Oslo Sports Trauma
RESEARCH CENTER

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Head Impacts in Football

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“When in doubt, sit them out!”

(Aubry et al. 2002)

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Summary

The background for this study was a concern that heading and sub-concussive head impacts could cause cognitive impairments among football (soccer) players. Controlled heading is however, no longer considered as a major risk factor for developing cognitive deficits, but the neuropsychological consequences of football-related sub-concussive and concussive impacts await further confirmatory investigation. In addition, no prospective study has previously investigated the acute effects of sub-concussive head impacts on neuropsychological performance.

Thus, the overall main objective of this study was to examine the effect of minor head impacts in professional football with respect to signs of neuronal tissue damage or reduced neuropsychological function.

The main effect variables in the study were the changes in serum concentration for protein S100B, a biochemical marker of brain injury, and neuropsychological performance as assessed by a commercially available computerised test battery (CogSport).

The participants were players in the Norwegian professional top league (Tippeligaen). Baseline blood sampling and neuropsychological testing were performed for all players in Tippeligaen prior to the 2004 and 2005 seasons (>70% estimated participation rate). A player who experienced a head impact during a league match was followed up with blood sampling within one hour after the match and the following morning along with a neuropsychological follow-up test. Videotapes of the incidents were collected from the Norwegian Broadcasting Corporation (NRK) and reviewed. A group of players without head impact was also tested after a league match to serve as controls.

Paper I: The reproducibility for the CogSport test was investigated based on 232 Norwegian professional football league players completing two consecutive neuropsychological tests at the baseline testing prior to the 2004 season. The computerised test battery showed excellent reproducibility for the reaction time measures and these measures were therefore recommended as the test's primary outcome variables. However, a small but significant practise effect was found and a dual baseline testing with rejection of the first test is advised to minimise this effect.

Paper II: In this paper we found no effect of previous concussions and self-reported heading exposure on the neuropsychological performance in Norwegian professional football players. The results were based on the neuropsychological test results for the 271 players who were tested at baseline 2004. The vast majority (96.1%) of these football players revealed in addition no evidence of cognitive impairments when compared to normative data.

Paper III: This paper discussed the results from the analysis of the S100B samples. In addition to the head impacts and the controls that were recruited from the regular league matches, three teams (N=48) performed one high-intensity exercise session without heading and one low-intensity exercise with heading exercises. The serum levels of S100B were measured before the first training and within one and twelve hours after each of the two training sessions.

Of the total of 228 head impacts registered during the two football seasons, 65 (28.5%) impacts were followed up with blood samples one hour after the impact and 40 (17.5%) the following morning. Both football training and football matches led to a transient increase in serum S100B up to the cut-off level for what is considered as borderline pathological values. Minor head impacts did not cause an additional increase in the S100B level beyond what was measured after a regular match. All serum S100B values were below what is measured for hospital-admitted minor head trauma patients. Thus, there is no evidence suggesting that there is significant brain tissue injury associated with minor head impacts in football. However, the S100B sample might not be an ideal marker for brain injury in athletes due to the increases seen after physical activity only.

Paper IV: A total of 44 (19.3%) of the 228 identified head impacts in the two seasons were followed up with neuropsychological testing the following day. The video analyses indicated that there seemed to be a shift towards a concentration of the more severe incidents in the followed-up group. Nevertheless, in more than 60% of these incidents the player went back to play immediately after the impact and only six of the impacts were reported in as concussions that resulted in time-loss from football activities.

Still, an acute reduction in neuropsychological performance was found after these minor head impacts in football, even in allegedly asymptomatic players. However, the followed-up impacts represented the more severe spectrum of the mild head traumas in football. Still, only six of these impacts were reported as concussions. The test performance was reduced from one year to the next in footballers who had experienced head impacts during the season, but

all tests were within the normal range. Consequently, the clinical significance of this finding is uncertain.

Sammendrag

Bakgrunnen for denne studien var en bekymring for at nikking og små hodeskader kunne føre til kognitive svekkelser hos fotballspillere. Kontrollert nikking har derimot i det siste nærmest blitt avskrevet som en risikofaktor for å utvikle slike skader, mens følgene av gjentatte milde hodeskader med eller uten hjernerystelse som resultat, er ikke avklart. Ingen tidligere studier har prospektivt undersøkt den akutte nevropsykologiske effekten av slike milde hodeskader hos toppidrettsutøvere.

Studiens hovedmål var derfor å undersøke den akutte effekten av små hodetraumer i elitefotball med tanke på å avdekke eventuelle skader på nervevevet, eller nedsatt nevropsykologisk funksjon. Et hodetraume er her definert som et potensielt skadelig sammenstøt mot hodet under en kamp.

Effektmålene som ble benyttet, var endring i serumnivået av proteinet S100B som er en markør på nervecelleskade, samt nevropsykologisk funksjon målt ved hjelp av et databasert nevropsykologisk testbatteri (CogSport).

Deltakerne i studien var alle spillerne i den øverste fotballdivisjonen for menn i Norge (Tippeligaen) i sesongene 2004 og 2005. Baselinetesting av alle spillerne i Tippeligaen ble gjennomført før de respektive sesongene og inkluderte blodprøvetaking og nevropsykologisk testing (deltakerprosenten ble estimert til >70 %). Oppfølgingsprøver ble så tatt av de spillerne som var utsatt for et hodetraume i en Tippeligakamp i løpet av sesongen. Det ble da tatt en blodprøve innen en time etter kampslutt samt påfølgende morgen, hvor også den nevropsykologiske testingen ble gjennomført. Video av hendelsene ble innhentet fra NRK og analysert. Kontrollgruppen bestod av en gruppe spillere som ble testet på samme måte etter en Tippeligakamp der de ikke hadde vært utsatt for noen hodetraumer.

Artikkel I: Reproduserbarheten for CogSport-testen var basert på undersøkelser av 232 spillere som gjennomførte to påfølgende tester ved baselineundersøkelsene forut for 2004-sesongen. Det databaserte testbatteriet viste en svært høy reproduserbarhet for reaksjonstidsmålingene. Målingene av reaksjonstid ble derfor anbefalt som hovedeffektvariabler for den videre benyttelsen av testen. Men selv for reaksjonstidsvariablene ble det avdekket en liten, men signifikant, læringseffekt. Denne

effekten opptrer hovedsakelig mellom første og andre test, og det er derfor anbefalt å gjennomføre en ”prøveomgang” før baselinetestingen.

Artikkel II: Nevropsykologisk funksjon ble undersøkt hos 271 fotballspillere forut for 2004 sesongen og korrelert med egenrapportert forekomst av tidligere hjernerystelser og nikkefrekvens. Men verken tidligere antall hjernerystelser eller nikkefrekvens hadde noen effekt på spillernes testprestasjon. Sammenlignet med normative data, så var i tillegg hele 96,1 % av spillerne innenfor normalen.

Artikkel III: I denne artikkelen, som tok for seg blodprøveresultatene, så ble testprotokollen utvidet med to kontrollgrupper. Dette var spillere fra tre lag (N=48) som gjennomførte en høyintensiv trening uten å nikke ball, samt en ren nikketrening med svært lav intensitet. Blodprøver ble innhentet før første trening samt en og tolv timer etter de respektive treningene.

I de to sesongene i Tippeligaen ble det avdekket 228 hodetraumer (19,6 per 1000 kamptimer). Det ble tatt blodprøver innen en time i 65 (28,5 %) av tilfellene og ved 40 (17,5 %) av tilfellene ble det også tatt blodprøve neste morgen. En signifikant forbigående stigning i S100B ble funnet både etter kamp og trening. Små hodetraumer førte ikke til en ytterligere stigning utover det som ble målt etter bare å ha spilt en seriekamp. Alle S100B-verdiene var i tillegg på trygg avstand fra de verdiene som er påvist hos pasienter som er blitt brakt til sykehus med milde hodetraumer. Det er derfor ingen grunn til å mistenke at små hodetraumer i fotball gir store skader på nervevevet. På den annen side så viste det seg at S100B var svært påvirkelig av fysisk aktivitet og er således ingen ideell markør på hjerneskade etter små hodetraumer hos idrettsutøvere.

Artikkel IV: I alt 44 (19,3 %) av de 228 hodetraumene ble fulgt opp med en nevropsykologisk test dagen etter kampen. Resultatene fra videoanalysen kan tyde på at det var en opphopning av de mer alvorlige traumene i den gruppen som var fulgt opp. Men på den annen side så fortsatte spillerne kampen i 60 % av tilfellene, og kun 6 hjernerystelser, som førte til fravær fra trening eller kamp, ble rapportert for denne gruppen.

Selv om dette skulle indikere at det generelt var snakk om svært milde hodeskader, så ble det påvist en redusert prestasjon på de nevropsykologiske testene for hodetraumegruppen, også for spillere som ikke rapporterte noen symptomer etter hendelsen. De spillerne som ble testet, representerte riktignok de mer alvorlige hendelsene innenfor spektrumet av milde hodeskader,

men likevel var kun 6 av disse rapportert som hjernerystelser. Videre fant vi også en redusert testprestasjon fra det ene året til det neste hos de spillerne hvor vi hadde registrert en eller flere hodetraumer i løpet av sesongen. Men alle disse testene var innenfor normalområdet, og den kliniske betydningen av dette funnet er dermed usikkert.

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List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. Reproducibility of computer-based neuropsychological testing among Norwegian elite football players. Straume-Naesheim TM, Andersen TE, Bahr R. Br J Sports Med 2005a; 39 Suppl 1: i64-i69.

II. Effects of heading exposure and previous concussions on neuropsychological performance among Norwegian elite footballers. Straume-Naesheim TM, Andersen TE, Dvorak J, Bahr R. Br J Sports Med 2005b; 39 Suppl 1: i70-i77.

III. Minor Head Trauma in Football and Serum Levels of S100B. Straume-Naesheim TM, Andersen TE, Jochum M, Dvorak J, Bahr R. Neurosurgery 2007; Accepted for publication.

IV. Do Minor Head Impacts in Football Cause Concussive Injury? – A Prospective Case Control Study. Straume-Næsheim TM, Andersen TE, Holme IM, McIntosh AS, Dvorak J, Bahr R. Brain 2007; Submitted

Introduction

Football and Brain Injuries

Needless to say, football (soccer) is one of the most widespread and popular sports in the world. Approximately 250 million active footballers are registered by FIFA's 204 member countries, in addition to the even higher number of players outside of the officially organised sphere (FIFA, 2000). Football is a vigorous sport, averaging one event with an injury potential every sixth second of a competitive match at the professional level, resulting in approximately one injury every 45 minutes, or one injury per team per match (Rahnama *et al.*, 2002). About 6% to 13% of these injuries are recorded as injuries to the head (Andersen *et al.*, 2004b; Fuller *et al.*, 2005), mainly as a result of aerial challenges for the ball (Andersen *et al.*, 2004a; Fuller *et al.*, 2005).

Heading is one of the unique features of football, where an unprotected head is used purposefully to control and advance the ball. This exposes the players to a risk of head injuries both as a direct consequence of impacts of the ball (Pickett *et al.*, 2005), but mainly from collisions with other players (Andersen *et al.*, 2004a; Fuller *et al.*, 2005; Pickett *et al.*, 2005). The subsequent consequences for the brain have been the subject of repeated attention among the players, coaches, referees, parents, media and the official football associations. FIFA has through its associated Medical Assessment and Research Centre (F-MARC) been one of the organisers of two International Symposia on Concussion in Sport (Aubry *et al.*, 2002; McCrory *et al.*, 2005), and prior to the World Cup in Germany the International Football Association Board gave referees the authority to severely sanction what were felt to be injurious fouls such as intentional elbows to the head (Dvorak *et al.*, 2007a). In addition, this concern has also initiated the development of protective football head gear (Delaney and Drummond, 1999).

As early as in 1972, Matthews introduced the term footballer's migraine following a case series of 5 footballers who described classical migraine after receiving blows to the head while playing football. A few years later, based on a series of cross-sectional studies using neurological exams, neuropsychological tests, computer tomography (CT) scans and electroencephalography (EEG) on active and older retired Norwegian football players,

Tysvaer (1992) postulated that heading the ball could lead to chronic brain injury as seen in boxing. Since then, several cross-sectional studies on both amateur and professional footballers have identified inferior cognitive function in footballers compared to controls (Jordan *et al.*, 1996; Matser *et al.*, 1998; Matser *et al.*, 1999; Matser *et al.*, 2001; Downs and Abwender, 2002; Witol and Webbe, 2003), although not all studies have seen such a relationship (Guskiewicz, 2002).

However, a comprehensive review of the literature within the field has raised several concerns regarding the methodology and design used in these previous studies (Rutherford *et al.*, 2003). Their first and main criticism is the use of inadequate control groups. The control groups used in the previous studies showed unequal proportions of men and women (Downs and Abwender, 2002), alcohol consumption (Matser *et al.*, 1999) or activity level (i.e. participation in professional sport) (Tysvaer, 1992). As a consequence, these studies were considered by Rutherford *et al*. (2003) as quasi-experimental because the participants were not, and could not, be allocated randomly to different sports groups. Secondly, the control principle that participants should differ only on the variable under examination was not adequately fulfilled.

Furthermore, most of the preceding studies have been criticised for the lack of proper reporting of response rates, which raises the concern that the investigated football players may not be representative of the footballer population (Rutherford *et al.*, 2003). In addition, all the mentioned studies lacked proper adjustment for the number of hypotheses tested (type 1 error) and had problems related to the retrospective design (Matser *et al.*, 1998; Matser *et al.*, 1999; Matser *et al.*, 2001; Downs and Abwender, 2002; Rutherford *et al.*, 2003; Webbe and Ochs, 2003). The latter is especially related to the self-reporting of heading frequency and previous concussions, which makes it difficult to separate the effects between the two. Hence, the review concludes “that there is no reliable and certainly no definitive evidence that neurocognitive impairments occur as a result of general football play or normal heading” (Rutherford *et al.*, 2003). However, in agreement with other reviews within the same field (Kirkendall *et al.*, 2001; Kirkendall and Garrett, 2001), Rutherford *et al*. (2003) do acknowledge that the number of prior concussions in footballers predicted the number of cognitive and somatic symptoms (Jordan *et al.*, 1996; Matser *et al.*, 1999). This indicates that the number of concussions suffered rather than football headings and play in general, is more likely to be the major determinant of the neuropsychological impairments observed.

