology indicating both peripheral and central deficits, the pathology was classified as combined.

vHIT

The vHIT was performed according to manufacturer's instructions (EyeSeeCam, Interacoustics, Middelfart, Denmark). The subject was sitting upright wearing goggles with an infrared camera that analyzes eye movement, and a motion sensor that records head movement. While the gaze was focused on a target at a distance of 1 m, head movements of 10-20 degrees for 150-200ms was induced in the plane of each pair of semicircular canals[232, 233]. To stimulate left lateral semicircular canal (LLSC) the head is in a neutral position and movement is induced to the left, and to activate the right lateral semicircular canal (RLSC) movement will be induced to the right. To stimulate the vertical canals the head is turned 45 degrees to the right and an anterior or posterior movement is induced to test the left anterior right posterior (LARP) canals and laterally inversed movements to the left tests the right anterior left posterior (RALP) canals[232, 233]. Evaluation was done both by calculating gains in the vestibular-ocular reflex, but mainly by classifying responses as normal or abnormal, due to the risk of possible shortcomings in calculations of the measuring system, especially for the vertical canals[234].

Caloric testing

Hot and cold (44°C and 30°C) water was rinsed into the ear over 25-30 seconds and nystagmus were recorded by infrared cameras mounted in goggles worn by the participants (VisualEyes 525, Interacoustics, Middelfart, Denmark). Pathological outcome was defined as a reaction differing 25% or more from the opposite side.

cVEMP

Tests were performed according to manufacturers instructions (Eclipse, Interacoustics, Middelfart, Denmark). The subject was sitting down and presented with 500 Hz tone burst in one ear while having the head turned to the side. Surface

electrodes was placed on the contralateral sternocleidomastoid muscle and the myogenic responses recorded. Evaluation was done both by inspecting the recorded curve and by assessing calculated amplitudes, latencies and asymmetries. The overall responses were then classified as normal or abnormal for one or both sides according to standardized lab procedures.

VNG

The subjects wore goggles with infrared cameras registering eye movements (VisualEyes 525, Interacoustics, Middelfart, Denmark). The subjects were instructed to sit upright, look to the left, right, up, down and straight ahead to register spontaneous nystagmus in different directions. To register horizontal and vertical nystagmus the subject laid downright turned to each side, and flat on the back with head flexed 15 degrees. Lastly the instructor did a sitting head shaking test, by shaking the head from one side to the other one to two times per second for a minimum of 10-15 seconds. The subjects were instructed to maintain their eyes in a central gaze position. Evaluation was done by standardized lab procedures, evaluating the different gaze direction, headshake and positional tests together and classify the response pattern as normal, peripheral or central pattern. Nystagmus with a peripheral pattern beats towards the contralateral side, improves with gaze towards the lesion, worsen with gaze away from the lesion and suppresses with visual fixation. Nystagmus with a central pattern can be solely vertical or torsional, is not affected by fixation and can change direction with the gaze[235].

Posturography

The participant stood on a platform equipped with strain-gauge sensors looking at a focus point 1.5 m ahead or blindfolded, with and without stimulations with vibratory perturbation from the platform. The test was performed in four sessions, either the subject standing with open or closed eyes for 30 s. or with Open or closed eyes for 230s where after a 30s of recording, the subjects were exposed to a pseudorandomized binary sequence of perturbations caused by a vibration towards both calf muscle. The recorded body sway were analyzed initially for frequency peaks and the variance of the forces actuated against the support surface during the body sway, as detailed elsewhere[236].

Pursuit eye movements

In the PEM-test, the ability to fixate and track a visually moving object is evaluated. Visual information travels to the middle temporal area and frontal eye field of the cerebrum, to the oculomotor regions of the brainstem, projects to the striatum and cerebellum, back to the brainstem before controlling eye movement[237]. Hence, it is a test of comprehensive visual function and is dependent on several central structures, including the cerebellum. Abnormal PEM was defined as prominently reduced velocity versus the stimuli, saccadic, or loss of pursuit.

MRI

Imaging was performed on a 7T Philips Achieva system. The MRI protocol comprised three sequences: a 3D T1-weighted MPRAGE sequence (FOV: 230×230×180 mm^3, resolution 0.80×0.80×0.80 mm^3, TR/TE: 8.00/1.97 ms); a diffusion-weighed imaging (DWI) sequence for DTI (FOV: 224×224×110 mm^3, resolution 2×2×2 mm^3, and TR/TE: 9200/65 ms) in which the diffusion encoding was applied in six directions with b = 100 s/mm^2 and 30 directions with a b = 1000 s/mm^2 and; a DWI sequence for DKI (FOV: 224×224×120 mm^3, resolution 2×2×2 mm^3, and TR/TE: 9800/76 ms) in which the diffusion encoding in six directions with b = 100 s/mm^2, six with b = 500 s/mm^2, 10 with b = 1000 s/mm^2, and 30 with b = 2000 s/mm^2. For both DWI protocols, two b = 0 s/mm^2 volumes were acquired with opposing polarities of the phase-encode blips for use in distortion correction.

Figure 6. National 7T facility
The large 7T Philips Achieva system located at The National 7T facility at Skåne University Hospital in Lund. *Courtesy of Karin Markenroth Bloch.*

Volumetrics

For volumetry, regions-of-interest were segmented from the T1-weighed images using FreeSurfer[238] (http://surfer.nmr.mgh.harvard.edu). Volumes of the cerebellar white matter (WM) and grey matter (GM) were analyzed for *Paper II* and supratentorial WM and GM, and hippocampi were analyzed for *Paper IV*. An expert reader (ENK) inspected each three-dimensional segmentation image for points of misclassification of WM, GM, and pial surface boundaries in three separate editing steps[239]. Following initial labeling, images were inspected for WM omissions and control points were added, extending the boundaries of WM segmentation to accurately incorporate all WM tissue. Subsequently, the images were inspected for any meningeal residuals within the pial surface which, if present, was manually removed. Finally, an inspection of potential erroneous classification of WM as GM or *vice versa* was performed and edits were made to the parcellation image to redraw WM and GM boundaries. All images were verified by two trained supervisors (MN and NM) to ensure that edits were implemented correctly.

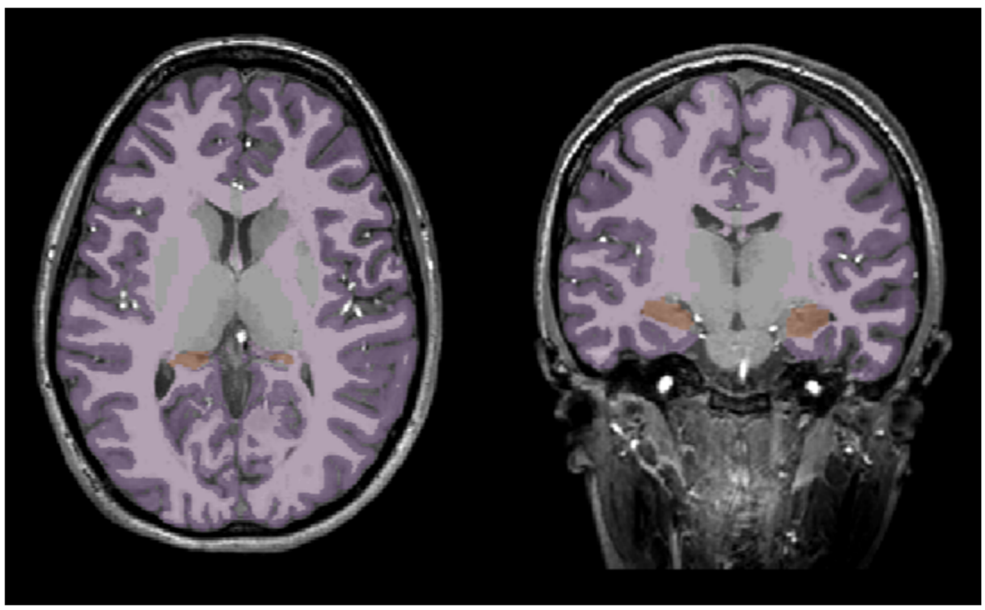

Figure 7. Volumetrics
An axial (left) and coronal (right) slice of the brain showing segmentation of white matter (purple), grey matter (pink) and the hippocampus (orange).

DTI and DKI

DTI and DKI processing comprised four steps: denoising, correction for Gibbs-ringing artefacts, brain extraction and correction of distortions due to head motion and eddy currents. Denoising was performed using Marchenko-Pastur principal

component analysis[240]. For mitigating Gibbs-ringing artefacts we used the method proposed by Kellner et al[241]. Brain extraction was performed with the use of a T1-weighted brain mask that was extracted via the ANTs brain extraction scheme[242]. Once a brain mask was extracted from the T1-weighted volume, the b-zero volume ($b = 0$ s/mm^2) was rigidly registered onto the T1-weighted volume using ANTs rigid registration scheme[243] and then the inverse transformation matrix was used to bring the brain mask onto the DTI or DKI space. Motion and eddy currents correction was applied using the eddy method provided by FSL[244]. Geometric distortions were corrected using topup by FSL[245]. DTI parameters were estimated through DTIFIT in FSL using weighted linear least squares[246]. DKI parameters were computed using the package dipy and its module DiffusionKurtosisModel, using weighted linear least squares in the fitting[153]. Median filtering with a kernel size of three was applied to the three kurtosis parameters (*i.e.* mean, axial and radial kurtosis), following their initial computation, in order to mitigate the issue with the black voxels in DKI[247]. To obtain tract-specific diffusion parameter values, WM tract segmentation was performed using TractSeg[248], which automatically segments 72 major WM tracts. The inferior, middle, and superior cerebellar peduncles were analyzed in *Paper II*. In *Paper IV* all 72 tracts were analyzed, and a "global WM metric value" which was the sum of all tracts divided by 72. The fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were analyzed for DTI and FA, MD, AD, RD, mean kurtosis (MK), axial kurtosis (AK) and radial kurtosis (RK) for DKI.