In spite of the upturn in the amount of research investigating the potential cognitive impairments of minor head trauma, heading and general participation in football, there are still many questions that await confirmatory investigation. Separating the effects of heading frequency and concussions is particularly difficult, as frequent headers will suffer more concussions (Andersen *et al.*, 2004b; Fuller *et al.*, 2005). In addition, the consequences of sub-concussive trauma (excluding football heading) during general football play have not been assessed properly by the previous retrospectively designed studies. Hence, a prospective study focusing on the acute and long-term consequences of minor head trauma in football is required.

Heading of the Ball

Heading in football was first considered to be ludicrous and "not football". However, it has developed to become a natural and important part of defensive and offensive play. Still, the safety of the skill has been an intermittent cause for discussion both in the media and among researchers (Baroff, 1998; Kirkendall and Garrett, 2001; Rutherford *et al.*, 2003; Mehnert *et al.*, 2005).

Adult footballers are able to kick the ball extremely fast. Initial horizontal velocities as the ball leaves the foot have been measured to 25-75 m/s (90 to 270 km/h) (Babbs, 2001). However, attempted headings on a rising ball at these velocities are rare. A six year prospective study of head and neck injuries sustained during 20 FIFA tournaments found only one injury that was caused by a purposeful heading of the ball (Fuller *et al.*, 2005). This was a neck strain that caused no absence from football activities. The study did however register one concussion from a ball to head contact in this period, but this was as a result of a ball kicked from close range hitting the side of the head of an unaware player (Fuller *et al.*, 2005).

Babbs (2001) measured the velocities of "headable" balls for youth and adults in 16 competitive matches and found that the mean horizontal velocity, which is most relevant to heading safety, was 5.7 m/s for adults and 7.1 m/s for youth. Notably, the highest mean value was measured for the younger players. Further estimations by this study revealed that the brain accelerations experienced during normal heading for adult players averaged less than 0.1% of the accepted levels required to produce brain injury in a single impact (Babbs, 2001). The corresponding value for a youth player was 1%. These findings are in line with other

biomechanical analyses indicating that the linear and angular accelerations of the head caused by heading is well below what is thought to be associated with traumatic brain injury (Schneider and Zernicke, 1988; Naunheim *et al.*, 2003) However, for accidental heading and young players, the risk for concussion is considerably higher (Schneider and Zernicke, 1988; Babbs, 2001). This is reflected in the results from a prospective study of youth football players with a mean age of 11.5 years where 49% complained of headaches after heading the ball (Janda *et al.*, 2002).

On the other hand, studies performed on young adults have been unable to detect acute changes in cognitive function or postural stability after a training session of repetitive headings (Putukian *et al.*, 2000; Broglio *et al.*, 2004). However, some studies have found a transient increase of protein S100B (a serum marker for neuronal injury) after controlled heading in a training session (Mussack *et al.*, 2003) and normal heading in a professional football match (Stalnacke *et al.*, 2004; Stalnacke *et al.*, 2006). Nevertheless, the increases were well below what is seen among concussed patients, and thus the clinical implications of these findings are not known (Stalnacke *et al.*, 2004; Stalnacke *et al.*, 2006). The same marker has also been measured in cerebrospinal fluid after a heading training session without finding any correlation to the number of headings performed (Zetterberg *et al.*, 2007) Tysvaer (1990; 1991; 1992) and Matser *et al*. (1998; 1999; 2001) have also proposed a relationship between high heading frequency and cognitive impairments among footballers, but a reanalysis of the data from these studies has somewhat repudiated purposeful heading as a major risk factor for the development of cognitive impairments (Kirkendall and Garrett, 2001).

Accordingly, there is no strong evidence suggesting that normal heading in football causes significant brain damage, and consequently the concern has become more focused on the number of concussive and sub-concussive head impacts that occur during a football match (Kirkendall *et al.*, 2001; Kirkendall and Garrett, 2001; Rutherford *et al.*, 2003). This was also the main focus in Paper II, although heading exposure data was also corrected for.

Minor Head Trauma in Sports

Although heading is a unique feature of football, minor head traumas are not. Over the past 30 years, the neuropsychological effects of minor head traumas have been assessed in a wide range of other contacts sports, such as boxing (Jordan, 2000; Moriarity *et al.*, 2004), gridiron

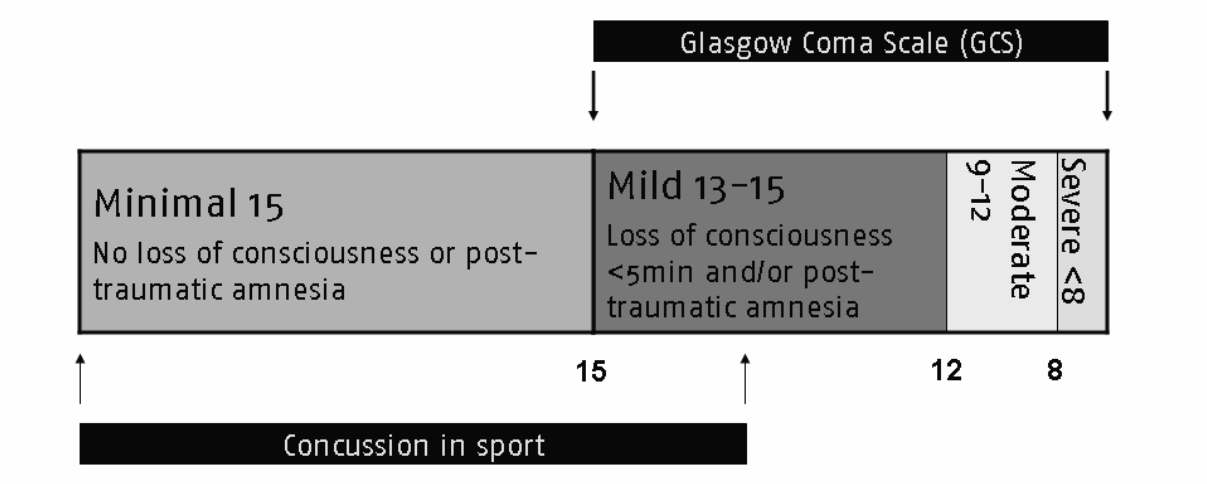
football (American and Canadian football)(Collins *et al.*, 1999), Australian rules football (Makdissi *et al.*, 2001), ice hockey and basketball (Belanger and Vanderploeg, 2005) as well as in the general population (Cassidy *et al.*, 2004; Belanger *et al.*, 2005). However, discrepancies in the definitions of minor head trauma, concussion and incidence and exposure make it difficult to determine whether there is a long-term effect of minor head trauma(s) in sport, and secondly whether the results from these studies are transferable to football.

Definition and Grading of Minor Head Trauma

Minor head trauma generally refers to the acute description of the injury, while concussion is the condition that results from this injury. However, the terms are often used synonymously in the literature. During the last decades, numerous definitions and grading scales describing minor head traumas or concussions have been published. In fact, Johnston *et al*. (2001) counted 25 published sports-related concussion severity scales and found none that had been properly validated in a prospective study of sports-related head injury. For hospitalised patients with head traumas, the most widely used grading scale has been the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974). The scale is typically scored at admission (research standard: 6 hours after the injury) and the main object for the scoring is to separate the patients into a mild, moderate and severe brain injury group with focus on identifying the patients who might need a neurosurgical intervention (e.g. risk of intracranial haemorrhage, scull fracture, increased intra-cerebral pressure, etc.) (Ingebrigtsen *et al.*, 2000a).

However, in clinical practise 90% of all concussions in sports are considered to be “mild” (GCS 13-15) with loss of consciousness shorter than five minutes and/or post-traumatic amnesia, or minimal (GCS = 15), characterised by no loss of consciousness, transient confusion, and/or a brief duration of post-traumatic amnesia (Figure 1) (Stein and Spettell, 1995; Johnston *et al.*, 2001). Although occurrence and duration of loss of consciousness is associated with the initial severity of the injury (Ingebrigtsen *et al.*, 2000a), post-traumatic amnesia has been found to correlate better with cognitive sequela and prolonged recovery of concussion (Lovell *et al.*, 1999; Erlanger *et al.*, 2003; Asplund *et al.*, 2004; Pellman *et al.*, 2004b). The GCS does not assess post-traumatic amnesia, and consequently, the GCS is not properly fine-tuned in the mild spectrum to pick up the nuances in concussions (Stein *et al.*, 1993).

Figure 1: *Head Injury Severity Scale (HISS, Stein and Spettell, 1995) in relation to the Glasgow Coma Scale and the severity spectrum of head traumas in sport. The size of the boxes represents the approximate distribution of the prevalence of each condition in the population (the figure is modified from McCrory, 1st World Congress on Sports Injury Prevention, Oslo, 2005, with permission).*



The numbers represent the corresponding score on GCS 6 hours after the incident/injury.

In addition, studies have found EEG changes (Gosselin *et al.*, 2006) and reduced postural stability (Guskiewicz *et al.*, 2001; McCrea *et al.*, 2003) in asymptomatic concussed players compared to controls, and these deficits were not significantly associated with loss of consciousness and post- traumatic amnesia. This was some of the rationale for the Concussion in Sports Group from the Vienna conference in 2001, to publish the following revised definition of concussion (Aubry *et al.*, 2002): "Concussion is defined as a complex patho-physiological process affecting the brain, induced by traumatic biomechanical forces. Several common features that incorporate clinical, pathological, and biomechanical injury constructs that may be used in defining the nature of a concussive head injury include: 1) Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head, 2) concussion typically results in the rapid onset of short lived impairment of neurological function that resolves spontaneously, 3) concussion may result in neuropathological changes but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury, 4) concussion results in a graded set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course and 5) concussion is typically associated with grossly normal structural neuroimaging studies."

Clinical Practise

Irrespective of the definition used, a definite diagnosis of a concussion can only be made retrospectively. This is an everyday challenge in the return to play decision-making process. In the National Football League (Am. Football), players have traditionally been allowed to return to the same match after a concussion if asymptomatic when assessed 15 minutes post injury (i.e. Grade 1 concussion as defined by the American Academy of Neurology (Kelly and Rosenberg, 1998)). However, an examination of a group of high school athletes (mainly American football) 36 hours after such "grade 1" concussions demonstrated a decline in memory function and an increase in self-reported symptoms compared to baseline performance (Lovell *et al.*, 2004).

The Vienna conference emphasised that a player never should return to play while symptomatic and published the following recommendations for the acute management of concussion (Aubry *et al.*, 2002): When a player shows ANY symptoms or signs of a concussion *(Table 1)*: 1) the player should not be allowed to return to play in the current match or practice, 2) the player should not be left alone; and regular monitoring for deterioration is essential, 3) the player should be medically evaluated after the injury and 4) return to play must follow a medically supervised stepwise process.

Table 1: *Symptoms and Signs of Concussion*

Feature	Description
Cognitive features	Unaware of period, opposition, score of the match, confusion, amnesia, loss of consciousness, unaware of time/date/place
Typical symptoms	Headache (85%)†, dizziness (70-90%)†, nausea, unsteadiness/loss of balance, feeling "dinged"/stunned/"dazed", "having my bell rung", seeing stars/flashing lights, ringing in the ears, double vision
Physical signs	Loss of consciousness/impaired conscious state, poor coordination or balance, gait unsteadiness/loss of balance, concussive convulsion/impact seizure, slow to answer questions or follow directions, easily distracted, poor concentration, displaying unusual or inappropriate emotions such as laughing or crying, nausea/vomiting, vacant stare/glassy eyed, slurred speech, personality changes, inappropriate playing behaviour (e.g. running in the wrong direction), appreciably decreased playing ability

†Guskiewicz et al., 2003

Still, there is currently some controversy in the return to play decision-making practise; especially with regard to the National Football League (NFL) and National College Football

Leagues (NCAA) (both Am. football), which have also been the arenas for the largest studies assessing the return to play practise after concussions (Guskiewicz *et al.*, 2003; Pellman *et al.*, 2005). While the NCAA study showed that the athletes who have suffered concussions were more susceptible to further concussions seven to ten days after the injury (Guskiewicz *et al.*, 2003), the NFL study did not find that returning to the same match when asymptomatic after a concussion involved any increased risk of a second injury in that current match or during the rest of the season (Pellman *et al.*, 2005). However, the author of the NFL study was recently accused in the media for being selective in his use of injury reports in reaching his conclusions and for omitting a large number of players from the study (Keatin, 2006). Nevertheless, none of the articles have been withdrawn.

On the other hand, evidence of long-term neuropsychological impairments caused by concussions or minor head trauma is not yet established. Meta-analyses of published studies within the field from 1970 to 2004 have concluded that minor head traumas or concussions have little to no effect on neuropsychological function by 7 days post impact for the sports-related concussions (Belanger and Vanderploeg, 2005), and by 3 months for the minor head trauma population at large (Belanger *et al.*, 2005).

In Norwegian professional football the Vienna guidelines have been adopted as the prevailing standard in the management of head impacts and have been stressed at several recent annual meetings for the medical personnel organised by the Medical Committee of the Norwegian Football Association (TE Andersen, chair, personal communication, November, 2004).