Biomarkers in the cerebrospinal fluid

In Lund, five ml of CSF was drawn by a lumbar puncture in a sitting or cumbent facing the side position. An atraumatic needle (22G, 90 mm) was used in the L3-L4, L4-L5 or L5-S1 intervertebral space. Samples were centrifuged at 3000 rpm at 4°C in 10 minutes before pipetted into 1 ml ampullas and stored at -80°C within one hour. CSF from Lund were analyzed for *Paper III* and *IV*.

In Uppsala CSF was collected by routine lumbar puncture, samples were centrifuged at 3450 rpm at room temperature for seven minutes and stored at -20°C for one to two days and then at -80°C.

In Stockholm CSF from healthy controls were obtained using the same procedure as in Lund, with an atraumatic needle (22G, 70 mm) in the L4-L5 or L5-S1 intervertebral space. A total volume of 25 ml of CSF was collected, with separation of cells by centrifugation for 10 min at room temperature at 350 G, division into aliquots and freezing at -80°C within one hour.

The samples from Uppsala and Stockholm were sent to Lund with express delivery on dried ice and were not thawed prior to or during transport. When delivered to Lund, samples were stored together at -80°C until time of the analysis for *Paper III*.

Inflammatory biomarkers

CSF samples were analyzed for inflammatory mediators using the Meso Scale Discovery (MSD; Rockville, MD, USA) MULTISPOT Assay System V-PLEX Human Proinflammatory Panel 1, Cytokine Panel 1, and Chemokine Panel 1. The inflammatory proteins were detected by enzyme-linked immunosorbent assay (ELISA), using antibodies as electrochemiluminescent labels to quantify concentrations. For each plate, or panel, a specific antibody solution containing nine antibodies were used:

Proinflammatory Panel 1: 60 µl of SULFO-TAG interferon gamma (IFN-γ), interleukin (IL)-1 beta (IL-1β), IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, and tumor necrosis factor alpha (TNF-α) were added to 2400 µl of diluent.

Cytokine Panel 1: 60 µl of SULFO-TAG IL-1 alfa (IL-1α), IL-5, IL-7, IL-12/IL-23p40, IL-15, IL-16, IL-17A, tumor necrosis factor beta (TNF-β), and vascular endothelial growth factor (VEGF) were added to 2400 µl of diluent.

Chemokine Panel 1:60 µl of SULFO-TAG Eotaxin, Eotaxin-3, interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), monocyte chemoattractant protein-4 (MCP-4), macrophage-derived chemokine (MDC), macrophage inflammatory protein-1 alfa (MIP-1α), macrophage inflammatory protein-1 beta (MIP-1β) and thymus- and activation-regulated chemokine (TARC) were added to 2400 µl of diluent.

Samples were thawed upon dried ice in room temperature until liquefied, they were not diluted. Plates were washed with 150 µl/well Wash Buffer (provided by MSD and diluted with deionized water from 20X to 1X concentration), the wash cycle was repeated three times. Sample or calibrator/standard (50 µl/well) were added, plates were sealed, and incubated at room temperature with shaking (1000 rpm) for two hours. Plates were washed by three cycles. Plate specific antibody solution (25 µl/well) were added, plates sealed and incubated at room temperature with shaking for two hours. Plates were again washed by three cycles. As a last step 2X Read Buffer T (150 µl/well) were added prior to plate analysis on the MESO QuickPlex SQ 120 instrument and with the MSD Discovery Workbench software version 4.0.13 (Rockville, MD, USA). All samples were analyzed in duplicates, on the same batch and by the PhD candidate.

NfL and GFAP

CSF NfL and GFAP concentrations was measured using an in-house enzyme-linked immunosorbent assay (ELISA)[249, 250]. All analyses were performed by technicians blinded to clinical data in one round of experiments. Intra-assay coefficients were below 10%.

Statistical analysis

Data was compiled in Excel (Microsoft Corporation, Washington) and exported to SPSS 25 to 28 (SPSS Inc., version 25-28, IBM Corporation, Armonk, NY) for statistical analyses. Data were analyzed for normal or skewed distribution using Shapiro-Wilk test, Q-Q-plots and histograms. Normally distributed data were compared using means and analyzed with *t*-tests and ANOVA regression analysis. Skewed or categorical data were presented as median and interquartile range (IQR) and analyzed with Mann-Whitney *U*-test for pairwise comparisons, with crosstabs and Chi-Square test for categorical and binominal values and for correlations, Pearman's or Spearman's coefficient (r_s) was calculated. If the sample sizes were deemed to small (<25 per group) non-parametric tests were used for analyses.

The vestibular tests were reported dichotomously. The results of the psychometric neuropsychological tests (RBANS, d2, SDMT, and WAIS-IV) are presented as raw scores and as Z-scores, based on test-specific published norms. Cognitive impairment was defined by performances ≤ –1.5 Z, *i.e.* 1.5 SD below normative means for each test[251]. Data for the self-rating questionnaires IES-R, SF-36, DHI, HADS, MFS, LiSat-11and BRIEF-A are presented in raw scores. For BRIEF-A, Z-scores are additionally reported and a Z ≥1.5 was used as a cut-off for impaired results.

The significance threshold was set to 0.05. In *Paper II* a Bonferroni correction was made to adjust for the three cerebellar peduncles, hence, the significant threshold was set to 0.017 (0.05/3). As *Paper IV* was an explorative study, corrections for multiple comparisons were not done. Applying correction in this small material would increase the risk of false negative findings (type II errors) and would make it difficult to draw any conclusions about our hypothesis[252]. We have presented all data and methods, clarifying that we have performed 72 test per DTI and DKI parameter. To be acknowledged is that if all tracts would yield independent observations, the expected number of significant tracts under a true null hypothesis (no difference) would follow a binominal distribution with parameters n = 72 and *p* = 0.05 and in 95% of all cases, up to seven tests would be expected to be false positives. Finding more than seven tracts with significant group differences could thus be interpreted as so unlikely that at least some of the significant tracts would

comprise true positive findings. This analysis applied only to the case where all tracts are independent.

To account for multiple comparisons and covariation between tracts and thus strengthen our results regarding DTI and DKI in *Paper IV*, we performed a permutation analysis with the test statistic defined as the number of tracts that displayed significant differences in their medians. In this analysis, the labels of the two groups were randomly permuted 10^4 times. For each permutation, a U-test was performed for each tract. This generated a distribution of the number of tracts with significant differences, under the null hypothesis. The exact p-value was computed as the relative number for which the number of significant tracts from the permutation analysis was higher than the number of significant tracts with the true labels. Using the results of the permutation analysis, we also computed the 95^{th} percentile of the number of tracts that was significant under the null hypothesis. This number can be considered as a significance threshold: for parameters with fever significant tracts, all significant tracts for that parameter may be considered as false positives. For parameters with a higher number of significant tracts, some but not all of the significant tracts can be considered as false positives. This whole analysis was repeated for significance thresholds (α) in the per-tract U-tests of 0.05 and 0.01.

In *Paper IV* effect sizes was calculated for differences between SRC athletes and controls in the metrics of DTI and DKI, with a significant threshold of 0.64. The latter is the lower threshold of a 95% confidence interval for the effect sizes computed in the study, as defined by a previously published formula[253].

Results

Paper I

Study population

Ninety-five players were identified and verified to have retired from ice hockey due to concussions. Of these 82 responded, of whom five decided not to partake and one player could not define the reason for retirement and was therefore excluded. Of the 76 participating athletes, 30 answered the questionnaires in written form and 46 digitally.

Of the participating players, 70 (92%) were male and six (8%) were female. The age ranged from 19 to 56 years (mean 30 ± 8 years). The athletes had predominantly played at a professional (41%) or semi-professional (55%) level, while only three athletes (4%) played at an amateur level. Duration of the career was 19 ± 6 (range 5-30) years. Age at first concussion was 16 ± 5 (range 5-31) years and age at last concussion was 25 ± 6 years. The players sustained 6 ± 3 (range 1-20) concussions during their careers. Most athletes (82%) experienced that they were more susceptible to injury by each additional concussion. Forty-nine (64%) of the athletes had been admitted to the hospital due to concussion.

The predominant reason for terminating the career was due to persistent post-concussive symptoms (group Concussion Symptoms; gCS, 58%). The remaining athletes (group Concussion Concerns; gCC: 42%) stated that the reason for termination was due to a fear of attaining additional concussions. It took 6 ± 5 months from the last concussion until the decision to terminate the career was made. The mean age at retirement was 25 years (range 13-39). After retirement from the sporting career 61% worked fulltime in another job or studied.

Comparing gCS to gCC, the groups differed only concerning ability to work or study fulltime (41% in gCS and 88% in gCC, $p<0.001$) and whether they had been hospitalized due to concussion (77% in gCS and 47% in gCC, $p=0.021$).

Symptom evaluation forms

Sport Concussion Assessment Tool 5th edition

All participating athletes completed the SCAT5 graded symptom checklist. Nervousness/anxiousness was the most frequent symptom, reported by 86% of subjects (Figure 8). The median number of symptoms was 16 (IQR 11-21), and all but three athletes suffered from any symptoms. Symptom severity scores ranged from 0 to 102, with a median of 39 (IQR 15.5-69). Age and number of SRCs did not correlate with symptom severity score, $p=0.416$ and $p=0.474$.

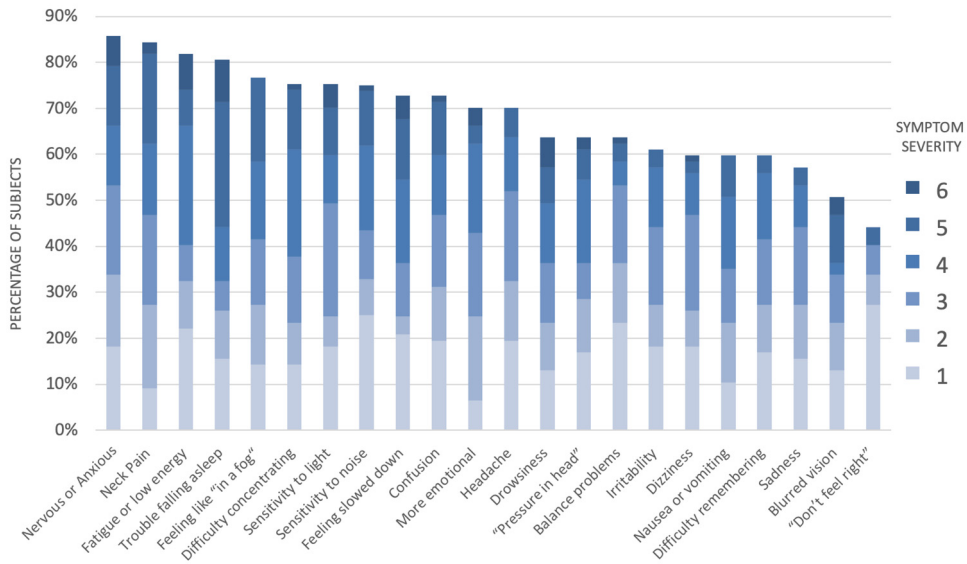

Figure 8. SCAT5
Twenty-two post-concussive symptoms in six severity grades, reported by the ice-hockey players. Increasing severity of symptom is represented by a more intense deep blue color. The most common symptom was "Nervous or Anxious".

In gCS, the median number of symptoms was 20 (IQR 14-21) and the median symptom severity score was 65 (IQR 36-80). In gCC, the median number of symptoms was 11 (IQR 6-17) and median symptom severity was 26 (IQR 7-39), both significantly lower when compared with gCS ($p<0.001$, respectively, for both analyses).

The Short Form Health Survey

As SF-36 is dependent on sex and age, we evaluated male and females separately in age-groups, and gCS with gCC. In comparison with norms, males aged 15-44 in

gCS differs significantly in all domains of quality of life (QoL) and males aged 15-44 in gCC differs significantly in RP, GH, VT, SF, RE and MH. Women aged 15-44 in gCS differs significantly in RP, BP, VT, SF and RE. Males aged 15-44 differs significantly between gCS and gCC in all domains but RE and MH. Women in gCC and males aged 45-64 has small sample sizes, thus no statistical conclusion can be made. Comparing all male and female players, separated into gCS and gCC, the groups significantly differed in all domains but RE, though, RE differs significantly from norms in both gCS and gCC.

The Impact of Event Scale-Revised

Out of the 76 included athletes, 68 males and six women filled out the IES-R formulary. There was no statistical difference between men and women concerning total IES-R scores, men had a mean score of 27.7 and women 27.5 ($p=0.987$). Comparing gCS and gCC there were several differences, including a higher total score in gCS compared to gCC (31.7 *vs.* 22.2; $p=0.028$) and a higher mean hyperarousal score in gCS (1.4 *vs.* 0.7; $p=0.001$). There were no statistical differences between gCS and gCC in mean intrusion (1.5 vs 1.2, $p=0.171$) and avoidance (1.4 vs 1.1, $p=0.102$) scores.

Correlations

Correlations between SCAT5 symptom severity and number of symptoms with total scores of SF-36 and IES-R, was calculated using Pearman's correlation coefficient. Significant correlations between SCAT5 symptom severity and SF-36 (r=-0.80, CI: -1.30- -0.91, $p<0.001$), SCAT5 number of symptoms and SF-36 (r=-0.78, CI: -0.28- -0.19, $p<0.001$), SCAT5 symptom severity and IES-R (r=0.54, CI: 0.54-1.16, $p<0.001$) and SCAT5 number of symptoms and IES-R (r=0.51, CI: 0.10-0.24, $p<0.001$) were observed. Analyzed separately, gCS had significant correlations between SCAT5 symptom severity and SF-36 (r= -0.77, CI: -1.31- -0.77, $p<0.001$), SCAT5 number of symptoms and SF-36 (r= -0.77, CI: -0.25- -0.15, $p<0.001$), SCAT5 symptom severity and IES-R (r=0.62, CI: 0.54-1.26, $p<0.001$) and SCAT5 number of symptoms and IES-R (r=0.55, CI: 0.08-0.22, $p<0.001$). In gCC significant correlations was found between SCAT5 symptom severity and SF-36 (r= -0.66, CI: -1.27- -0.51, $p<0.001$) and SCAT5 number of symptoms and SF-36 (r= -0.69, CI: -0.39- -0.17, $p<0.001$), however not between SCAT5 symptom severity and IES-R (r=0.24, CI: -0.17-0.77, $p=0.20$) or SCAT5 number of symptoms and IES-R (r=0.35, CI: -0.002-0.27, $p=0.053$).

Paper II

Study population

Forty-two subjects were included, 21 athletes with previous SRCs and persistent symptoms, and 21 healthy age- and sex-matched controls. One patient did not complete the MRI.

Mean age was 26 (range 18-43) years and 60% were males. The SRC athletes were involved in ice hockey, soccer, karate, handball, indoor hockey, wrestling, or endurance riding for a mean of 18 years of practice. The SRC athletes had a mean of five (range 1-20) SRCs with a mean age of 18 years when sustaining their first SRC. On average 2.5 years had passed since their last SRC until inclusion in the study.

Symptom evaluation forms

On SCAT5, SRC athletes reported a median 20 symptoms (IQR 20-22) and symptom severity 64 (IQR 44.5-81.5). Fatigue was reported by everyone, and the least common symptoms, nausea or vomiting, by 60%. Symptoms of vestibular disturbance was reported by a vast majority. Number of SRCs, age or sex did not correlate with SCAT5 symptom severity, $p=0.347$, $p=0.204$ and $p=0.343$, respectively.

SRC athletes reported higher scores on DHI (median 40; IQR 27-55) compared to controls (median 0; IQR 0-0; $p<0.001$). The number of previous SRCs, age or sex did not correlate with the DHI score, $p=0.356$, $p=0.147$ and $p=0.603$, respectively.

SRC athletes reported elevated rating on HADS anxiety and depression subscale (median 16; IQR 11.5-19) compared to controls (median 4; IQR 2.5-6; $p<0.001$), 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). The number of SRCs, age or sex did not correlate with the HADS score, $p=0.316$, $p=0.684$ and $p=0.817$, respectively.

7 Tesla MRI – volumetrics, DTI and DKI

Due to artefacts, two athletes and three controls were excluded from the volumetric segmentations, and one control from the DKI. DTI data was missing for one athlete and DKI data from two athletes. Images were reviewed by an independent neuroradiologist and a researcher (IB-B), and no structural abnormalities were observed.

Cerebellar white matter volume was 27.3±4.0 ml in SRC athletes and 28.5±4.8 ml in controls; grey matter volume was 114±12.2 ml in athletes and 116±14.9 ml in controls, similar between groups ($p=0.441$ and $p=0.722$, respectively) and there was no correlation with vestibular dysfunction ($p=0.361$ and $p=0.774$, respectively). DKI metrics revealed a decrease in MK in the superior and inferior cerebellar peduncle (both $p=0.010$) and in RK in the superior cerebellar peduncle ($p=0.006$) for SRC athletes compared with controls. No other differences in DKI and DTI metrics were observed. No DTI or DKI metric correlated with vestibular dysfunction, $p>0.017$. TractSeg analysis found similar cerebellar tract volumes in SRC athletes and controls using DTI and DKI (data not shown).

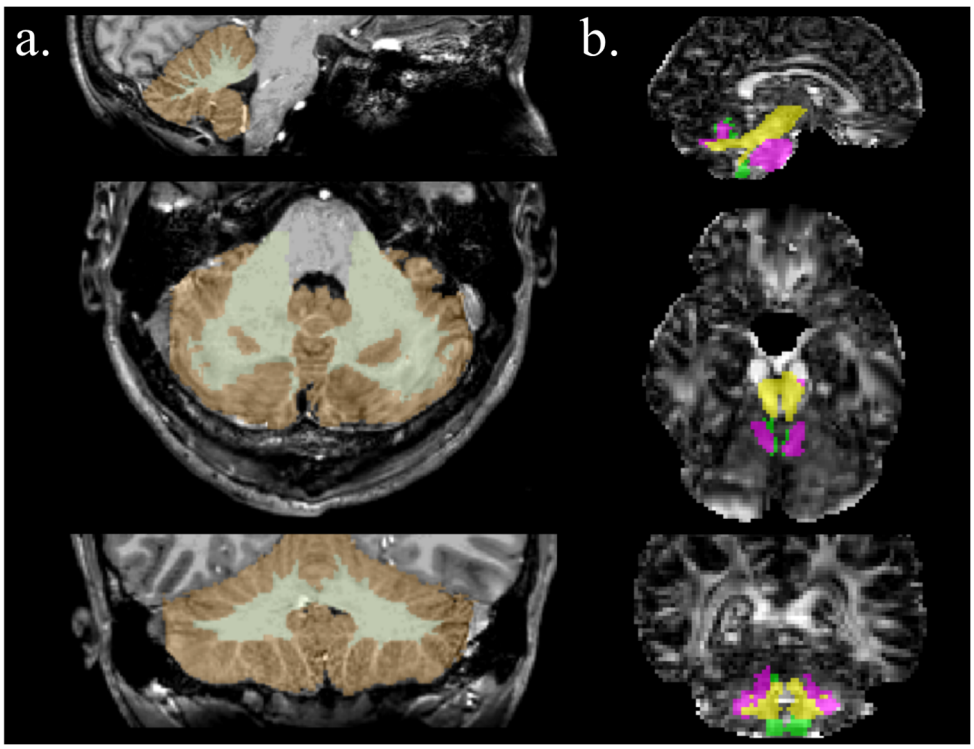

Figure 9. 7T cerebellar MRI
Cerebellar segmentation (a) of the white (yellow) and grey (brown) matter and diffusion kurtosis imaging with the segmentation of the superior (yellow), middle (purple, and inferior (green) cerebellar tracts (b). Images are shown as sagittal (upper row), axial (middle row), and coronal (lower row) slices.