Pathology of Concussion

Concussions may occur as a result of a direct or indirect impact to the head that causes sudden acceleration of the brain tissue (Gennarelli, 1993; Giza and Hovda, 2001). Rotational or shear forces transmitted to the brain cause an axonal shearing of the neurones and a primary defect in the axonal membrane (Gennarelli, 1993). This initiates a complex cascade starting with an ionic shift within the axon, particularly involving calcium ions, resulting in a depolarisation of the axons, which in turn leads to altered transmission of the neural networks, widespread neurological dysfunction involving the deeper structures of the brain like the reticular activation system in the midbrain and brainstem, and finally coma. The cascade can be thought of as a traumatic depolarisation of the brain (Asplund *et al.*, 2004) where the accelerating force determines the outcome; from no injury through concussion to a more

prolonged coma with diffuse axonal injury (DAI) (Gennarelli, 1993). Concussive events have been shown to lead to an abnormal cellular increase of glucose utilisation and a cerebral hyperglycolysis (Giza and Hovda, 2001). Under normal conditions the cerebral blood flow would adjust to the increased metabolic demand, but this mechanism has been shown to not function properly after a concussion. This results in a relative ischemia with regard to the metabolic demand of the tissue, and some studies suggest that this entails an increased vulnerability for a second injury the first few days (Bergsneider *et al.*, 1997; Giza and Hovda, 2001).

Second Impact Syndrome (SIS)

The Second Impact Syndrome (SIS) is defined as an athlete sustaining a second head injury before the symptoms associated with the first one have fully cleared, and this second impact sets in motion cerebral vascular congestion resulting in cerebral swelling and rapid death due to transtentorial brainstem herniation (Cantu, 1998; McCrory, 2001). Diffuse cerebral swelling or "malignant brain oedema" as such, is a rare but well-known cause of delayed catastrophic condition in children and adolescents resulting in death or persistent vegetative state after a minor head trauma (Bruce *et al.*, 1981; McCrory, 2001). The aetiology is reported to be disordered cerebral auto-regulation following brain injury (Bruce *et al.*, 1981).

McCrory and Berkovic (1998) have critically reviewed the 17 case reports of this condition and questioned the existence of the syndrome, due to the lack of confirmatory details concerning the "second impact" (McCrory and Berkovic, 1998; McCrory, 2001). Their view is supported by a large meta-analysis of minor traumatic brain injury (Cassidy *et al.*, 2004). McCrory *et al*. (2000) have later examined sudden deaths in the State of Victoria, Australia, in the period 1968 to 1999 due to playing Australian Rules Football, without being able to find evidence for any incidents of SIS (McCrory *et al.*, 2000). Consequently, they propose to refer to the syndrome as diffuse cerebral swelling (McCrory, 2001).

Still, a recent publication on catastrophic head injuries in American High School and College Football players (am. football) did identify that 71% of the athletes have had a previous head injury within the same season as the catastrophic event and 39% of them were playing with residual neurological symptoms from this prior event (Boden *et al.*, 2007).

However, irrespective of the existence of SIS, returning to training or match while symptomatic is strongly discouraged by both sides in this ongoing debate (Aubry *et al.*, 2002; McCrory *et al.*, 2005; Boden *et al.*, 2007).

Post-Concussion Syndrome

The Vienna definition is based on the premise that the acute symptoms of a concussion are largely due to functional disturbances rather than structural injury, and that the symptoms are short-lived and resolve spontaneously (Aubry *et al.*, 2002). However, the long-term effects of concussions are currently debated (Dikmen *et al.*, 1986; Carlsson *et al.*, 1987; Alexander, 1995; Erlanger *et al.*, 1999; Echemendia *et al.*, 2001; Bleiberg *et al.*, 2004; Frencham *et al.*, 2005; Belanger and Vanderploeg, 2005). Outside the sporting arena the majority of the cases recover within the first three months (Gronwall and Wrightson, 1975; Dikmen *et al.*, 1986; Levin *et al.*, 1987). However, a significant minority continues to exhibit cognitive deficits beyond that point, with a prevalence ranging from 7% to 8% (Binder *et al.*, 1997) up to 33% (Rimel *et al.*, 1981) across studies. The persistence of symptoms and signs beyond 3 or 6 months is called the Post Concussion Syndrome (PCS) or Persistent Post Concussion Syndrome (Alexander, 1995). The symptoms and signs, as summarised in *Table 2*, involves impairment in attention, memory and/or executive functions, coupled with symptoms of depression, poor sleep, dizziness and chronic pain, especially headache (Alexander, 1995). The symptoms are also correlated with neuropsychological impairments in speed of information processing (Bohnen *et al.*, 1992).

Table 2: *Post Concussion Syndrome (Alexander, 1995)*

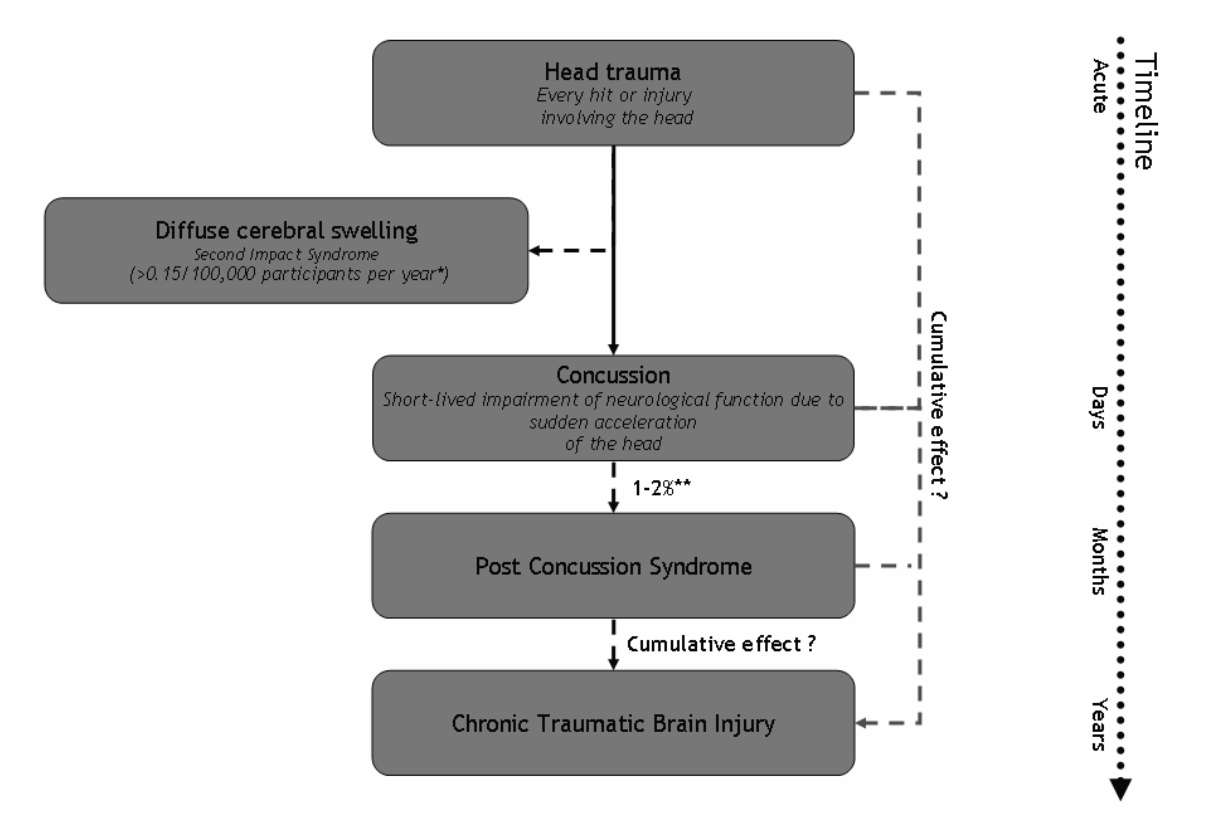
Feature	Description
Prolonged duration of symptoms	Headache, dizziness, balance problems, sensory sensitiveness, etc.
Cognitive symptoms	Impaired attention; especially divided attention, poor memory, reduced concentration, reduced executive function
Trouble with activities of daily living	Trouble driving in heavy traffic, problems maintaining work or study commitments, social problems, etc.
Psychological symptoms	Depression, nervousness, anxiety

Within the sports arena, the studies assessing the duration of cognitive impairments after a concussion conclude that the cognitive deficits resolve faster than for the general population, and the vast majority recovers within 3-7 days (Peterson *et al.*, 2003; McCrea *et al.*, 2003; Bleiberg *et al.*, 2004; Belanger and Vanderploeg, 2005). However, persisting PCS is reported among athletes as well, although with lower prevalence estimates around 1-2% (Pellman *et al.*, 2004b).

Nevertheless, the cognitive PCS symptoms are not specific to head injury and there is an ongoing debate whether the syndrome is of organic or psychological origin (King, 2003). There is an increasing number of studies suggesting that non-neurological factors may be more closely related to the PCS symptoms reported than head injury status, especially within the litigation literature (Mittenberg *et al.*, 1992; Gouvier *et al.*, 1992; Binder *et al.*, 1997; Binder, 1997; Gasquoine, 2000; Suhr and Gunstad, 2002a; Suhr and Gunstad, 2002b; Gunstad and Suhr, 2004). An extensive review of the general literature on minor head trauma concluded that "there are no objectively measured cognitive deficits attributable to minor head traumas beyond 1-3 months post injury for the majority of cases", and the only predictive factors identified for developing PCS are pre-morbid characteristics, the experience and aftermath of sustaining *any* injury, and/or compensation/litigation (Cassidy *et al.*, 2004).

Data on the risk factors for persisting PCS in athletes is sparse, partially due to the small incidence of PCS within this group, and as a result of that, the main focus until now has been the recognition, diagnosis and management of the concussions in the acute phase (Guskiewicz *et al.*, 2003; Collins *et al.*, 2003b; Pellman *et al.*, 2004a; Collie *et al.*, 2006b). As a result, the follow-up time in most of the studies is one to two weeks (Belanger and Vanderploeg, 2005), which is too short for diagnosing persisting PCS (Alexander, 1995). However, loss of consciousness, retrograde amnesia, previous concussions, persistent headache, memory problems, fatigue and disorientation at the acute assessment after the concussion have been shown to predict a prolonged recovery of more than 7 days (Guskiewicz *et al.*, 2003; Erlanger *et al.*, 2003; Asplund *et al.*, 2004; Pellman *et al.*, 2004b). Nevertheless, according to research on the general population it is first when the PCS has persisted for more than a year that there is an increased risk of a chronic condition (Binder, 1997).

Figure 2: *Potential Consequences of Minor Head Trauma in Sport*



**Calculated annual incidence from Boden et al. 2007. **Pellman et al., 2004b*

Chronic Traumatic Brain Injury (Punch Drunk)

Chronic Traumatic Brain Injury was described in professional boxing already in 1928 when Martland introduced the term "Punch Drunk" (Martland, 1928). There seems to be an agreement that this condition has a prevalence of 17-23% among these athletes and as illustrated in *Figure 2*, the cumulative effect of both concussive and sub-concussive head traumas has been suspected as aetiology (Roberts, 1969; Kaste *et al.*, 1982; Jordan *et al.*, 1997; Blennow *et al.*, 2005). The condition involves deteriorations in motor and cognitive functions in addition to psychological and behavioural features *(Table 3)*. However, the vast majority of the evidence behind chronic traumatic brain injury in professional boxing is based on research performed on boxers that were active 30 to 70 years ago (Roberts, 1969; Kaste *et al.*, 1982; Jordan *et al.*, 1997), and it is worth noting from these studies that the number of knock outs (concussions) was not identified as a predictive factor for developing the condition, but the career length and the total number of matches were (Roberts, 1969). Since the 1930s, the average career length has dropped from 19 years to 5 years and the mean number of professional bouts has been reduced correspondingly from 336 to 13 (Clausen *et*

al., 2005). Consequently, it is questioned whether the findings from these previous studies are transferable to today's professional boxing population.

Table 3: *Chronic Traumatic Brain Injury "Punch Drunk" (Jordan et al., 1997)*

Feature	Description
Motor function	In-coordination, dysarthria, parkinsonism, gait disturbance, other pyramidal signs
Cognitive deficits	Mental speed, memory, attention, executive function, language, visuospatial function, Mini-Mental State Examination
Psychological features	Agitation or aggression, delusions, hallucinations, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability or lability, aberrant motor behaviour

Recent evidence has suggested that the harbouring of a specific gene, Apolipoprotein E ε4 allele (APOE ε4), may be associated with a less favourable outcome after a head injury (Teasdale *et al.*, 2005), longer duration of unconsciousness (Friedman *et al.*, 1999), neuropsychological performance (Sundstrom *et al.*, 2004) and the development of chronic traumatic brain injury in boxers (Jordan *et al.*, 1997). APOE ε4 has been established as a major risk factor for Alzheimer's disease (Corder *et al.*, 2006) and a recent study has indicated an additive effect of APOE ε4 and head trauma on the risk of developing dementia (Sundstrom *et al.*, 2006). However, the study population of these studies is small and consequently the results must be considered as exploratory.

Chronic traumatic brain injury has not convincingly been proven to affect amateur boxers (Haglund and Eriksson, 1993; Butler, 1994; Porter, 2003; Blennow *et al.*, 2005), and it is debated whether other athletes, like footballers, are at risk (Tysvaer, 1992; Matser *et al.*, 2001; Guskiewicz, 2002; Rutherford *et al.*, 2003; Blennow *et al.*, 2005; Broglio *et al.*, 2006; Iverson *et al.*, 2006b; Collie *et al.*, 2006c). More recent studies outside the field of professional boxing, using modern computer-based neuropsychological assessments, have failed in identifying previous concussions as a predictive factor of cognitive impairments (Broglio *et al.*, 2006; Iverson *et al.*, 2006b; Collie *et al.*, 2006c). Still, all these studies are based on self-reported retrospective assessment of the individual's concussion history, and must be interpreted with caution. In addition, chronic traumatic brain injuries were mainly found in retired boxers older than 50 years (Roberts, 1969; Jordan *et al.*, 1997), while the athletes

assessed in the more recent studies have been in their mid-20s (Broglio *et al.*, 2006; Iverson *et al.*, 2006b; Collie *et al.*, 2006c).

A recent longitudinal study on age trajectories for episodic and semantic memory has indicated that these functions are quite stable until the age of 60 and 55, respectively, where these functions starts to deteriorate (Ronnlund *et al.*, 2005). And it is further hypothised that a head trauma could accelerate the development of dementia and hence, lower the age for when the deterioration of the episodic and semantic memory starts (Mortimer *et al.*, 1985; Sundstrom *et al.*, 2006). However, the latest research in this field suggests that this vulnerability is attached to a genetic disposition (APOE ε4) (Sundstrom *et al.*, 2004; 2006), and some results have indicated that at age <15 years, carriage of APOE ε4 is equivalent to ageing by 25 years (Teasdale *et al.*, 2005). Thus, there seem to be a reserve capacity in the cognitive function that enables the brain to compensate for the damages inflicted by head traumas, and the symptoms will then first become evident when added to the effects of aging (Sundstrom *et al.*, 2004).

This seems to be the case in football as well. In the studies by Tysvær (1989; 1991; 1992) the cognitive deficits were mainly identified among former football players aged 35 to 64 (mean: 48.6). Although the results are not directly comparable, Tysvaer (1992) reported significant differences in 7 out of 14 neuropsychological tests and found some degree of neuropsychological impairment in 81% of the players (30 of 37), while the deficits were much more subtle in the studies examining the younger athletes (Matser *et al.*, 1998; Matser *et al.*, 1999; Downs and Abwender, 2002; Witol and Webbe, 2003). In addition, one study on college football players with a mean age of 19 years, has not found any signs of cognitive deficits (Guskiewicz, 2002).

The two longitudinal prospective studies in the field have examined amateur boxers and controls for 2 years (Butler *et al.*, 1993) and 9 years (Porter, 2003) respectively, without finding any evidence of neuropsychological deterioration. In fact, in the latter study, the amateur boxers showed a superior performance after nine years compared to the control group (Porter, 2003). However, it should be noted that in both studies the sample sizes were small, and the control group participants were involved in contact sports like American football, rugby, water polo and football. Moreover, in the study by Porter (2003), five of the controls reported a concussive episode during the follow-up period.

Secondly, the studies assessing the effect of previous concussions could be confounded by the previously mentioned diversity in the definitions and classifications of minor head traumas or concussions (Johnston *et al.*, 2001). In addition, many concussions remain unrecognised by the athletes and medical personnel (Delaney *et al.*, 2002). In the worst case, athletes will recognise one out of five concussions and remember 60% of these when assessed retrospectively (Delaney *et al.*, 2002; Gabbe *et al.*, 2003). In conclusion, the evidence for chronic traumatic brain injury among athletes is not well founded, at least not for other sports than professional boxing. Head injuries, both concussive and sub-concussive have been suggested as risk factors for developing this condition in addition to genetic vulnerability. In paper II the focus was to assess the prevalence of cognitive deficits among Norwegian elite footballers and the effect of previous concussions and heading exposure.

The Magnitude of the Problem

Head injuries in football mainly occur as a result of contact with another player (Pickett *et al.*, 2005). In close to 60% of the cases, the main aetiology is a heading duel (Andersen *et al.*, 2004a). The remaining 40% are due to a large variety of different mechanisms such as a kick to the head, a hit by the ball, encounter with the goal post, ground, etc. However, none of these mechanisms contribute to more than 10% of the impacts alone (Andersen *et al.*, 2004a). The upper extremity has been identified as the most frequent striking object closely followed by head to head collisions (Andersen *et al.*, 2004a; Fuller *et al.*, 2005), and the player is usually struck at the side or the front of the head (Fuller *et al.*, 2005).

The incidence of head injuries vary depending on age, skill, level of play and gender of the player (Dvorak *et al.*, 2007b). In general the incidence increases with age and the level of play, but due to lack of uniform definitions both with respect to type of injury and exposure makes it difficult to compare the results from the different studies and the different study populations (Fuller *et al.*, 2006). However, the vast majority of the recent studies have reported time-loss injuries per 1000 training and match hours as recommended by Fuller *et al*. (2006). The reported incidences of time-loss head/neck injuries ranges from 1.1 per 1000 match hours among footballers aged 14-18 (Junge *et al.*, 2004) to 3.5 per 1000 match hours at the World Cup level (Fuller *et al.*, 2005). However, these numbers incorporate all types of injuries, including lacerations, facial bone fractures, muscular strains to the neck, etc. The corresponding concussion incidences in these studies were 0.3 and 0.5 per 1000 match hours.

In females both the head injury and concussion incidences are reported to be slightly higher in most studies (Delaney *et al.*, 2002; Covassin *et al.*, 2003; Hootman *et al.*, 2007; Dvorak *et al.*, 2007b), although some earlier studies by Boden *et al*. (1998) and Barnes *et al*. (1998) have reported the opposite. The reported head injury incidence for the Norwegian elite league is 1.7 per 1000 match hours with a corresponding concussion incidence of 0.3 per 1000 match hours (Andersen *et al.*, 2004a).

In professional boxing, where the data regarding the presence of chronic traumatic brain injury is the most reliable, a 16 year prospective study of Australian professional boxers has reported an injury rate of 250.6 per 1000 fight participations, including 39.8 concussions per 1000 fight participations (estimated to 66.3 per 1000 hours) (Zazryn *et al.*, 2003). This is in strong contrast to the reported incidences in football. Nevertheless, the study from the Norwegian football elite league, revealed an incidence of events with a head injury potential of 22.0 per 1000 playing hours (Andersen *et al.*, 2004a). And according to Delaney *et al*. (2002), many of these impacts may represent non-recognised concussions. In addition, there is a significant difference between the hours spent in a competitive match situation during the career of a footballer and a professional boxer. In 2002, the mean number of career bouts for a professional boxer was 13 (approximately 7.8 hours) (Clausen *et al.*, 2005) compared to professional football where the majority of players play more than 450 matches in the course of their career (more than 675 hours) (Turner *et al.*, 2000).

Hence, the total career exposure to head traumas in football is substantial, at least if the potential non-recognised concussions are counted as well. Keeping in mind that the long-term consequences of these impacts are still unresolved (Rutherford *et al.*, 2003), no prospective study has assessed the acute effect of these sub-concussive impacts. This was however, the main focus of Paper III and IV in this thesis.

Evaluation of Minor Head Trauma in Sport

As stated in the Vienna definition of concussion “a concussion is typically associated with grossly normal structural neuroimaging studies,” and “the acute clinical symptoms largely reflect a functional disturbance rather than structural injury”. This narrows down the opportunities of investigating these injuries with objective methods. All prior studies assessing the cognitive effects of football head traumas in football have relied on self-report

of prior history of head traumas and concussions (Tysvaer and Storli, 1989; 1991; 1992; Jordan *et al.*, 1996; Matser *et al.*, 1998; 1999; 2001; Downs and Abwender, 2002), however the validity of this information based on individual recall is questioned (Delaney *et al.*, 2002; Rutherford *et al.*, 2003; McCrea *et al.*, 2004).

Delaney *et al*. (2002) asked more than 500 football players and American football players in the Canadian Interuniversity Athletic Union several questions pertaining to the commonly recognised symptoms of concussion, and to list the number of times they experienced this (these) symptom(s) after a hit to the head in the same period. Secondly, they were asked to list the number of times they experienced a concussion when having this (these) symptom(s) after being hit in the head during the same period. Only 1 out of 5 athletes realised that they had suffered a concussion. In another study, approximately one third of the athletes that were allegedly asymptomatic and returned to play after suffering a concussion, developed symptoms three hours after the match (Guskiewicz *et al.*, 2003).

At the same time, it should be noted that not all athletes spontaneously report their symptoms to others. A recent survey in American football reported that only 47% of the athletes reported their symptoms to others due to a range of different reasons, such as not feeling that the injury was severe, not wanting to leave the match or a general lack of awareness about concussions (McCrea *et al.*, 2004). Hence, the evaluation of the possible concussive effect of a head impact cannot rely on symptom assessments or self-report alone.

However, for practical reasons the on-field evaluations still have to rely on fast and simple assessments of symptoms and orientation. This has led to the development of various on-field checklists like Maddocks' questions (Maddocks *et al.*, 1995), Standardized Assessment of Concussion (SAC, (McCrea, 2001)), Post Concussion Symptom Scale (PCSS, (Lovell and Collins, 1998)) and the recently published Sports Concussion Assessment Tool (SCAT). SCAT basically includes all the three previous tools (McCrory *et al.*, 2005). Maddocks' questions are probably the most commonly used assessment tool in Norwegian professional football (TE Andersen, Chair Medical Committee of the Norwegian Football Association, personal communication, November, 2004). The basic principle of all these tools is to reveal the presence of any symptoms of concussion and to make a quick assessment of cognitive function by asking questions of recently acquired memory (e.g. Which half is it? Who scored the last goal? Did we win the last match?). These questions of recent memory have been

proven be more sensitive in identifying concussed athletes than questions of more general orientation (e.g. time, place, person) (Maddocks *et al.*, 1995; McCrea, 2001).

With regard to the evaluation on the sideline or the following day, there are several instruments and assessment tools that are being developed. Neuroimaging of brain injury such as different magnetic resonance imaging (MRI) modalities and especially functional MRI (F-MRI) have shown a good correlation with clinical outcome after a concussion (Bazarian *et al.*, 2006a). Electrophysiological recording (ERP or EEG) has shown reproducible abnormalities in the post-concussive state for both symptomatic and asymptomatic athletes (Gosselin *et al.*, 2006) and indicated that there were cumulative effects of concussions in a small group of junior hockey players (Gaetz *et al.*, 2000). Similarly, assessments of postural stability, in particular in combination with cognitive tasks, have also identified impairments in concussed patients (Guskiewicz *et al.*, 2001; McCrea *et al.*, 2003; Broglio *et al.*, 2005). In addition, several biochemical markers, including protein S100B, neuron-specific enolase (NSE), myelin basic protein, cleaved-tau and creatine kinase BB (CKBB), have been proposed as means of detecting cellular damage after a minor head trauma (Mussack *et al.*, 2000; Ingebrigtsen *et al.*, 2000b; DeKruijk *et al.*, 2001; Biberthaler *et al.*, 2001b; Biberthaler *et al.*, 2002; Mussack *et al.*, 2002a; Stalnacke *et al.*, 2005; Biberthaler *et al.*, 2006). Among these, protein S100B has been suggested as the most promising (Ingebrigtsen and Romner, 2003; Bazarian *et al.*, 2006a).

Still, the most commonly used application in the evaluation of concussions is the neuropsychological assessment. Neuropsychological testing was also acknowledged as one of the cornerstones in concussion evaluation by the Vienna Concussion in Sports Group (Aubry *et al.*, 2002). For the current study, neuropsychological testing and assessment of protein S100B were chosen as the main assessment tools and they will therefore be described in more detail.

Protein S100B

Protein S100B is the most abundant member of a Ca^{2+}-binding protein family called S100, due to its solubility in a 100% saturated solution with ammonium sulphate (Moore, 1965). The S100B measured in serum refers to the summed concentration of the S100B monomers in the heterodimer S100A1B and the homodimer S100BB (Nygren De Boussard *et al.*, 2004). These proteins are mainly attached to the membranes in glial cells in the central and

peripheral nervous system (astrocytes or Schwan cells). They are also expressed in melanocytes, adipocytes and chondrocytes outside the nervous system (Zimmer *et al.*, 1995; Donato, 1999; Stroick *et al.*, 2006), but the concentrations here are very small (Haimoto *et al.*, 1987; Zimmer *et al.*, 1995; Ingebrigtsen *et al.*, 1999).S100B has a wide range of potential functions including regulation of cell growth, regulation of cell energy metabolism, regulation of cell contraction, regulation of cell structure, memory and learning, intracellular signal transduction and cell differentiation (Zimmer *et al.*, 1995). In small concentrations, released glial S100B has been proved to have neurotrophic effects (Kligman and Marshak, 1985), while it is associated with apoptotic neuronal cell death in high concentrations (Mariggio *et al.*, 1994; Hu *et al.*, 1996; Hu *et al.*, 1997; Fulle *et al.*, 1997). For a more thorough description of the protein and its function, see Donato (1999).

After a traumatic brain injury the concentration of S100B increases in the cerebrospinal fluid. Whether this increase reflects passive release from damaged astrocytes or active secretion during the glial response to injury, has not been fully investigated (Korfias *et al.*, 2006). Furthermore, the serum levels of S100B also increase rapidly after a traumatic brain injury because the energy of the trauma leads to an immediate opening of the blood brain barrier (BBB) (Barzo *et al.*, 1996; Barzo *et al.*, 1997; Stroick *et al.*, 2006). Some studies have reported a 10-15 fold increase above baseline levels, followed by a significant decrease the next 4-6 hours (Rothoerl *et al.*, 1998; Ingebrigtsen *et al.*, 1999; Mussack *et al.*, 2000; Jonsson *et al.*, 2000; Biberthaler *et al.*, 2001a; Townend *et al.*, 2006).

An increased level of S100B after minor head traumas has been reported to be associated with pathological findings on CT scans (Mussack *et al.*, 2002a; Biberthaler *et al.*, 2006), prolonged hospital stays (Mussack *et al.*, 2000), prolonged absence from work (Stranjalis *et al.*, 2004), post-concussive complaints (DeKruijk *et al.*, 2002; Savola and Hillbom, 2003) and disability one year after the incident (Stalnacke *et al.*, 2005). In addition, the S100B level has been shown to be associated with the Glasgow Coma Scale score at admission and the outcome after more severe head injuries (Raabe *et al.*, 1999; Townend *et al.*, 2002).

Still, not all studies have found that the S100B level predicts long-term outcome in mild traumatic brain injuries (Begaz *et al.*, 2006; Bazarian *et al.*, 2006b), and the specificity of S100B to brain injury has been questioned (Anderson, 2002; Pelinka *et al.*, 2003; Dietrich *et al.*, 2004; Marchi *et al.*, 2004; Stapert *et al.*, 2005; Unden *et al.*, 2005; Mussack *et al.*, 2006). Highly increased values have been reported after multi-traumas and burns without head injury

(Anderson *et al.*, 2001), as well as for patients with acute single bone fracture without apparent cerebral injury (Unden *et al.*, 2005). In addition, smaller increases have been measured after exercise without head injury such as playing basketball (Stalnacke *et al.*, 2003), ice hockey (Stalnacke *et al.*, 2003), swimming (Dietrich *et al.*, 2003), running, boxing (Otto *et al.*, 2000; Dietrich *et al.*, 2003) and football (Stalnacke *et al.*, 2004; 2006). The latter study also found that the increase in S100B after a match was somewhat related to the number of headings. Yet, they argue that the increase in S100B concentration after these exercise conditions were lower than the values reported after minor head traumas.