Vestibular tests

Vestibular dysfunction was present in 13 of 21 SRC athletes and in three of 21 controls ($p=0.001$). SRC athletes with were diagnosed with vestibular dysfunction

of peripheral (n=9) or combined (n=4) origin and controls with peripheral (n=1), central (n=1) or combined (n=1) origin. All participants had a normal audiogram, except one SRC athlete with left-sided peripheral vestibular dysfunction although right-sided hearing impairment. SRC athletes had worse results in vHIT ($p<0.001$) and cVEMP ($p=0.002$). The combination of pathology on the posterior semicircular canal in vHIT and the ipsilateral cVEMP (Figure 10) argues for an injury to the inferior vestibular nerve since responses are dependent on the integrity of the posterior semicircular canal (vHIT) or the saccule (cVEMP), both innervated by the inferior vestibular nerve. Vestibular dysfunction did not correlate with the number of previous SRCs ($p=0.971$), age ($p=0.141$), sex ($p=0.758$) or SCAT5 symptom severity ($p=0.418$). Subjects with vestibular dysfunction assessed 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 five, IQR 3-12.25, $p=0.004$) compared to subjects without vestibular dysfunction.

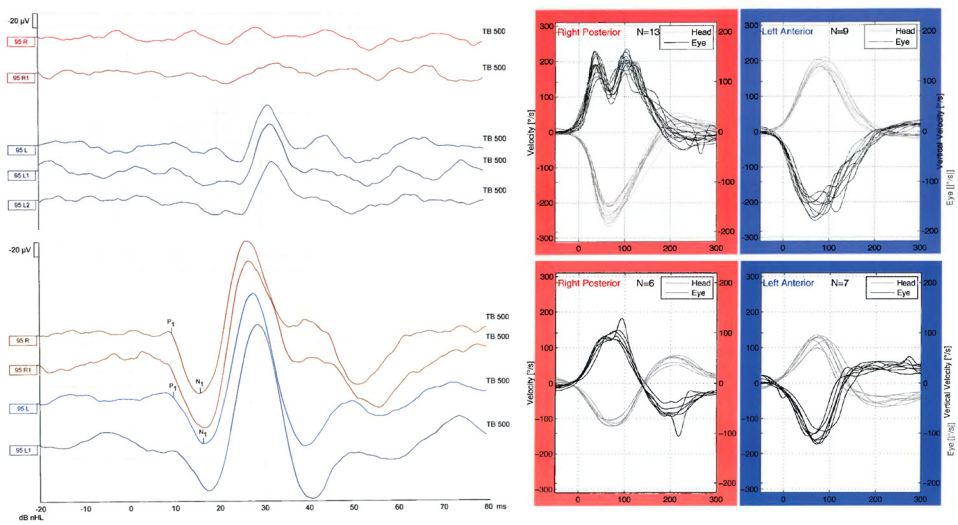

Figure 10. cVEMP and VHIT
The results of cervical vestibular evoked myogenic potentials (cVEMP, to the left) and video head impulse test (vHIT, to the right) for one SRC athlete (upper curves) and one control (lower curves). The SRC athlete displays abnormally low cVEMP amplitudes on the left side and a biphasic prolonged response of the right posterior semicircular canal on vHIT, as compared to the normal curves seen for the control.

Paper III

Study Population

Thirty-six subjects were included, 24 athletes with previous SRCs and persistent symptoms, and 12 healthy age-, sex- and athletically matched controls. Of the SRC athletes, 15 were recruited in Lund and nine in Uppsala. There was an equal number of men and women in both groups with the mean age of 26 (range 18-36) years, without differences among the groups (*p>0.05*). The SRC athletes were involved in ice hockey, soccer, alpine skiing, indoor hockey, handball, and wrestling, the controls were active runners. The SRC athletes had sustained a median of five (IQR 1-10) concussions, at a median of 17 (IQR 10.5-26) months since the last SRC (Figure 11).

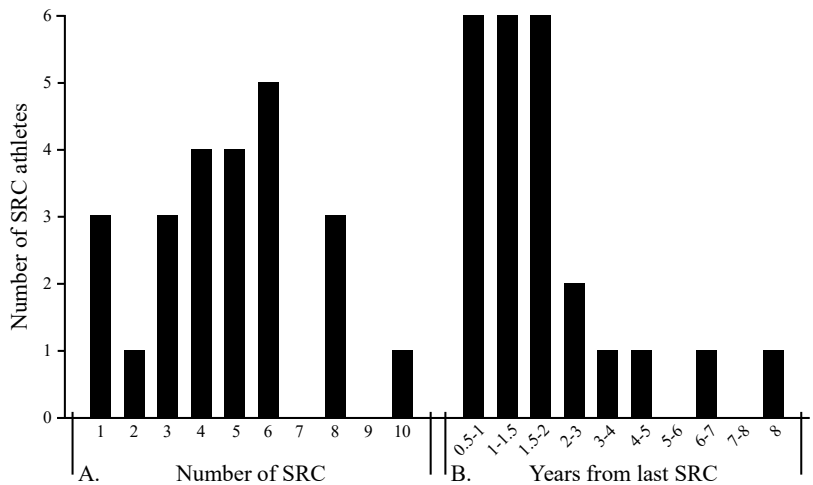

Figure 11. SRC details
A Number of sport-related concussions (SRC)s and **B** time from last SRC to study inclusion in years.

The SRC athletes reported a median of 19 (IQR 14-22) SCAT5 symptoms and a median SCAT5 symptom severity score of 51 (IQR 33-74). Cognitive function measured with RBANS global score was impaired in 10 out of the 24 athletes. Thus, the proportion of SRC athletes with impaired performance below Z < -1,5 was six times more common than would be expected in an age-related normal population (42% vs. 7%). However, when comparing SRC athletes as a group with published norm data[223] a significant difference was not obtained. There were no differences between male and female athletes in number of SRCs, RBANS, SCAT5 symptom severity scores and number of symptoms.

Biomarkers

Of the 27 tested biomarkers, the cytokines IL-4 and IL-1α had concentrations under the limit of detection suggested by the manufacturer in 21 and 36 analyzed subjects respectively and were therefore excluded. Thus, 25 inflammatory markers were therefore included for further analyses.

Of the 25 included biomarkers of inflammation, there was a pattern of increased levels in the SRC athletes of which eight markers were significantly higher than the levels observed in controls (IL-2; *p=0.032*, TNF-α; *p=0.011*, IL-15; *p=0.025*, TNF-β; *p=0.002*, VEGF; *p=0.012*, Eotaxin; *p=0.008*, IP-10*; p=0.019*, and TARC; *p=0.027*). The CSF level of one biomarker (Eotaxin-3) was significantly lower in SRC athletes than in controls (*p=0.006*).

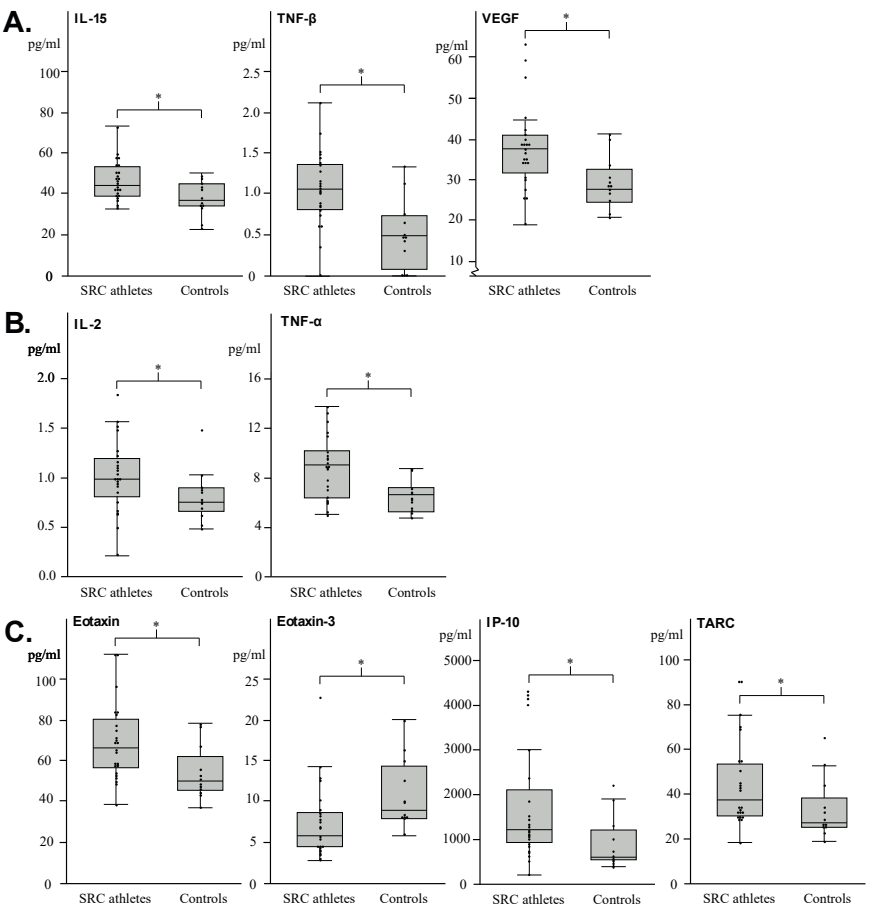

Figure 12. Biomarkers
A Cerebrospinal fluid biomarkers that were significantly differing between SRC athletes and controls with *p*<0.05. **A** cytokine panel, **B** Proinflammatory panel, and **C** Chemokine panel.

Correlations

RBANS global score correlated negatively with MIP-1α (r_s=-0.432, *p=0.035*). SCAT5 number of symptoms correlated negatively with Eotaxin-3 (r_s=-0.512, *p=0.013*) and TARC (r_s=-0.428, *p=0.041*). SCAT5 symptom severity score correlated negatively with IP-10 (r_s=-0.413, *p=0.050*) No other biomarker correlated with RBANS or SCAT5 number of symptoms or symptom severity score.

Paper IV

Study Population

Forty-four subjects were included, 22 athletes with previous SRCs, and 22 healthy age- and sex-matched controls. One SRC athlete did not complete the MRI, and five controls did not complete the neuropsychology testing and self-reported measures, these subjects were excluded from the specific analyses.