Nevertheless, the effect of physical activity on the serum level of S100B and the source of S100B release into serum under these circumstances are unresolved (Stalnacke *et al.*, 2004; Dietrich *et al.*, 2004; Stalnacke *et al.*, 2006; Korfias *et al.*, 2006). Hence, the absence of a head trauma does not necessarily exclude the nervous system as the main source for the increase due to indirect disturbance of nervous cells caused by cytokines and other inflammatory factors being released in high amounts under these circumstances (Mussack *et al.*, 2002b; Korfias *et al.*, 2006; Fehrenbach and Schneider, 2006). Similar mechanisms may occur as a result of an intensive physical work-out and could explain the increases reported after exercise, indicating that the increase of S100B in serum under these circumstances may originate from the nervous tissue (Pershin *et al.*, 2002; Steinacker *et al.*, 2004; Stalnacke *et al.*, 2006). Severe brain damage is typically accompanied by a breakdown of the BBB function (Marchi *et al.*, 2004), but recent studies have established that the permeability of the BBB also can be altered due to physical activity (Sharma *et al.*, 1991; Watson *et al.*, 2005) in addition to stress and increased levels of epinephrine (Abdul-Rahman *et al.*, 1979; Hanin, 1996; Scaccianoce *et al.*, 2004), enabling a rise in serum S100B.

However, no study has systematically compared the S100B values from these different conditions (minor head trauma with lesions on CT/MRI, minor head trauma patients with negative CT/MRI, physical activity/sports). Hence, a meta-analysis was conducted to assess the effect of minor head traumas and exercise on the S100B serum concentration from the studies available, and thus, create a broader base for the interpretation of the S100B results presented in paper III.

Meta-analysis of S100B Measurements after Minor Head Traumas and Physical Activity

Pubmed was searched for relevant articles within the two fields. The search was limited to articles published in English or Norwegian using human participants. The key words were; "Craniocerebral Trauma"[MeSH], "Head Injuries, Closed"[MeSH], "S-100 calcium-binding protein beta subunit"[Substance Name] and "S100 Proteins"[MeSH] for the minor head trauma studies. The corresponding key word for the sports studies were; "Sports"[Mesh], "S-100 calcium-binding protein beta subunit"[Substance Name] and "S100 Proteins"[MeSH]. In addition, relevant studies were selected from the reference lists of the studies retrieved. Only studies that measured S100B within 3 hours after the trauma or activity were included, and for the head trauma studies the initial GCS score had to be above 13. In order to be included in the meta-analysis, the studies had to present mean or median values for the S100B measurements in addition to standard deviation or interquartile ranges, this enabling a calculation of an estimate of the standard deviation. The pooled means and standard deviations for the different conditions were calculated weighted by the number of participants in each study.

Data from a total of seven studies were included in the meta-analysis assessing S100B after minor head traumas, while four studies had measured S100B after different sporting activities. In total, 1910 cases with minor head traumas were included in the analysis. In 144 cases a trauma relevant lesion was identified on CT or MRI scans, 1562 cases had a negative CT/MRI scan and in 204 cases the CT/MRI status was unknown. The sports studies were generally smaller and only 142 cases were included in the analysis in total, of which 102 were male. All eleven studies will be briefly described in the following section, and the values extracted from these studies are presented in *Figure 3* along with the pooled values for each of the conditions.

Minor Head Trauma Studies

Bieberthaler *et al*. (2006) measured S100B in 1309 minor head trauma cases (GCS 13-15) admitted to three different trauma centres in Germany from June 2002 to October 2003 and compared the results to 55 cases of severe head trauma (GCS 3-12) and 540 healthy volunteers. A computer tomography (CT) was performed on all included head trauma patients. They found that the S100B concentration was significantly higher in patients with trauma-relevant lesions on the initial CT scan (N=93) compared to the minor head trauma group without such lesions (N=1216). This was also the case when the patients were

separated into different groups according to their GCS score (13, 14 or 15). The minor head trauma group was also significantly different from both the severe head trauma group and the healthy controls.

The same group had earlier performed a similar study in an effort to create an appropriate cut-off level for S100B after minor head traumas (Biberthaler *et al.*, 2002). This study involved S100B measurements and CT scans of 104 patients. A total of 24 of the patients had post-traumatic lesions on CT scans and this group had significantly higher values than the negative CT scan group. The analyses revealed a cut-off level of 0.12 ng/ml at a sensitivity of 100% and a specificity of 46%. Hence, they concluded that the positive predictive value for S100B was poor, but the negative predictive value was very good.

Mussack *et al*. (2002a) assessed S100B in alcohol-intoxicated minor head trauma patients that were admitted to the emergency department during the October festival in Munich in 2000. A total of 19 patients had lesions on CT scans and showed significantly higher values than the negative group (N=120). Also, they found no correlation with blood alcohol concentrations.

In a study by Nygren de Boussard *et al*. (2004), S100B, S100A1B and S100BB were measured in sera from patients with minor head traumas, patients with orthopaedic injuries and non-injured objects. Their objective was to assess whether a direct measurement of these hetero/homodimers could increase the brain specificity for the sample. Even though they did find a significant difference in the S100B concentrations between the minor head trauma group with no CT/MRI pathology (N=58) and the group with CT/MRI pathology (N=8), the S100B measurements for the minor head trauma group were not significantly different from the group with orthopaedic injuries. However, S100A1B concentrations were different, suggesting that this sample was more specific to brain injury than S100B within the milder part of the minor head trauma spectrum. However, only the S100B measurements were included in the present meta-analysis.

Another Swedish group (Stalnacke *et al.*, 2005) assessed the one-year outcome of patients with minor head trauma in relation to initial serum levels of S100B. A total of 88 patients were included, and a CT scan was performed in 10 patients and was normal in all cases. The S100B values measured in the acute phase were entered in the present meta-analysis. The one-year results revealed a high frequency of persistent symptoms and low levels of life

satisfaction, while sick leave was low. Interestingly, high S100B levels on admission were significantly correlated to the level of disability at the one year follow up.

DeKruijk *et al*. (2001) measured S100B in 104 patients with minor head trauma and compared them to 92 healthy controls. They found significantly higher S100B concentrations in patients compared to controls and also found an association between S100B concentrations and vomiting patients.

In a study by Stranjalis *et al*. (2004), the serum S100B level was determined in 100 subjects that were referred to the emergency department after a minor head trauma, all with GCS of 15, and their initial S100B values were correlated with failure to return to work/other activities within one week. Subjects with a S100B above 0.15 ng/ml had a failure rate of 37.5% vs. 4.9% of those with values below this cut-off. The initial mean value for the whole minor head trauma group was entered in the meta-analysis.

Sport Studies

The previously mentioned group from Sweden, Stalnacke *et al*., conducted a small study in 2004 assessing S100B in elite male footballers (N=28) after playing a regular league match and found a significant increase compared to pre-match values. This increase was also correlated to the manually counted number of headings and head-accelerating events during the match.

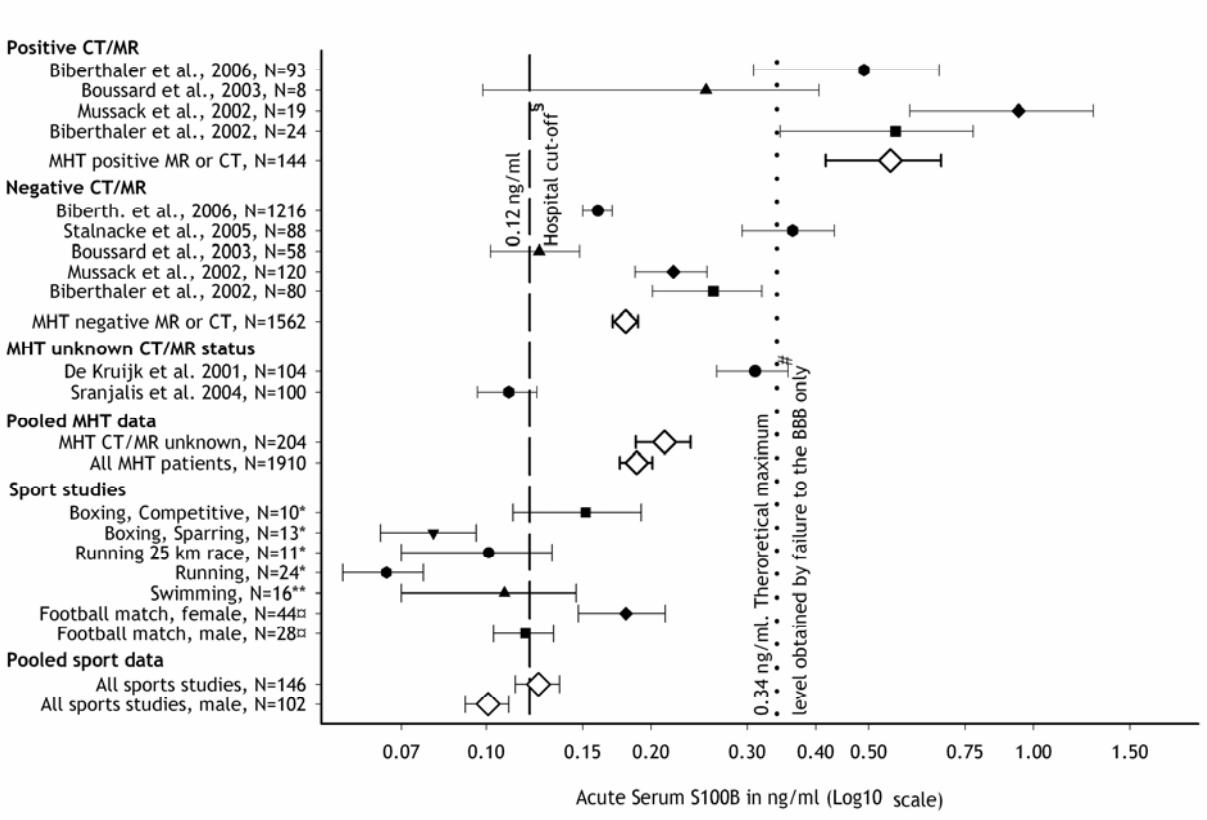
In 2006, a similar study was conducted on 44 female elite footballers revealing similar results (Stalnacke *et al.*, 2006), although the females had both higher baseline and post-match values compared to the males from the prior study.

Dietrich *et al.* (2003) measured S100B before and after a 7600 meter swimming race (N=16) and found a significant post-race increase in S100B compared to the baseline levels.

Finally, Otto *et al*. (Otto *et al.*, 2000) assessed S100B before and after amateur boxing competitions (N=10) and sparring bouts (N=15). As controls they measured S100B in other groups of athletes before and after running a 25 km race (N=11), jogging 10 km (N=12), short term running (2 min. max sprint, N=12), ergometer cycling (N=12) and heading footballs (N=12). Although the groups were small, they found a significantly higher increase in S100B after the competitive boxing compared to sparring, but the increase was not significantly

different from the 25 km race. The heading group in this study had no significant increase in S100B compared to their baseline levels.

Figure 3: *Meta-analysis of studies measuring S100B in hospital-admitted minor head trauma patients with and without CT/MRI scans and meta-analysis of the studies assessing S100B in various sporting activities. A log10 scale is used on the x-axis and the error bars represent the 95% confidence interval of the mean.*



**Otto et al. (2000), **Dietrich et al. (2003), ¤Stalnacke et al. (2004; 2006). §Cut-off used in a hospital setting to screen patients for CT/MRI scans (Biberthaler et al., 2002). #From Marchi et al. (2004).*

Interpretation of the Meta-Analysis

Based on mathematical modelling of the S100B kinetics across the blood-brain barrier, Marchi *et al*. (2004) proposed that up to a level 0.34 ng/ml, serum S100B is primarily a marker of increased blood-brain barrier permeability, whereas higher values are associated with neuronal damage and poor patient outcome. In a recent review on the topic (Korfias *et al.*, 2006), it is suggested that values between 0.12 ng/mL and 0.34 ng/mL are considered as "borderline" while values above 0.34 ng/mL are more likely to represent true "neuropathology". This is in line with the results from the meta-analysis, where only the pooled data for the minor head trauma patients with lesions on CT/MRI scans was above 0.34 ng/mL *(Figure 3)*, while the remaining minor head trauma cases were within this "borderline" area. Thus, the vast majority of the minor head trauma cases were above the proposed cut-off

used in hospitals to screen for further radiological investigations at admission (i.e. increased risk of structural injuries which are visible on a CT scan) (Mussack *et al.*, 2000; Biberthaler *et al.*, 2001b; Biberthaler *et al.*, 2002; Ingebrigtsen and Romner, 2003; Biberthaler *et al.*, 2006).

The pooled value for the sports studies was approximately at the hospital cut-off at 0.12 ng/mL. However, when the female athletes were excluded, the pooled value was even lower. The cut-off at 0.12 ng/mL is set this low in order to maximise the sensitivity of the test because the consequence of a false positive result would only be a CT scan. This will decrease the specificity and the positive predictive value of the sample. However, the negative predictive value is high, indicating that the finding of a normal S100B value shortly after a trauma should exclude significant brain injury (Savola *et al.*, 2004). This represents some problems for the studies assessing S100B after physical activity, since it seems like activity itself increases S100B up to this lower cut-off level *(Figure 3)*. Nevertheless, the values for the sports studies were well below those measured for the minor head trauma cases with lesions visible on CT or MRI-scans.

Still, the meta-analysis must be interpreted with some caution. Although the results were generally slightly skewed to the right, they were treated as normally distributed to simplify the calculations in the meta-analysis. As an example, for the 1216 minor head trauma patients with a normal CT scan in the study by Bieberthaler *et al*. (2006), the median was 0.16 ng/mL with an interquartile range from 0.10 to 0.33 ng/mL. This skewness could be corrected for by a log10 transformation of the data, but this was not possible for all the data in the meta-analysis.

In addition, different methods were used for analysing S100B in the different studies. These were mainly RIA-mat (radioimmunoassay), Liason or Lia-mat (Sangtec Medical AB, Bromma, Sweden) or Elecsys (ROCHE Diagnostics, Basel, Switzerland). There is some inconsistency in the literature on whether these analytical models are comparable or not (Biberthaler *et al.*, 2002; Muller *et al.*, 2006), but only S100B values from the RIA-mat analyses were excluded due to a lower detection limit (0.2 ng/mL) (Ingebrigtsen *et al.*, 1999). On the other hand, the largest study included in the meta-analysis, Bieberthaler *et al*. (2006) contributed with more than 1300 minor head trauma patients (76% of total N) and used the same instrument to analyse the samples as in this current study.

Nevertheless, apart from a small study showing comparable increases in a group of 10 boxers assessed before and within 15 minutes after a bout in the German amateur boxing championship (Otto *et al.*, 2000), no studies have measured S100B in athletes after minor head impacts that were not initially diagnosed as concussions. Thus the effect of such minor head impacts in football on S100B is not known. Consequently, serum S100B measurements could be a valuable test to screen for potential neuronal damage after such incidents on the football field. This was the main focus of Paper III.

Heading and S100B

As mentioned previously, heading is a unique feature of football. A few studies have looked at the effect of heading on S100B and found a correlation between the number of headings and S100B (Mussack *et al.*, 2003; Stalnacke *et al.*, 2004; 2006). However, there are some problems related to these results:

The studies by Stalnacke *et al*. (2004; 2006) were small (N=28 in 2004 and 44 in 2006), and no information was provided regarding the goaltenders. However, Stalnacke *et al*. recruited their participants from two competitive male and female matches, 8 teams in total. Hence, the maximum number of goaltenders in the material would be 4 male (14% of male cohort) and 4 female (9% of female cohort). The goaltenders practically never head the ball and will thus be grouped among the low frequency headers. But since their level of exertion during a match is also lower compared to outfield players (Reilly, 2003; Arnason *et al.*, 2004), there is a chance that the correlation between the number of headings and the increase in S100B would be confounded by differences in physical activity.

Mussack *et al*. (2003) assessed S100B after a controlled heading session and a football exercise session without heading in a group of amateur football players aged 12 to 17 years. They found a higher transient increase for the heading group compared to the exercise group. However, the results were only significant for the youngest players aged 12 to 15 years.

Heading is a complicated skill and many coaches do not incorporate heading in training sessions until the players are 12 years or older (Kirkendall and Garrett, 2001). Consequently, controlled repetitive heading for 55 minutes was most likely a heavier exposure for the youngest players compared to the more experienced 16- and 17-year olds in this study by Mussack et al. (2003). This is in line with the results from biomechanical simulations of football headings, showing that controlled heading is associated with a very small risk of

sustaining a concussion, while accidental impacts or heading with poor technique could produce brain accelerations within the concussive range (Schneider and Zernicke, 1988; Babbs, 2001).

Thus, the effect of controlled heading on S100B is not completely understood and further investigations are needed to control for the physical activity component when assessing this effect. This effect was examined in Paper III.

Neuropsychological Testing

One of the first studies that reported to use neuropsychological assessment of athletes was a study by Kaste *et al*. (1982) where chronic brain damage in boxers was assessed using parts of the Wechsler adult intelligence and memory scale (Wechsler, 1945; 1955), the Wisconsin card-sorting test (Berg, 1948; Milner, 1963), the Trial Making Test (Davies, 1968), the Benton visual retention test (Benton, 1963) and the Perdue pegboard (Costa *et al.*, 1963). The traditional neuropsychological assessment of athletes using a baseline preseason model began in the mid-1980s at university level in the USA (Barth *et al.*, 2006). Here, a paper and pencil test battery was used which consisted of the vocabulary subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1955), the Trail Making Test A and B from the Halsted-Reitan Neuropsychological Test Battery (Reitan and Wolfson, 1985), the Paced Auditory Serial Addition Test (Gronwall, 1977) and the Symbol Digit Test (Wechsler, 1955). These tests provided a general indication of the overall cognitive function in addition to measures of attention, concentration and rapid problem solving that were shown to be sensitive to changes due to concussion (Rimel *et al.*, 1981; Barth *et al.*, 2006). Although these studies on college athletes demonstrated a transient neuropsychological decline in areas of information problem-solving and attention as a result of uncomplicated head traumas without LOC, it would take nearly a decade before neuropsychological testing was adopted by the American professional football (NFL, 1993) and hockey leagues (NHL, 1996) (Zillmer *et al.*, 2006).

Throughout the nineties, neuropsychological testing was used more extensively for evaluating concussion in sports and the number of tests was expanded. A meta-analysis of the literature within the field from 1970 to 2004, indicated that more than 70 different tests and subtests have been used to assess cognitive function within nine different domains; orientation, global cognitive ability, attention, executive functioning, memory acquisition, delayed memory, language, visuospatial ability and motor abilities (Belanger and Vanderploeg, 2005).

Consequently the testing became quite time-consuming and vulnerable for statistical errors associated with multiple testing (type 1 errors). For instance a single test battery could include more than 18 different tests yielding 27 outcome variables (Matser *et al.*, 1998). In addition, the results were difficult to interpret and all athletes need to be assessed by a trained neuropsychologist. In response to these problems, computerised neuropsychological assessments were developed. The current leading programmes are the Internet-based Concussion Resolution Index (Erlanger *et al.*, 2001; Erlanger *et al.*, 2003), the software-based Immediate Post-Concussion Assessment and Neurocognitive Testing (ImPACT) (Collins *et al.*, 2003b), the Automated Neuropsychological Assessment Metrics (ANAM) (Cernich *et al.*, 2006), and CogSport (Collie *et al.*, 2001). In spite of their unique distinctions, all these test batteries focus on efficient assessment of cognitive functions that are sensitive to the effects of cerebral concussion, such as attention, reaction time, complex problem solving, multitasking and memory, and there are currently no indications towards one being superior compared to the others (Broderick *et al.*, 2004; Echemendia, 2006). CogSport is however the only test that has been translated into Norwegian and was therefore our neuropsychological test of choice. The test itself will be described more thoroughly in the methods section.

The CogSport-test has been used for concussion management in various sports on elite and amateur level (Makdissi *et al.*, 2001; Moriarity *et al.*, 2004), but the reliability and practise effects of the test have only been studied on native English speaking students (Collie *et al.*, 2003b) and elderly volunteers (Collie *et al.*, 2003a). Even though the test has been translated into Norwegian and uses a universal playing card metaphor as stimuli, the results from the investigations on the students and elderly Australians are not necessarily directly transferable to a group of mainly native Norwegian-speaking professional athletes. Thus, the reproducibility of the test in this group of footballers needed to be investigated, as well. This was the focus of Paper I.

Conventional versus Computerised Tests

Studies using computerised neuropsychological tests have suggested that this test modality is particularly sensitive to the cognitive consequences of sports-related concussions (Makdissi *et al.*, 2001; Lovell *et al.*, 2003; Collins *et al.*, 2003a; Lovell *et al.*, 2004), and computerised tests have shown evidence of persisting impairments in sports concussions, even in the presence of normal conventional test results (Bleiberg *et al.*, 1998; Collie *et al.*, 2003b). All the previous studies assessing the neuropsychological consequences of football used

conventional neuropsychological test batteries (Tysvaer, 1992; Jordan *et al.*, 1996; Matser *et al.*, 1998; Matser *et al.*, 1999; Matser *et al.*, 2001; Downs and Abwender, 2002; Witol and Webbe, 2003). Although many of these instruments have a long history in the field of both general and sports neuropsychology (Echemendia, 2006), it has been argued that many of these tests have problems with normal ranges, sensitivity and specificity, as well as practise effects (Grindel *et al.*, 2001). A meta-analytic review of the neuropsychological consequences of minor head traumas argued that conventional neuropsychological assessments had a positive predictive value of less than 50% (Binder *et al.*, 1997). Nevertheless, it must be noted that this was partially due to the detected low prevalence of cognitive deficits associated with minor head traumas in this review.

Some of these problems are also present for the computerised tests, but there are some important differences between the two test platforms. The main difference is related to the output data which for the conventional tests is typically either an accuracy score or a gross measure of the total time to perform the task (Tysvaer, 1992; Matser *et al.*, 1998; Downs and Abwender, 2002; Witol and Webbe, 2003; Webbe and Ochs, 2003). In contrast, the computer-based tests batteries provide close to exact measures of reaction time (Collie *et al.*, 2001; Erlanger *et al.*, 2001; Erlanger *et al.*, 2003; Collins *et al.*, 2003b; Cernich *et al.*, 2006). The reaction time measures have been proved to be more reliable than measures of accuracy in healthy young adults (Collie *et al.*, 2006a), and as consequence, these measures have been shown to be particularly sensitive to changes following concussions (Stuss *et al.*, 1989). In addition, persisting impairments after sports concussions have been identified by computerised reaction time measures, even in the presence of normal performance on traditional clinical neuropsychological measures (Collie *et al.*, 2006a).

Furthermore, accuracy data can be used to correct for "gambling" in the reaction time measures creating a cognitive efficiency score (throughput) reflecting the number of correct responses per unit of time (Darby *et al.*, 2002; Cernich *et al.*, 2006). This measure has been proven to be sensitive in discriminating elderly with mild cognitive impairments from controls in a study using multiple assessment of the CogSport test in a single day (Darby *et al.*, 2002). However, no comparative studies have been performed assessing whether this approach is preferable when examining young adults or athletes using a single session approach. Accuracy data have also showed the highest practise effects (Collie *et al.*, 2003a; Iverson *et al.*, 2006a), and by combining the accuracy data with the more stable reaction time data, this practise effect will be transferred into this new variable as well. In practical terms, a

practise effect such as this makes the interpretation of follow-up tests like the post-concussion tests, more difficult. As a consequence, a "return to baseline" is not as clear a sign of normal performance as "exceeds baseline" when assessing accuracy or throughput data (Darby *et al.*, 2002; Cernich *et al.*, 2006).

Still, one of the biggest benefits of the computerised test is that they are fast and can be administrated by a non-expert. This makes it possible to conduct preseason baseline testing of a large cohort of players and thus enabling the assessment of within-person changes after a minor head trauma (Collie *et al.*, 2003b). At follow up, the athletes can be compared to their own baseline performance and the analysing process is automated, enabling a close to instant feedback (Collie *et al.*, 2003a). Secondly, this fast administration makes it possible to perform full practise rounds of the test at baseline to tease out potential practise effects.

Practise Effects

For both the computerised test and for several of the conventional tests in particular, the practise effect is a problem (Macciocchi, 1990; Falleti *et al.*, 2003; Collie *et al.*, 2003a). However, repeated computerised neuropsychological testing of students and elderly has indicated that the vast majority of the practise effect was evident between the 1st and 2nd administration of the test, while only small and non-significant improvements were noted between the 2nd, 3rd and 4th administration (Falleti *et al.*, 2003; Collie *et al.*, 2003a). Hence, it has been suggested that a dual administration of the baseline, where the first test is discarded, would minimise the practise effect at large. This practise effect is assessed in Paper I.

Change in Neuropsychological Performance due to Minor Head Trauma

There are no prospective studies which have assessed neuropsychological function after minor head impacts in regular football matches, irrespective of whether the impacts were initially diagnosed as concussions or not. Moriarity *et al.* (2004) conducted neuropsychological tests on a group of boxers prior to and within two hours after one, two or three tournament bouts. Deficits were, however, only found among the boxers where the match was stopped by the referee (referee-stopped contest, (AIBA, 2003)) or where the boxer had experienced epistaxis. The deficits were limited to the Psychomotor function and Decision-making tasks only. Nevertheless, the authors concluded that these boxers should be considered to have acute cognitive impairments until proven otherwise (Moriarity *et al.*, 2004). None of these boxers

were initially diagnosed as concussed by the medical personnel supervising the tournament. However, the Concussion in Sports Group from the Vienna Conference in 2001 defines a concussion as any impairment of neurological function caused by a direct blow or an impulsive force to the head (Aubry *et al.*, 2002). And according to this definition, the boxers showing cognitive impairments in the study of Moriarity *et al*. were most likely concussed initially as well.

In contrast, significant deteriorations were found for five of the six CogSport tasks after 24 hours of sustained wakefulness (Falleti *et al.*, 2003), and the magnitude of the relative change from baseline to follow up was twice that of the boxers of Moriarity *et al*. (2004). However, when the same group of students were tested under the influence of alcohol (0.5‰ blood alcohol concentration), the patterns of their deficits were more similar to the boxers (Falleti *et al.*, 2003).

On the other hand, there are several studies that have investigated neuropsychological changes in athletes that were initially diagnosed as concussed (Makdissi *et al.*, 2001; Erlanger *et al.*, 2001; Iverson *et al.*, 2003; Collins *et al.*, 2003b; Lovell *et al.*, 2004; Bleiberg *et al.*, 2004; Pellman *et al.*, 2004a; Collie *et al.*, 2006b). Also, several studies have assessed initially concussed athletes where the symptoms have resolved after a few minutes or by the time of testing (Warden *et al.*, 2001; Collins *et al.*, 2003a; Lovell *et al.*, 2004; Pellman *et al.*, 2004a; Gosselin *et al.*, 2006; Collie *et al.*, 2006b). From these studies there seems to be an agreement that the largest deficits in neuropsychological performance are found among the players being symptomatic at the time of the test (Lovell *et al.*, 2004; Pellman *et al.*, 2004a; Collie *et al.*, 2006b). Nevertheless, other studies have revealed electrophysiological changes (Gosselin *et al.*, 2006) as well as neuropsychological deficits (Warden *et al.*, 2001) among concussed athletes where the symptoms have allegedly resolved.