The mean age was 26 (range 18 to 43) years and 61% were males. The groups were similar in most of the demographics although the SRC athletes had shorter education (13 vs. 16 years; *p<0.001*) and were more frequently on sick leave (50 vs. 0%; *p<0.001*). The SRC athletes had a mean of five previous SRCs with the most recent being sustained 2.6 years from inclusion. The SRC athletes were involved in ice hockey, soccer, karate, handball, indoor hockey, wrestling, and endurance riding. The SRC athletes reported many and severe SCAT5 symptoms with a median of 20 symptoms (max 22) and a symptom severity score of 64 (max 132).

Neuropsychological assessment

Self-rated symptoms of anxiety (HADS-A), depression (HADS-D), and mental fatigue (MFS) significantly exceeded those reported by matched controls (*p<0.001*). A majority of SRC athletes, 59 %, scored above levels indicative of clinical anxiety on HADS-A[217], and all SRC athletes reported symptoms of mental fatigue beyond normal[219]. On LiSat-11, 18 (82 %) of the SRC athletes reported not being satisfied with life, with the least satisfaction in the psychological health domain (0 %). On self-reported executive function (BRIEF-A) the SRC athletes rated significantly more problems than controls (*p<0.001*) and deviated significantly (≤ –1.5 Z) from normative reference data[221].

A high proportion of SRC athletes performed significantly below normative means, *i.e.* Z≤ –1.5, on neuropsychological psychometric tests: 41% on RBANS global score, 18% on d2, and 32% on SDMT. More than half of the SRC athletes (12 out of 22) had significant impairment in at least one cognitive domain. RBANS List

learning was the most sensitive test with 41% of SRC athletes having a Z-score below –1.5 and where SRC athletes had a median Z of –1.23. SRC athletes scored significantly worse than the 17 controls on all but the WAIS-IV digit span.

7 Tesla MRI

Images were assessed by a neuroradiologist (IB-B), and no gross abnormalities were detected. The SRC athletes had all previously undergone routine neuroimaging (CT or 1.5/3T MRI) following their SRC/SRCs and these images were reported to the research team as normal. Volumetric segmentation was successfully performed in 19 athletes (missing data n=1, artefacts n=2) and 19 controls (artefacts n=3). DTI evaluation was successfully performed in 20 athletes (missing data n=2) and 21 controls (excessive head motion n=1) and DKI evaluation in 19 athletes (missing data n=3) and 20 controls (artefacts n=1, excessive head motion n=1).

There were no significant differences in WM volume, GM volume or hippocampal volume between SRC athletes and controls. Supratentorial WM volume was 476 ml (IQR 445-552) in SRC athletes and 487 ml (IQR 464-560) in controls ($p=0.589$); GM volume was 555 ml (IQR 555-611) in athletes and 598 ml (IQR 538-616) in controls ($p=0.737$); hippocampal volume was 8.07 ml (IQR 7.69-8.75) in athletes and 8.08 ml (IQR 7.43-8.26) in controls ($p=0.672$).

There was a significant difference between SRC athletes and controls in 16% of the 72 examined tracts analysed by DTI metrics and 35% of the tracts by DKI. In total 28% of all comparisons showed significant differences between SRC athletes and controls (*i.e.* 224 out of 792 comparisons in total, as one test was performed for each of the 72 tracts and each of the 11 metrics). DTI FA differed in three tracts, DTI MD in 18 tracts, DTI AD in 14 tracts, DTI RD in 12 tracts, DKI FA in 52 tracts, DKI MD in 19 tracts, DKI AD in zero tracts, DKI RD in 36 tracts, DKI MK in six tract, DKI AK in 35 tracts and DKI RK in 29 tracts. For details in DTI and DKI metrics for the specific tracts, see Supplemental material for paper IV. The global WM metric values differed significantly in four metrics; DKI FA where SRC athletes had higher values compared with controls (median 0.459 (IQR 0.448-0.464) vs. 0.438 (0.436-0.449), $p<0.001$), DKI RD where SRC athletes had lower values compared with controls (0.698 (0.681-0.711) vs. 0.710 (0.700-0.728), $p=0.011$), DKI AK where SRC athletes had higher values compared with controls (0.861 (0.851-0.872) vs. 0.842 (0.827-0.860), $p=0.023$), and DKI RK where SRC athletes had lower values compared with controls (1.121 (1.008-1.182) vs. 1.185 (1.134-1.263), $p=0.026$). These results were further strengthened by a permutation analysis, which showed that the number of tracts with significant tracts between SRC athletes and controls exceeded the number of significant tracts under the null hypothesis for DKI FA, MD, RD, AK, and RK. The alterations were widespread in all areas of WM. There were no significant differences in WM volumes between SRC athletes and controls analysed with DTI and DKI TractSeg ($p>0.05$).

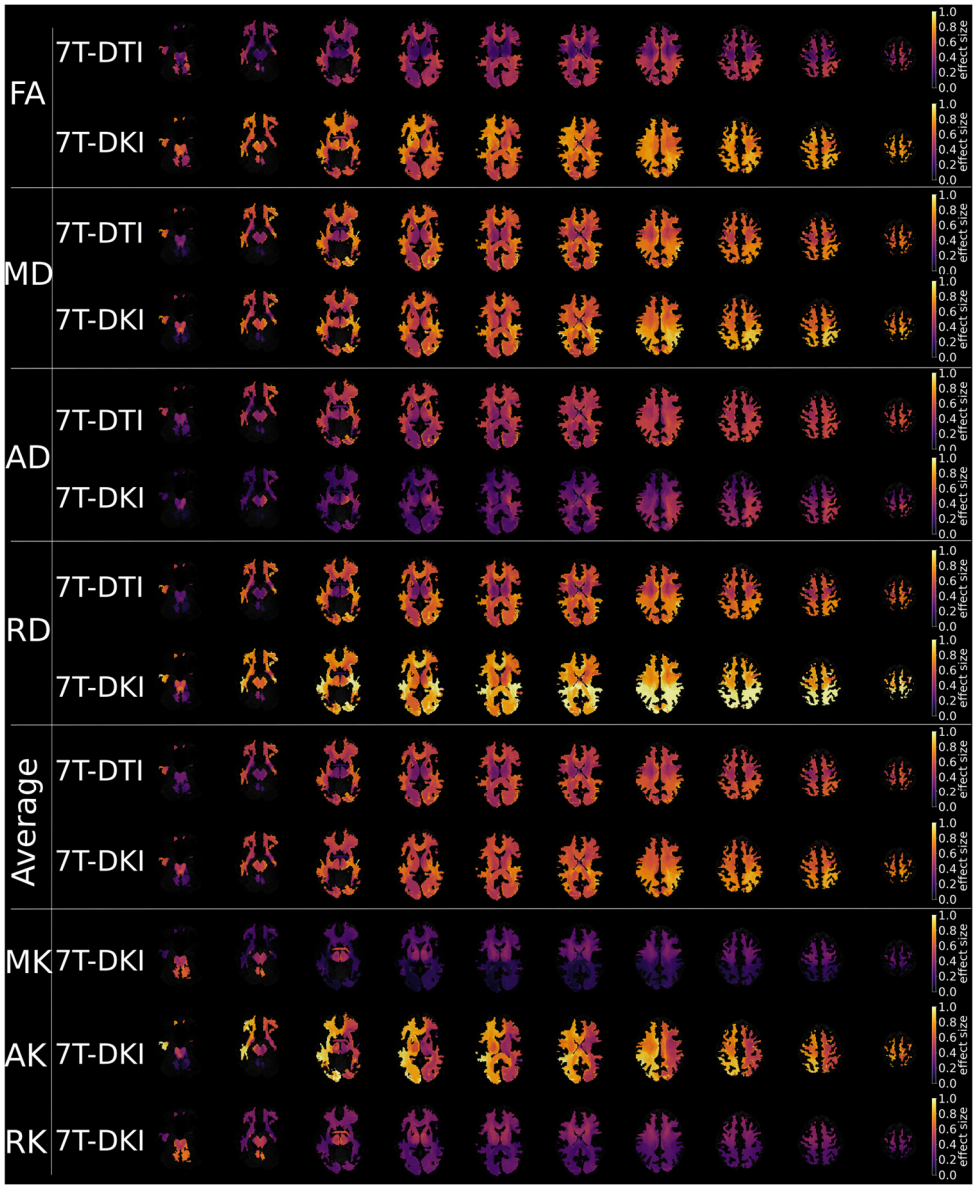

Figure 13. Diffusion parameters

Effect sizes of diffusion parameters for differences between SRC athletes and controls, plotted in axial slices, in the metrics of diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI). Metrics: Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK). Lighter yellow colors represent high effect sizes, and hence a larger difference between the groups.

Biomarkers

Sixteen SRC athletes consented to CSF sampling. SRC athletes had a median NfL of 219 ng/L (IQR 153-279) and GFAP of 248 ng/L (IQR 194-299).

Correlation analyses

Correlations were analyzed for the SRC athletes only. Number of SRCs, SCAT5 and sex did not correlate significantly with the psychometric neuropsychology tests, with brain volumes or with DTI and DKI metrics averaged across all tracts.

To evaluate correlations between global measures of cognition and impaired global diffusion metrics RBANS whole scale, SDMT, d2, MFS, BRIEF whole scale, and BRIEF working memory was correlated to the global WM average for each DTI and DKI metrics. No significant correlations were found. BRIEF behavioral regulation index correlated significantly with DKI MD (r_s=0.499, *p=0.030*) and DKI RD (r_s=0.573, *p=0.010*) in the left cingulum. To test for a relation between the hippocampus and episodic memory we correlated hippocampal volume to RBANS list learning and list recall, which were not significant (*p=0.611* and *p=0.561*, respectively).

NfL correlated negatively with global WM average for DTI MD (r_s=–0.620, *p=0.014*), DTI AD (r_s=–0.542, *p=0.037*), DTI RD (r_s=– 0.558, *p=0.031*), DKI MD (r_s=–0.583, *p=0.029*) and DKI RD (r_s=–0.601, *p =0.023*), and positively with global WM average for DKI FA (r_s=0.664, *p=0.010*). GFAP did not correlate significantly with any DTI or DKI metrics.