The Pattern of Neuropsychological Deficits in Concussion

Collie *et al*. (2006) used CogSport to assess concussed Australian Rules Footballers (AFL) within three days after the incident and only found deficits among the athletes who reported to be symptomatic at the time of testing. In agreement with the results of Moriarity *et al*. (2004), the deteriorations were mainly visible for the reaction time measurements for the simplest tasks. However, there is no consensus in the literature to which specific tasks will detect cognitive deficits after concussions (Frencham *et al.*, 2005). Nevertheless, previous studies investigating the neurocognitive function after concussions have found the largest effect sizes

in the simpler cognitive domains as assessed by tests of simple and choice reaction time, and simple and divided attention (Van Zomeren and Deelman, 1976; Van Zomeren and Deelman, 1978; Stuss *et al.*, 1989; Warden *et al.*, 2001; Bleiberg *et al.*, 2004; Collie *et al.*, 2006b). Simultaneously, according to a review by Frencham *et al.* (2005), there seems to be an agreement that traumatic brain injuries caused by minor head impacts are not associated with gross deficits in higher cognitive domains such as intelligence and memory.

Furthermore, comparisons of individual change from baseline to follow up have been suggested to be more sensitive than cross-sectional control group comparisons in detecting head injury related neuropsychological effects (Sundstrom *et al.*, 2004). This is supported by Iverson *et al.* (2006a) who found no performance decrement or symptoms in group analyses of 30 concussed athletes after 10 days, although individual analyses revealed that 11 (37%) had a declined performance on two or more tests (2 out of 5 test composites in total).

In conclusion, neuropsychological testing is a sensitive instrument to detect acute cognitive changes after minor head traumas in athletes, and therefore also represent a valuable objective tool in the assessment of possible concussive changes in allegedly asymptomatic players after a minor head impact, as was the main focus of Paper IV.

Neuropsychological Assessment of Long-Term Effects

As previously discussed, long-term and cumulative effects of concussions have been suggested as a possible aetiology of impairments of cognitive function by several studies based on assessments of both athletes and the general population (Roberts, 1969; Gronwall and Wrightson, 1975; Carlsson *et al.*, 1987; Gaetz *et al.*, 2000; Matser *et al.*, 2001). On the other hand, more recent studies utilising computer-based neuropsychological instruments have not been able to identify concussion history in athletes as a predictor of neuropsychological performance (Macciocchi *et al.*, 2001; Broglio *et al.*, 2006; Iverson *et al.*, 2006b; Collie *et al.*, 2006c). In addition, a comprehensive meta-analysis from 2005 found no evidence of impairments in athletes when neuropsychological testing was completed later than 7 days post injury (Belanger and Vanderploeg, 2005).

Nevertheless, neuropsychological tasks measuring choice reaction time comparable to the Decision-making task in the CogSport battery have been proven to detect deficits 3-10 months after closed head traumas in patients with allegedly good outcome (Stuss *et al.*, 1985; Hugenholtz *et al.*, 1988; Stuss DT *et al.*, 1989). However, these previous studies consisted of

cases initially hospitalised for their injury and thus represented a more severe spectrum of minor head traumas than the minor head injuries in an athlete population. No prospective studies have assessed the long-term effect of minor head impacts in football players. Hence, the neuropsychological effect of minor head traumas in football players 3-10 months after the incident is uncertain. This topic was addressed in Paper IV.

Main objective

The overall objective of this study was to examine the acute effect of minor head impacts in professional football with respect to possible neuronal tissue damage and deteriorated neuropsychological function.

Specific objectives

To assess the reproducibility of a computerised neuropsychological test battery (CogSport) on Norwegian professional football players and secondly to identify possible primary outcome measures to be used in the further applications of the test (Paper I)

To examine the effect of previous concussions and heading exposure on neuropsychological performance among Norwegian professional footballers, and to compare their performance with normative data and other athletes (Paper II)

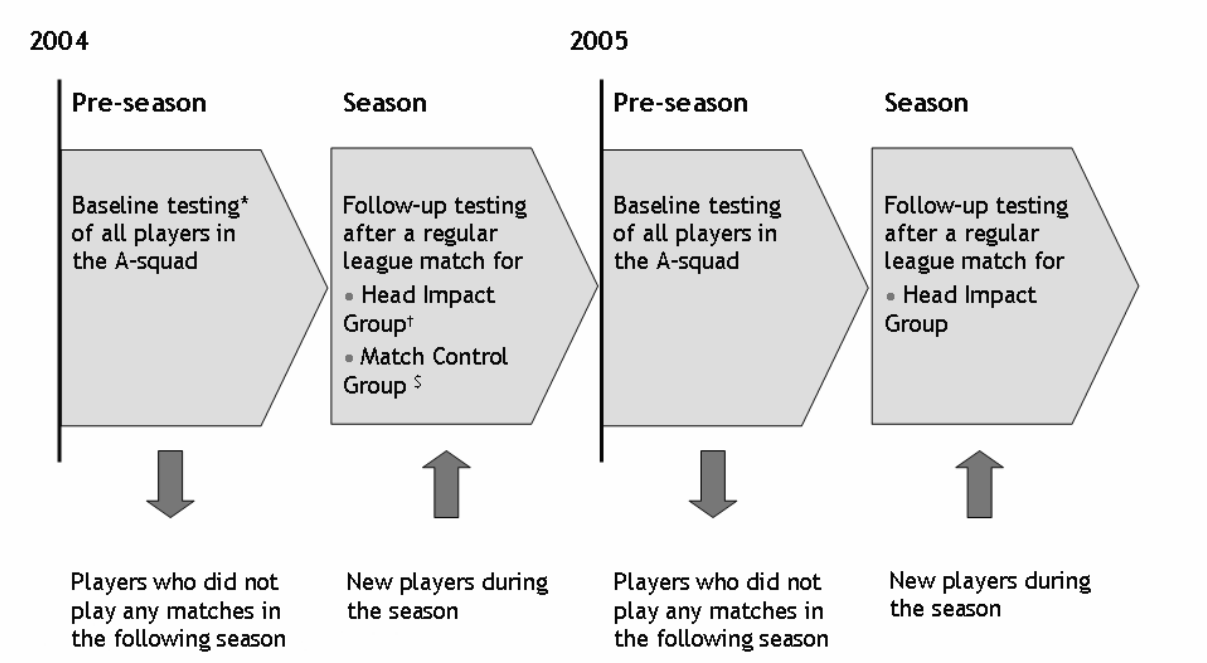
To identify possible brain tissue damage in minor head impacts by comparing serum concentration of S100B after a football-related head impact to the effect of heading, high-intensity exercise and playing a regular match (without head trauma) (Paper III)

To determine whether minor head impacts cause measurable brain function impairment among elite football players, irrespective of whether or not the player was symptomatic or removed from play. And further on, to investigate whether there is any change in neuropsychological test performance from one year to the next in individuals who experience one or more minor head impacts during the course of a regular season (Paper IV)

Methods

Outline of the Study Design and Participants

Figure 4: *Outline of the study design and time frame*



**Symptom assessment, neuropsychological testing and blood sampling were performed at both baseline and follow up. †The players who suffered a head impact in a regular league match were tested straight after the match (Head Impact Group). $Teammates that did not suffer any head impacts were also tested after playing a regular league match as controls (Match Control Group).*

All four papers in this thesis are based on data from the same prospective cohort study of Norwegian elite football players *(Figure 4)*. All 14 teams in the Norwegian professional football league were invited to participate with their A-squad contract players in both 2004 and 2005, with a total of 320 to 390 players available for testing each year. Baseline testing was performed prior to both seasons at the league's preseason training camp at La Manga in Spain and included blood sampling, two consecutive neuropsychological tests, and a questionnaire assessing player and heading characteristics and concussion history. The players were then followed prospectively for all regular league matches in each season. Players suffering a head impact during a regular match (Head Impact Group) were followed up with symptom assessment, and neuropsychological testing the following day supervised by the team's medical staff. The study protocol also included blood sampling of the player one and

twelve hours after the head impact for assessing the serum level of S100B (*Figure 5)*. The Head Impact Group was compared to a control group of players who were tested according to the same algorithm after a regular match where no head impacts were recorded (Match Control Group). The head impacts and the control matches were recorded on videotape supplied by the Norwegian Broadcasting Corporation (NRK) and analysed.

The participation rate was retrospectively checked up against the official match statistics for the two respective seasons. These statistics that are published in the Norwegian mass media, provides the total number of matches and minutes of play for each player in the elite league during the last season. About two thirds of the players participated both seasons. These players were separated into two groups according to whether they had experienced a head impact the last season or not, and changes in neuropsychological performance from baseline 2004 to baseline 2005 were assessed.

In addition, three teams in the original cohort agreed to participate in two separate training sessions prior to the 2006 season (N=48); one high-intensity football training session where heading of the ball was not allowed (High Intensity Exercise Group) and one low intensity training session with heading exercises (Heading Group). Baseline testing was performed before the first training and after each of the two sessions following the same algorithm as sketched out in *Figure 5*.

Ethics

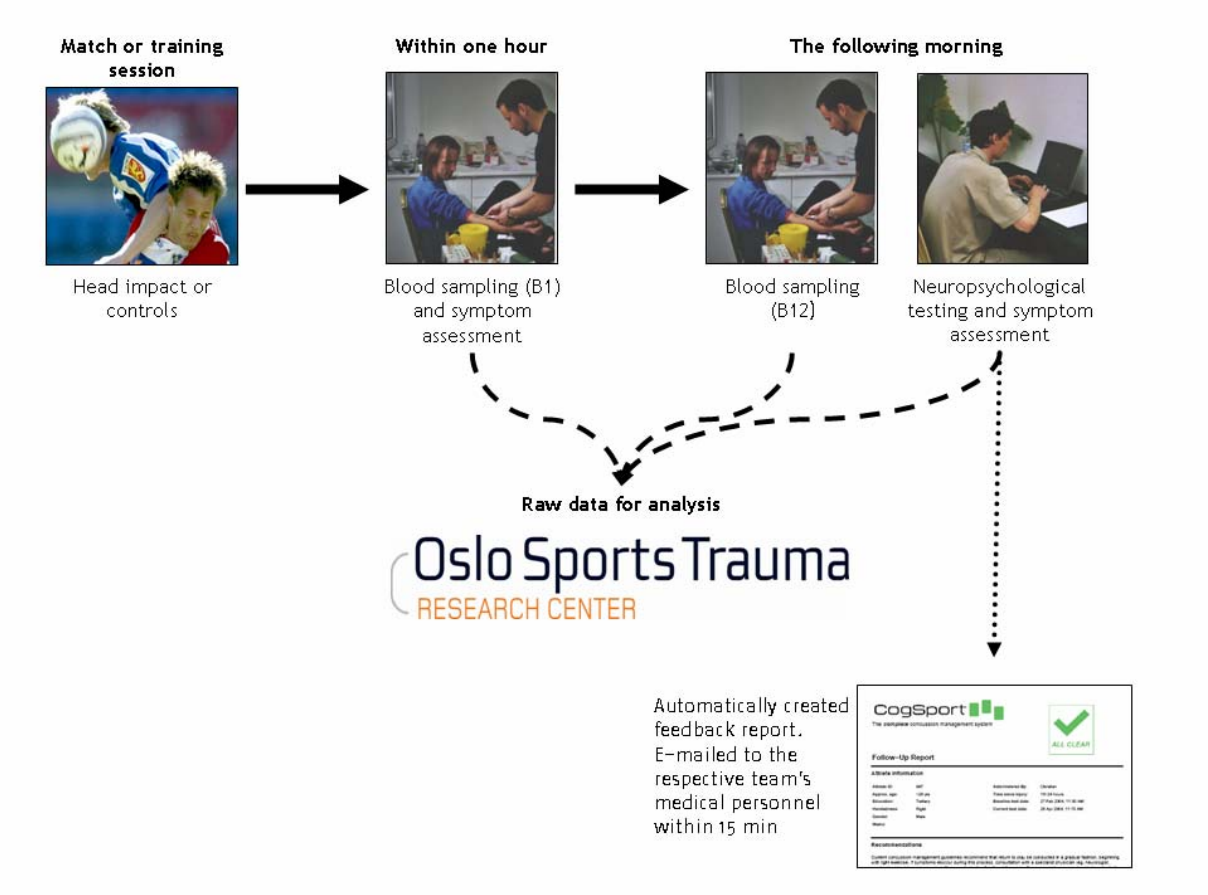
The study protocol was approved by the Data Inspectorate and the Regional Committee for Medical Research Ethics, Helse Sør. All participants in the study received both oral and written information of the design and purposes of all parts of the study. Written informed consent was obtained at baseline for all participants.

Assessment Tools

A computer-based neuropsychological test (CogSport, CogState Ltd, Charlton South, Victoria, Australia) and a biochemical marker; protein S100B, were chosen as our evaluation tools. The rationale behind this was that both these assessments could quite easily be applied to a large cohort of football players throughout the country without requiring much special

equipment, trained personnel or facilities and without being too time-consuming for the athletes. In addition, the team's medical personnel would get online feedback within 15 minutes with results of the neuropsychological testing, which could be helpful in further treatment and monitoring of the player. It was thought that this fast feedback could also enhance compliance with the test protocol.

Figure 5: *The test algorithm that was applied for all follow-up assessments*



S100B Assay

Venous blood samples were collected from an antecubital vein and drawn into a standard gel 7 mL tube (BD Vacutainer® Blood Collection Tube, New Jersey, USA) and allowed to clot for 30 min before centrifugation (3000g) for 10 min. The resulting serum was divided into two 1.5 mL Eppendorf tubes and frozen within two hours. Serum S100B concentrations were measured using an electro-chemiluminescence assay (ROCHE Elecsys®, ROCHE Diagnostics, F. Hoffmann-La Roche Ltd, Basel, Switzerland). The lower detection limit of the assay is 0.005 ng/mL (ROCHE, 2004) All analyses were performed at the Department of Clinical Chemistry and Clinical Biochemistry, University of Munich, Germany according to

the procedure described by Mussack *et al*. (Mussack *et al.*, 2006) and Bieberthaler *et al*. (Biberthaler *et al.*, 2006). Based on previous studies on S100B after minor head traumas (Mussack *et al.*, 2000; Biberthaler *et al.*, 2001b; Biberthaler *et al.*, 2002; Ingebrigtsen and Romner, 2003; Biberthaler *et al.*, 2006), a cut-off value of 0.12 ng/mL was used to classify the B1 samples as elevated or within the normal range.