Discussion

In this thesis we studied ice hockey players who retired due to SRCs and athletes with persistent post-concussion symptoms (PPCS) for over six months. The athletes suffered from a substantial symptom burden with a negative impact on their health and quality of life due to dizziness, mental fatigue, depression, and anxiety. Despite having no gross findings on routine clinical neuroimaging, advanced neuroimaging, biomarkers, and specialized functional tests, there was evidence of several pathophysiological processes. Athletes with PPCS had signs of a peripheral vestibular injury to the inferior vestibular nerve, ongoing neuroinflammation, white matter alterations, and cognitive impairments. These results emphasize that repeated concussions may trigger a pathological process in the brain with neuroinflammation and neuronal injury lasting for several months or years following the last SRC, and which potentially contributes to the persistent symptoms in these athletes.

In this thesis we had the aim to capture the clinical presentation of athletes with PPCS, to explore which diagnostic means can be used to quantify these issues, and to explain the underlying pathophysiological processes of long-term disabilities following SRC.

Clinical presentation

In all four papers we show evidence of severe, debilitating, and prolonged symptoms in athletes with SRC.

Using SCAT5 (where there is a maximum of 22 symptoms and 132 in symptom severity score; SSS), the athletes in *Paper I-IV* reported many and severe post-concussion symptoms, ranging from 16 to 20 symptoms and 39 to 64 in SSS. Increased symptom severity >10 on SCAT3 has been shown to lead to longer return to play[254], a number by far exceeded in our studies. Amongst the most common symptoms were fatigue and nervousness/anxiousness. Three athletes in *Paper I* did not suffer from any symptom and the athletes in Paper *II-IV* all reported at least one symptom, as ongoing PPCS was an inclusion criterion for these studies. Ice hockey players retiring due to symptoms in *Paper I* had higher scores on IES-R in the domain of hyperarousal, indicating issues with mood and vigilance compared with

those athletes retiring due to fear of additional concussions. Since the hyperarousal subscale of IES-R was the only independently differing between groups, the correlations between IES-R and SCAT5, represent a correlation between PPCS burden and issues with mood and vigilance. Athletes with PPCS in *Paper II* and *IV* had symptoms of anxiety and depression at a clinically significant level. In *Paper IV*, SRC athletes additionally suffered from mental fatigue and experienced executive dysfunction.

A single SRC or mTBI does not necessarily result in PPCS, although there seem to be a cumulative effect with more SRCs leading to a higher risk of PPCS especially when a new SRC occurs within 10 days of a previous SRC and if the number exceeds three[255]. In our studies we could not demonstrate a correlation between the number of concussions and the severity of PPCS. However, we have small and selected cohorts of athletes with many SRCs and severe PPCS, not enabling us to draw firm conclusions regarding this correlation. We also do not have any data about sub-concussive injuries, which may add to the SRCs effect on the development of PPCS and on brain pathology, such as atrophy[17], white matter integrity[256], vestibulo-ocular function[257] and performance on neuropsychological tests[258]. In *Paper I* most players stated that for each new SRC they were more susceptible for a new SRC, that less and less trauma was needed to induce an SRC. A similar experience was described by the athletes recruited from Lund in *Paper II-IV* (data not presented in the articles), since the athletes did experience an increased susceptibility for new injuries. This experience of susceptibility does affect the decision to continue sport participation or to retire permanently. A higher rating of the fear of re-injury have been found to correlate with PPCS[259], which may indicate that these athletes rate their symptoms as more severe and this in turn can lead to the decision of retirement.

Every disease, somatic or psychological, may cause a reduction in perceived overall health and QoL if symptoms are grave. In many diseases it is a cornerstone of the diagnosis, the disease must be debilitating enough to cause interference with daily life to lead to a diagnosis. If a person suffers from a symptom, but it does not affect daily life, it is not commonly regarded very seriously. On the other hand, if an athlete suffers severe symptoms impacting everyday life with impaired ability to work, attend school, execute activities of daily life, or attend social activities as wished, the disease or state is regarded much graver. Following SRC and mTBI, increased levels of anxiety, depression, and PPCS, have been found to lead to lower QoL[27, 213, 260]. In our studies we do not only highlight which symptoms are present and at what severity, we can also state with certainty that these symptoms have a negative impact on the overall health and QoL of athletes with SRC. In *Paper I* athletes had a reduced QoL measured with SF-36, with the lowest scores in the domains of role physical and vitality, indicating difficulties with work or daily activities due to poor physical health and feelings of tiredness[214]. In *Paper II* athletes reported a high negative impact on their QoL due to dizziness in all three domains of physical,

emotional, and functional aspects of the DHI. Finally, in *Paper IV* athletes reported impaired life-satisfaction on LiSat-11.

In both *Paper I* and *IV* we observed that the athletes had a reduced capacity to work or study full-time, in *Paper IV* 50% of SRC athletes were on sick leave. In Sweden 2023 7.7% was unemployed according to the Central Bureau of Statistics[261] and about 3.9% were on sick-leave according to the National Insurance Office[262]. It is well-known that post-concussion symptoms often are exacerbated by physical and mental activity, noisy environments, and social activities, so it is not surprising that these athletes cannot attend work, school, sports, or social activities as prior to their SRCs. Athletes with SRC and PPCS also have impaired ability to work or go to school compared with recovered SRC athletes[26]. The incapability of doing these tasks can further lead to a negative spiral with enhanced symptoms and even worse QoL. Unemployment has been correlated to worse physical and mental health[263, 264], ultimately leading to a reduced QoL. As a high-performing elite athlete, it can be particularly difficult to not be able to return to work, or to sport as in their case, as their professional role often extends to their personal identity. In a qualitative study by several of the co-authors in *Paper I*, elite athletes retiring due to concussion were interviewed. The athletes described pressure not to quit their sport, and experienced that this resulted in more headaches, fatigue, and cognitive symptoms. Nevertheless, the athletes wanted to return as soon as possible even if symptoms persisted. The decision to retire was described as extremely challenging and traumatic, and many experienced a loss of identity and depression[265]. In other studies, similar results have been found with athletes tending to underreport their concussion symptoms and continue playing at the time of the event[266-268].

There are several factors that can influence the development of PPCS and contribute to its continuation. Psychiatric history, physiological health, sleep difficulties, insufficient social support, certain personality traits such as low resilience, internalizing, risk positive behaviors, or a 'all-or-nothing' approach can lead to higher risk[254, 255, 269]. It has been suggested that females are particularly sensitive to concussions, reporting more symptoms and having longer recovery times[54]. There are diverging results concerning age, some studies indicating young age at first SRC or age over 40 as related with worse outcome[255, 269]. However, neither sex nor age was associated with time to recovery from PPCS in a follow up study of SRC athletes[26]. We could not see any correlations between sex or age and PPCS outcome in *Paper I-IV*. Head- and neck pain following SRC commonly lead to states of chronic pain in patients with PPCS, which further negatively affects QoL[270]. In a study of patients with posttraumatic neck pain, patients with a lower education level, anxiety, depression, and especially a low level of acceptance, had more pain[271]. Patients with pain frequently suffers from anxiety, depression, unfavorable experiences of health, and limitations in ability to work[272]. In *Paper I-IV* our included athletes had a wide range of post-concussion symptoms, depression, anxiety, impaired ability to work, reduced level of education compared to controls.

Factors that most probably are inter-related and amplifies each other, resulting in a cumulative negative impact on their overall QoL.

A fundamental challenge with finding and eventually treating athletes with PPCS is the non-specificity of the symptoms. Post-concussion symptoms are common in numerous diseases and can exist even without an SRC diagnosis. Moreover, the causes of PPCS may be multifactorial, and psychological processes and pre-injury factors could contribute to how symptoms are experienced and reported[273]. It has been suggested that applying a network analysis to cluster symptoms, might be beneficial in choosing treatment strategy for patients following mTBI[274]. We argue that biological processes are indeed present at prolonged times post-injury, supported by *Paper II-IV*, although receiving a diagnosis may not be the most important factor for these athletes. Instead, information about expected natural course following SRC and PPCS, proper social support, and individualized symptom-based treatment, may be the best strategy to minimize symptoms and improve quality of life.

Diagnostics and Pathophysiology

In this thesis we investigated the diagnostic utility of vestibular laboratory tests, CSF biomarkers, psychometric neuropsychology, and ultra-high field strength MRI, in athletes with SRC and PPCS. We found evidence of a peripheral vestibulopathy with injury to the inferior vestibular nerve, ongoing neuroinflammation, cognitive dysfunction and microstructural alterations indicating white matter pathology.

Psychometric neuropsychology

In *Paper III* cognitive function as measured with the RBANS global score, was impaired in 10 of the 24 SRC athletes. *In Paper IV* SRC athletes performed below expectations on RBANS, SDMT and d2, indicating a decline in total cognitive function including immediate memory, working memory, delayed memory, attention, language function, visuospatial/constructional ability and processing speed. In both papers, statistical analyses were conducted on RBANS global score, not the five separate index scores in order to avoid multiple comparisons and statistical error. In *Paper IV* we reported the index scores to present what areas of cognitive functions were most afflicted. RBANS index of immediate memory, verbal functions, and attention functions was particularly sensitive in discriminating SRC athletes, impairments that may affect the athlete's ability to perform both in school and at work.

In *Paper III* and *IV* we evaluated correlations between cognitive results with CSF biomarkers and with white matter alterations as seen with DTI and DKI but did not

find any convincing associations. To evaluate if a reduced hippocampal volume was associated with impaired memory function, we correlated volumetric measures of the hippocampus with RBANS list learning and list recall, but again these did not correlate. Similarly, the number of SRCs and SCAT5 data did not correlate with the psychometric neuropsychology tests. The lack of correlations may of course reflect the reality. However as mentioned earlier, we have small and homogenous cohorts and are therefore not confident about drawing conclusions about the absence of correlations.

A neuropsychologist performed all tests in a traditional face-to-face method, which may have been very beneficial in our patient group who had several cognitive dysfunctions that could have influenced the execution of the tests. For example, a decline in attention and language function may make it difficult to understand instructions and maintain concentration during a test. At a face-to-face consultation the psychologist has the possibility to check that the patient understands the task and correct if needed, to improve the validity of the test[132]. A traditional face-to-face interview is more time consuming and hence more costly than digitalized tools[131]. In our relatively small cohort, the economic benefit of digitalized tests was not that big. However, the gain of the neuropsychologist to being able to improve test accuracy in this group of athletes which may suffer various symptoms influencing test results, was very important.

Vestibular deficits

In *Paper II 21* SRC athletes with PPCS did vestibular laboratory tests consisting of video head impulse test (vHIT), caloric test, cervical vestibular evoked myogenic potentials (cVEMP), videonystagmography (VNG), posturography, pursuit eye movements (PEM), and an audiogram. Depending on the results the athletes was diagnosed with a vestibular deficit (12 of 21 SRC athletes), and these were sub-classified into a central (n=0), peripheral (n=9), or combined (n=4) origin. We observed that many SRC athletes differed from controls on vHIT, cVEMP, VNG and posturography, significantly on vHIT and cVEMP. With vHIT it is possible to test all three semicircular canals and the cVEMP tests the saccule, in each ear. We found that vHIT was commonly affected together with the ipsilateral cVEMP, which are dependent on the integrity of the vestibular nerve. The inferior branch of the vestibular nerve is tested directly by cVEMP and thru the posterior semicircular canal and sacculus by vHIT. Both vHIT and cVEMP confirmed the location of injury to the inferior vestibular nerve, in a repeatable manner. The results of the caloric test, VNG, PEM and posturography were inconclusive, but did not argue against an injury to the inferior vestibular nerve. We analyzed volumetrics of grey and white matter in the cerebellum, and diffusion metrics in the three cerebellar peduncles. No difference in cerebellar volumes or DTI metrics was seen, and only minor changes in DKI metrics with a decrease in MK in the superior and inferior

cerebellar tracts and a decrease in RK in the superior cerebellar tracts were observed. In this paper we argued that the lack of central pathology supported our hypothesis of a peripheral vestibular injury. The mechanism behind the lesion was not established. Hypothetically, the shorter route of the inferior branch in the temporal bone compared with the superior branch of the vestibular nerve[275] may make it more prone to stretching injuries caused by acceleration-deacceleration relative to the skull base. A surgical experience, not yet confirmed by clinical studies, is that the vestibulocochlear nerve is more sensitive to surgical manipulation and to radiation compared to other cranial nerves. Hence, it may be a particularly sensitive cranial nerve that might lose function by the rotational forces at time of SRC.

It is well known that vestibular dysfunction with dizziness, vertigo and disturbed vision is a consequence of SRC. During the latest Consensus on Concussion in Sports meeting it was discussed, but not decided, to include Vestibular-Ocular Motor Screen (VOMS) for all concussion evaluations, and instead a dual gait task was recommended to be included in the new SCAT6[13]. In *Paper I-IV* almost all athletes reported balance problems, dizziness, blurred vision, and nausea or vomiting on SCAT5 and in *Paper II* athletes with vestibular dysfunction had higher scores on DHI and HADS. It is well recognized that vestibular dysfunction causes substantial morbidity following SRC, and our results may open possibilities for targeted therapies.

Our results suggesting a peripheral cause are supported by a few earlier studies. A peripheral vestibular disorder was found four months post-SRC[276]. In TBI patients acute unilateral peripheral vestibular loss has been observed[277] and degeneration of the superior and inferior vestibular nerves seen *post-mortem*[278, 279]. However, previously the vestibular dysfunction following concussion has been suggested to mainly be correlated to central pathology as a consequence of white matter pathology. As will be discussed later, the rotational forces arising from an SRC are believed to disrupt white matter integrity[280, 281]. White matter alterations have been found to correlate to vestibular dysfunction in mTBI patients, but vestibular laboratory tests were not reported[282]. Furthermore, a central cause has been suggested based on lack of abnormality on tests of peripheral vestibular structures at 10-14 days[283, 284] and four to six months after concussion[285], without central structures being tested. To our knowledge, only one previous study test both central and peripheral structures, a cohort of mixed-TBI patients 2-77 days post-injury showing correlations between central microstructural alterations on DTI and vestibular dysfunction[286]. In *Paper II* we argue against a central cause, since we did not see any convincing microstructural alterations on DTI or DKI, no decreases in cerebellar volumes, and no central patterns on the vestibular laboratory tests. For this study we used MRI evaluation of the cerebellum. Today we know a little more about these athletes. The vestibular system is dependent on multisensory integration demanding function in several central structures of the brainstem, cerebellum, and deep supratentorial nuclei, numerous supratentorial cortical areas, and projections

between these structures[174-176]. Therefore, the widespread white matter alterations seen in *Paper IV* could influence vestibular function in these athletes, maybe explaining the four athletes having combined origin of their vestibular deficit in *Paper II*. We also studied the posturography results more in depth and found that athletes used more energy to maintain balance during normal conditions and had poorer sensorimotor adaption compared with the control group, leading to a reduced postural control and motor learning. This implies that central sensorimotor processes were not working efficiently at long-term following SRC[287].

Athletes with SRC and PPCS have impaired vestibular function with some of the pathology explained by an injury to the inferior vestibular nerve. However, it is probable that multiple pathological processes coexist in the brain which causes several types of vestibular pathology that are expressed differently amongst patients.

White matter injury

In *Paper IV* SRC athletes had disrupted white matter microstructure detected by 7T DKI. SRC athletes had diverging results compared to controls in 16% of DTI tracts and 35% of DKI tracts with the global white matter metric value differing in DKI FA, RD, AK and RK. The microstructural alterations detected at an average time of 2.6 years since their last SRC suggest persisting, or even evolving pathology in the WM. This was further supported by the correlations between several of the DTI and DKI metrics with the axonal injury marker NfL[190]. GFAP, a biomarker of astrogliosis[83], did not correlate with DTI or DKI metrics. Serum NfL and GFAP levels have been evaluated several years following injury[85], and while NfL and GFAP correlated with WM atrophy and DTI measures of axonal injury, the prognostic utility of GFAP was inferior to that of NfL[85].

At time of an SRC, rotational forces lead to tension and stretching of brain structures and cells, causing the most harm in junctions between different types of tissues with unmyelinated axons in the white matter being especially vulnerable[65, 66, 75]. The rotational forces are believed to disrupt white matter integrity which is considered to be a major contributor to the sequelae of SRC[66, 280, 281].

DTI is sensitive to the microstructural integrity of white matter fibers and axonal injury[149, 154] and has revealed reduced white matter integrity, not explained by structural damage or volume loss, following SRC[88, 165, 280, 288]. As explained by the rotational forces acting upon the whole brain, a general pattern of abnormalities has been observed[158, 160]. The microstructural changes found in *Paper IV* were widespread in the white matter, present in long tracts, central structures, in both hemispheres and were mainly supratentorial. They were not explained by volume loss, since grey and white matter volumes did not differ between SRC athletes and controls. Tension-driven destabilization of neurofilaments and axons may lead to disconnection of axonal integrity and scar-formation of varicosities along the axis

of an axon, axonal beading[73, 74], which may explain the increased AK in *Paper IV*[160, 163]. Axonal beading with increased AK and MK has also been found in an animal model of mTBI[289]. In *Paper IV* we observed increased DKI FA and AK, and decreased RD and RK, which according to a *post-mortem* study of SRC athletes has been seen with axonal beading, gliosis and astrogliosis[91]. In our athletes the pathology may be dominated by axonal and white matter injury, since we observed correlations between diffusion metrics and NfL, but not GFAP. However, in *Paper III* we see signs of ongoing long-term neuroinflammation with increased levels of cytokines, chemokines and proinflammatory proteins in the CSF of SRC athletes.

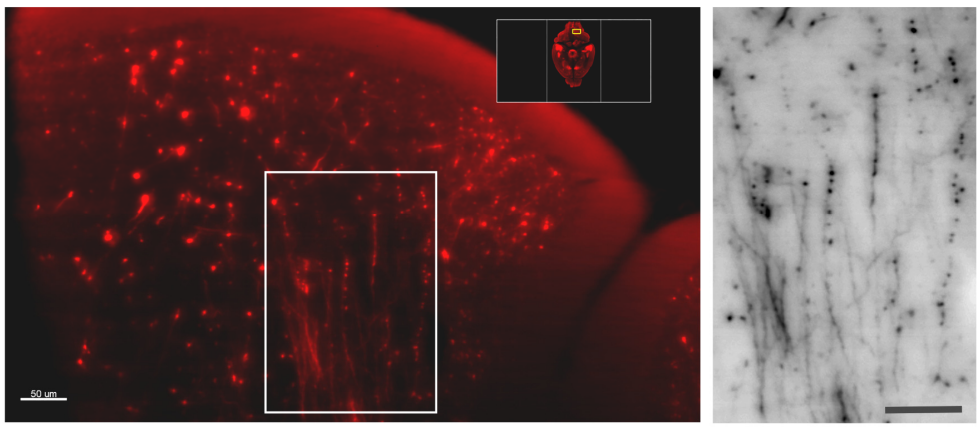

Figure 14. Axonal beading
Axonal beading in a mouse brain subjected to central fluid percussion injury to mimic a diffuse traumatic brain injury. Courtesy of *Ilknur Özen*.

Neuroinflammation

Forces applied at time of an SRC may be accompanied by a neuroinflammatory cascade, which can continue over years leading to a maladaptive chronic inflammatory state, further exacerbating the initial injury[90]. In *Paper III* we examined 25 CSF biomarkers of inflammation and found increased levels of IL-2, TNF-α, IL-15, TNF-β, VEGF, Eotaxin, IP-10, and TARK, and decreased levels of Eotaxin-3, in SRC athletes compared with controls. Cytokines are often classified as pro- or anti-inflammatory, which may be an oversimplification since many have a dual role determined by the activation signal, the timing and the target cell[195]. The temporal aspect is of particular importance since varied levels of cytokines have been found at varied timepoints following TBI[76, 78, 86, 196]. In *Paper III* we observe elevations of many cytokines at a mean of 17 months post-SRC, many of which may have both pro- and anti-inflammatory roles. Nevertheless, these results indicate a persistent inflammatory process in the brains of athletes with PPCS several months or years following injury.

Direct evidence of the inflammatory response in humans following SRC is rare, but in a *post-mortem* study of SRC athletes deceased due to other causes shortly following an SRC, clusters of activated perivascular microglia were observed in subcortical white matter tracts[290]. In a large longitudinal study increased levels of serum cytokines was observed for one-year post-mTBI[86], which further strengthens the idea of a prolonged inflammatory process. However, peripheral blood was analyzed reflecting systemic inflammation, which has large differences to brain parenchymal cytokine concentrations as shown in severe TBI[196]. In mice models of mTBI, elevated levels of cytokines in the serum and brain have been observed[76, 291] and parenchymal neuroinflammation seen on histology and micro-PET imaging[81]. CSF sampling is invasive and not without risks for the patient, with the most common side effect being leakage of spinal fluid and post-puncture headache. Therefore, it is of interest to explore other indirect measures of inflammation, such as PET imaging with different ligands depending on what is to be examined. In PET studies following SRC, signs of neuroinflammation in the hippocampus has been observed[87], neuroinflammation and hippocampal atrophy seen after retirement and seven years after injury[88, 89], and increased GFAP levels in the blood acutely and lasting for years following last SRC[84, 85].

Reactive pathological processes following SRC, such as astrogliosis, microglial activation, axonal beading, DNA damage and neurodegeneration may be a result of long-lasting inflammatory processes[73, 80, 91-93]. In models of both single and repeated mTBI, axonal injury and neuroinflammation play significant roles in the neuropathological events that include ongoing white matter degradation up to 12 months post-injury and chronic functional impairments[292, 293]. In mTBI patients, the inflammatory response correlates with functional and cognitive outcome[78, 294] and growing evidence suggests that inflammatory markers may predict recovery following brain injury[295]. Several of these processes are supported by the results of this thesis - in *Paper II* we see injury to a specific peripheral nerve, in *Paper III* neuroinflammation and in *Paper IV* white matter alterations. We did not find evidence of neurodegeneration as the SRC athletes in *Paper II* and *IV* had normal brain volumes. As mentioned before the temporal aspect of TBI and SRC are very important to acknowledge when interpreting study results. The patients have different clinical presentations and different pathology depending on at which time post-injury they are investigated, and if they suffer symptoms or not during the evaluation. The general aim of this study was to evaluate symptoms, diagnostic tools, and the pathophysiology behind long-term persistent symptoms following SRC. Hence, we have data from one time-point for athletes with PPCS. Regarding the pathology discussed above, it is probably an evolving process. Presumably, it starts as an acute injury with white matter injuries and axonal stretching initiating an inflammatory response, and in some individuals, it may proceed into a chronic inflammatory state with white matter and neuronal injuries that is followed by neurodegeneration. It is possible that our studies captured the 'in between' stage of neuronal injuries and inflammation, and if we would bring these athletes back in 20

to 30 years, or *post-mortem*, we may see neurodegenerative changes. For the sakes of these and future athletes, let's hope this is not the case. Hopefully the disease may heal by itself as years pass, or that scientists have discovered tools to cease the process before it hits the final non-reversable stage of brain atrophy.

Strengths and weaknesses

The studies included in this thesis has several limitations. In all four studies we aimed to include athletes with self-reported SRCs and there are potential selection and recruitment biases in this process. It has previously been indicated that athletes are reluctant to report concussions, which may lead to an underestimation of injuries[266]. However, athletes with greater symptom burden may be more motivated to participate. We might therefore have selected a cohort of highly motivated and symptomatic athletes, possibly missing those with milder symptoms or those who we did not manage to reach out to. Furthermore, we wanted to evaluate long-term persistent post-concussive symptoms, leading to highly characterized cohorts and relatively small sample sizes. Therefore, we do not state that this thesis is representative of all SRCs, and specific numbers should not be translated into a general population.

Several of the tests included in Paper II, III, and IV can influence one another and it is of importance that there was an order to which the tests were conducted. Vestibular laboratory tests are sensitive and can be influenced by *e.g.* tiredness and previous MRI[296], obviously the same applies to the neuropsychology tests. Furthermore, the MRI may be influenced by CSF drainage and cannot be completed after a lumbar puncture when analyzing these discrete alterations seen in our cohort. Therefore, the athletes were scheduled for a specific set up of examinations lasting two days. Initiated in the morning with an interview to update the medical history and answering the SCAT5, followed by the neuropsychology tests. After a break of 30-60 minutes, the vestibular laboratory tests and an audiogram were conducted, or these tests were performed during the morning the following day. In the afternoon the MRI-protocol lasting about 60 minutes excluding preparations was done. Lastly a lumbar puncture was performed followed by an hour of bed rest to minimize the risk of post-puncture headache. These athletes were thoroughly examined in several aspects of SRC outcomes and potential pathophysiology with the aim of giving an extensive representation of the entity of SRC. This was demanding for the athletes, time consuming, and costly, why these studies are relatively rare. This also explains why we were not able to include larger cohorts, which limits the statistical power of these studies probably partly contributing to the lack of correlations seen in the papers. The homogeneity of our athletes, with all having relatively severe PPCS, may also explain why we did not see as many correlations as expected amongst these examinations.

In several of the exploratory studies here, we did not correct for multiple comparisons. We acknowledge that the absence of such corrections may increase the risk of type I errors. However, correction also increase the risk of type II errors which is especially unfavorable in exploratory studies where a high sensitivity is essential.

The 7T MRI studies enables the acquisition of T1-weighed images at a submillimeter resolution benefitting volumetric calculation, DTI, and DKI. However, it is sensitive for motion and subcortical image artefacts caused by B1+ inhomogeneity[297], leading to exclusion of some subjects. In the diffusion analysis in *Paper IV*, DKI yielded higher effect sizes than DTI, being more sensitive in detecting white matter alterations. However, DKI is performed with longer echo times reducing the baseline signal-to-noise-ratio, which is often compensated for by decreasing the spatial resolution in DKI compared with DTI. In such a case, DKI might not demonstrate any additive values compared to DTI, therefore it has not yet been established whether DKI should replace DTI in clinical routine. DTI and DKI differ in sensitivity[57, 160, 161, 163], and can be sensitive to different changes at different time-points[125, 156], why their combined use as in *Paper II* and *IV* is advantageous.

Conclusions

Athletes with SRC and post-concussive symptoms experience long-term physical and mental difficulties that negatively affect their quality of life. Persistent symptoms following SRC are associated with several neurocognitive impairments including executive dysfunction, as well as signs of depression, anxiety, and mental fatigue. A sports related concussion may induce a multitude of pathologies in the peripheral and/or central parts of the vestibular system which correlates to problems with dizziness or impaired balance. The vestibular laboratory findings suggest an injury to the inferior vestibular nerve, however widespread white matter injury may also contribute to a combined origin of the vestibular impairment seen in the SRC athletes. Pathological processes in the brains of athletes with PPCS are present several months to years following SRC and involves neuroinflammation, axonal injuries, and global white matter alterations.

Paper I

- Ice hockey players who retired due to SRC reported PPCS, issues with mood and vigilance (hyperarousal), and a reduced quality of life.
- A higher burden of PPCS was associated with higher hyperarousal scores and a lower quality of life.

Paper II

- SRC athletes reported severe PPCS, anxiety, depression and dizziness causing a negative impact on their quality of life.
- SRC athletes with PPCS did not have reduced cerebellar grey or white matter volumes. On 7T DKI three metrics differed between athletes and controls, which was not enough to draw conclusions about potential white matter alterations.
- SRC athletes with PPCS had increased risk of vestibular dysfunction, of peripheral or combined origin. A combination of pathology on ipsilateral vHIT and cVEMP argues for an injury to the inferior vestibular nerve.
- Vestibular dysfunction on vestibular laboratory test correlated with higher scores on the dizziness handicap inventory.

Paper III

- SRC athletes reported severe PPCS, and 10 out of 24 athletes had impaired cognitive function.
- SRC athletes with PPCS had increased levels of eight CSF biomarkers of inflammation, and one decreased, compared to matched athletic controls. These results implied a persistent inflammatory process, at a median of 17 month since the last SRC.

Paper IV

- SRC athletes reported severe PPCS, anxiety, depression, mental fatigue, impaired executive function, a decline in life satisfaction, and had cognitive dysfunction measured by several psychometric neuropsychology tests.
- SRC athletes with PPCS had signs of white matter alterations on 7T DKI and DTI which correlated with the axonal injury marker NfL. Signs of neurodegeneration as declined brain volumes of supratentorial grey and white matter were not observed.

Future directions

It is established that SRC can cause long-term disabilities in a subset of predisposed athletes leading to a functional decline and an impaired ability to continue sport participation, work, go to school, socialize, and keep up tasks of daily life. This thesis provides knowledge about these individuals and suggests several underlying pathological features. We did not study the natural course of SRC, which individuals heal without sequelae, which ones gets PPCS that spontaneously resolves, which ones continues to have prolonged PPCS, nor their temporal aspects of their symptoms. Studies answering these questions are time and financially difficult studies to conduct. Large cohorts of motivated athletes need to be followed for years, if not decades, with repeated costly examinations at regular intervals. It is possible and will be necessary to establish a firm background about the pathophysiological processes of SRC and lay a foundation for future interventional studies with the aims of preventing, curing or alleviating PPCS.

On a personal level, there are some studies I would like to continue. I would like to complete the resting state functional MRI study that has been initiated in our cohort of PPCS athletes, but not yet analyzed, and a Tau-PET study using a 2nd generation tau-PET tracers that has been initiated. It would be interesting to do a follow up study of our included athletes, 10-15 years after first examinations, to see if we can establish any conclusion about the temporal aspects of SRC pathophysiology. As a resident in neurosurgery, during work I am mostly encountering patients with moderate and severe TBIs admitted to our neurointensive care unit, therefore it would be stimulating to extend my research to also include moderate and severe TBIs.

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