All baseline samples were taken before training between 7:30 and 10:00 am. Baseline blood sampling was performed in a subgroup of players (N=49) on three different days during their two-week training camp to assess the variation in baseline serum S100B concentration. The follow-up samples were drawn within one hour after the match or activity and the following morning.

Assessment of Neuropsychological Performance

In this study, the English or Norwegian version 2.2.2 or 2.3.1 of the CogSport test were used (CogSport, CogState Ltd, Charlton South, Victoria, Australia). The CogSport test battery consists of seven different tasks assessing the following different cognitive functions: Psychomotor function, Decision-making, Simple attention, Divided attention, Working memory, Complex attention and Learning & Memory. The different tasks are described more thoroughly in *Table 4*, but they all use on-screen playing cards as stimuli and the D "No" and K "Yes" keys are the only keys used throughout the whole test *(Figure 6)*. The response key designations are reversed for left-handed subjects. Mean reaction time in milliseconds, consistency (standard deviation) and accuracy (percent correct responses) data are provided for all tasks. The CogSport battery also includes a symptom check list assessing the presence of: dizziness, headache, nausea, vomiting, blurred vision, feeling confused, drowsiness, difficulty falling asleep, difficulty remembering, difficulty concentrating, irritability, balance problems, sensitivity to light and sensitivity to noise at the time of testing and at the time of the incident. The test file is sent as a coded file via the software to the manufacturer and an automated report is received by mail within 15 minutes.

All subtasks include 15 to 40 trials, and the data are reported by the CogSport program as the mean reaction times with their corresponding standard deviations for all subtasks, accompanied by accuracy data for all tasks but Simple Reaction Time and Monitoring. Anticipatory responses (reaction times <100 ms) and abnormally slow responses (reaction times >3500 ms) are recorded as errors and excluded from the analyses. Accuracy data are

Figure 6: *On-screen picture of the CogSport Learning and Memory task*

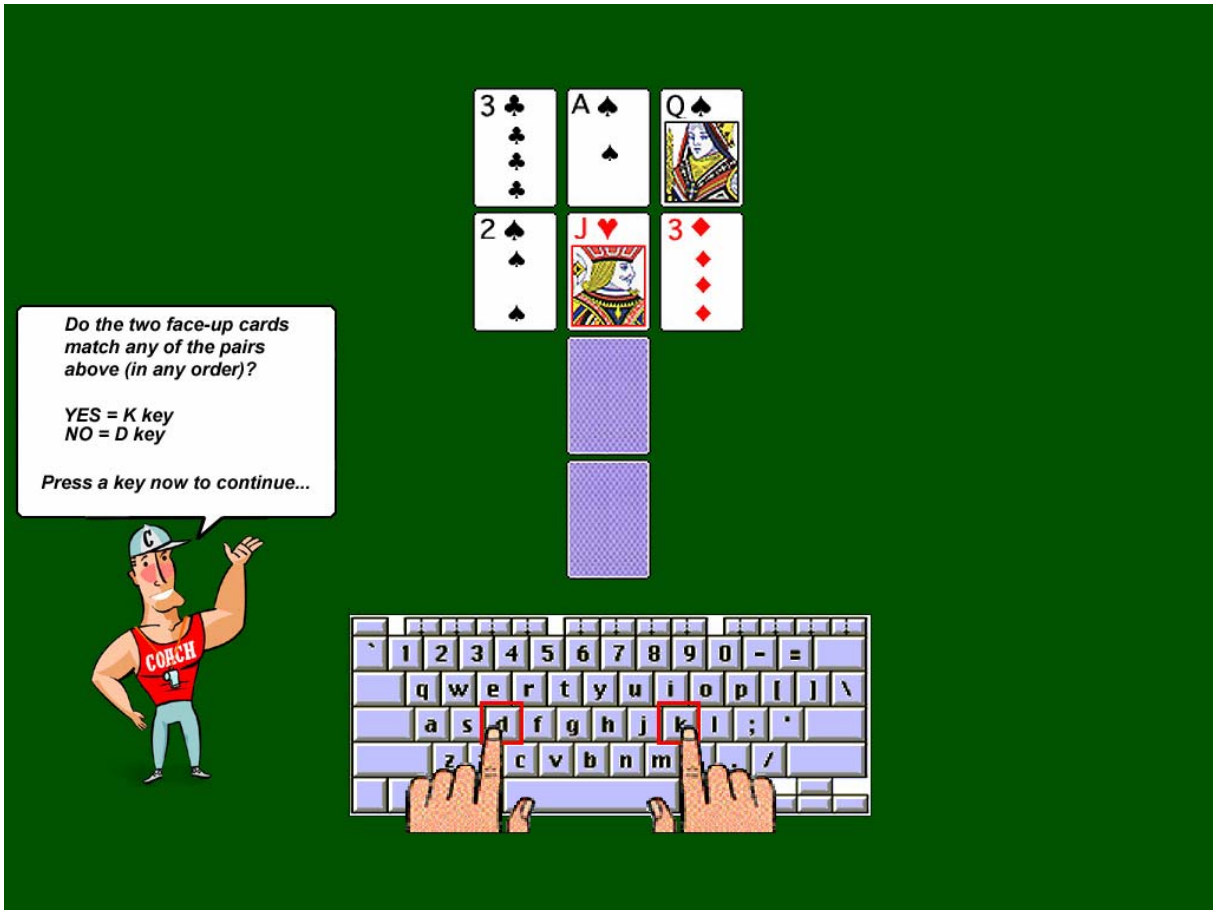


Table 4: *Description of the seven CogSport subtasks and the assessed cognitive function*

Test	Description	Cognition
Simple Reaction Time	A single card is presented face down at the centre of the screen, and the player is instructed to press "yes" whenever the card turned face-up. Fifteen trials are presented and the test is repeated three times; at the beginning, in the middle and at the end of the battery. All other tests are just presented once	Motor function
Choice Reaction Time	This test used the same stimuli as above, but the player is now instructed to indicate whether the card is red by pressing "yes" or black "no"	Decision-making
Congruent Reaction Time	Two cards are presented and the player had to indicate if they are the same colour or not by pressing "yes" or "no"	Simple attention
Monitoring	Five cards moves simultaneously on the screen and the player is instructed to press "yes" as soon as one card moves outside a predefined area	Divided attention
One-Back	The player is instructed to indicate whether a new card is identical or different from the last by pressing "yes" or "no"	Working memory
Matching	Six card pairs are presented at the top of the screen and the player has to decide whether a pair presented at to bottom of the screen matches any of the above	Complex attention
Learning	*Incidental learning:* Follows immediately after the Matching task, and is identical to this task except that the six pairs are turned face down.	Learning and memory
	Associate learning: Similar to the matching task, however the pairs turn face down when the player correctly indicates a matching pair presented at the bottom of the screen.	

calculated as the number of true positive responses divided by the number of trials. If one player has more than 40 incorrect responses on one task, the test is stopped.

Prior to the analyses of the follow-up tests, the Complex attention task was omitted from the test battery by the producer due to low reliability (Collie *et al.*, 2003b), and consequently only the six remaining variables were used in the follow-up analyses.

All testing was performed on personal computers with the sound switched off in a quiet room in groups of one to five, supervised by trained personnel. At baseline, all players conducted two consecutive tests, where the first was regarded as a practise round and discarded. The follow-up testing was performed locally, supervised by one of the administrators of the study or by the team's own medical personnel, the day after the head impact, match or training.

Prior to both seasons, the medical personnel from all included teams received written information about the study and the testing procedures and representatives for all teams attended a seminar where additional information and instructions regarding the study protocol were given.

Questionnaire

At baseline the players were asked to complete a two-page questionnaire addressing age, nationality, education level, player position, seasons in the Tippeliga and lower division leagues, highest level of education, and history of exposure to solvents, general anaesthesia, headache, migraine, epilepsy, depression, hyperkinetic activity disorders or learning disabilities (see paper II fro details). In addition, the players filled out an estimate of their typical number of headings per match, the number of previous concussions (football and non-football) and alcohol consumption. A 20-item post-concussion symptom scale (Lovell and Collins, 1998) was also included.

The Different Study Groups in the Prospective Study

Head Impact Group

During both seasons, the participants were followed during all regular league matches, and all head impacts were registered live by local medical personnel present at the arena (team

medical personnel or other local medical personnel recruited by the administrators of the study). The criteria for including head impacts in the sample were adopted from Andersen *et al*. (2004b): 1) All situations where a player appeared to receive an impact to the head (including the face and the neck), 2) The match was interrupted by the referee and 3) The player laid down on the pitch for more than 15 seconds. All three conditions had to be present to be defined as a head impact. It must be noted that these criteria do not include any characterisation or diagnosis of an injury, and the impact does not necessarily have to result in any injury to be included in the study. Thus, the term "impact" is used intentionally to distinguish these incidents from minor head injuries or minor head traumas, which have been the main focus in the previous research within the field.

In case of a head impact (irrespective of whether the player was taken out of play or not), the local medical personnel were instructed to perform a clinical evaluation of the player immediately after the match. This included filling in the post-concussion symptom scale (Lovell and Collins, 1998), the Glasgow Coma Scale (Teasdale and Jennett, 1974), and the presence and duration of loss of consciousness and post-traumatic amnesia. In addition, the player was followed up according to the algorithm outlined in *figure 5*.

Video Review of the Head Impacts

All matches were reviewed the following morning on video at the facilities of the Norwegian Broadcasting Company (NRK) at Marienlyst, Oslo. If a head impact was identified, the respective team's medical personnel were contacted by phone to check the follow-up status and, if necessary, arrange neuropsychological testing and blood sampling.

Video images of the identified head impacts were copied to a computer and analysed independently by TM. Straume-Næsheim and A. McIntosh at the end of the follow-up period. The results were then compared and disagreements were re-reviewed in a consensus group meeting (TM. Straume-Næsheim, A. McIntosh and TE. Andersen), where a final decision was made. The impacts that were followed up with either blood samples or neuropsychological testing were identified (Head Impact Group) and compared with the missed incidents to assess whether there was any selection bias with respect to the severity of the incidents.

Each head impact was classified as "definite", "doubtful" or "could not be assessed" with respect to whether the actual impact to the head was visible or not. This classification along with the global impression of severity (severe or not severe) and whether the player returned

to play in the same match or not, was considered as general assessments of the potential severity of each incident. In addition, a more specific impact severity assessment was created using the following four factors: relative speed (which included a gross estimate of the direction of the players involved; same direction or towards each other), head movement contribution, anatomical location of the impact to the head and striking body part (mass/hardness). See papers III and IV for more details.

Outcome of the Head Impacts

The head impacts were cross-referenced with the injuries reported by the team's medical staff to the league's (Tippeligaen) injury surveillance system (TISS), which is administrated by Oslo Sports Trauma Research Centre. This register receives data from all the teams in Tippeligaen on a monthly basis, and includes all injuries from all team activities that have resulted in absence from training or match (time-loss injuries, Fuller *et al*. (2006)), as well as the time and date of the injury, type of match, diagnosis, and the number of days before the player returned to training or match (Andersen *et al.*, 2004b).

Match Controls

Players from the same cohort, who had played a regular match without experiencing a head impact, were used as controls in both Paper III and IV (Match Control Group). The players were recruited from six different teams and the respective matches were copied to videotape and reviewed to verify that none of the controls had experienced any head impacts during the match. In addition, a count was made of the number of headings and other head accelerating events for each individual player in the group during the match (i.e. falls or collisions that did not qualify as head impacts).

Training Groups

Players from three of the included teams from the original cohort were asked to participate in two separate training studies after the 2005 season; one high-intensity football training session where heading was not allowed (High-Intensity Exercise Group) and one low-intensity training session with match-realistic heading exercises (Heading Group). These sessions were planned in cooperation with the team coach and led by the regular coaching staff. The high-intensity football play and heading exercise were organised to be as close to the match situation as possible in terms of the exercise intensity or the number and force of the headings.

Normal values for the number of headings per player per match was established by counting all headings in matches that were followed live by one of the study administrators during the 2005 season (N=241 players, 2-4 matches counted per player). However, this count exhibited large variations between the different playing positions, ranging from 0 headings per match for the goaltenders and up to 20 for some of the central defenders. Thus, no standard number of headings was set for the training sessions. The players were instead asked to rate their heading frequency compared to a regular match on a scale from 0 to 6 (0=much less, 3=same, 6=much more) on a questionnaire completed after the different training sessions. The same rating was applied for the level of fatigue in both the high-intensity and the heading session, since the level of exertion also varies according to the playing position (Reilly, 2003; Arnason *et al.*, 2004). Both these variables were dichotomised into "less" or "same or more" in the analyses.

Participants, Effect Variables and Statistics of the Different Papers

All statistics were performed on a computer using the Statistical Package for the Social Sciences versions 13.0 to 15.0 (SPSS, SPSS Inc. Chicago, USA). Categorical variables were tested for between-group differences using Chi-square or Fischer's exact tests and bivariate correlations were calculated with the Spearman's rho correlation coefficient. Relative risk (RR) was used for comparing risk between groups. Independent samples t-test was used for comparison between normally distributed data, while the Mann-Whitney U test was the non-parametric test of choice. Unless otherwise stated, the level of significance was set to $p<0.05$.

Paper I

The reproducibility analyses presented in this paper were based on the two consecutive baseline neuropsychological tests performed by all players prior to the 2004 season. The reproducibility was evaluated using the method error for calculating the coefficient of variation, which quantifies the variation between each test administration as a percentage of the joined mean of the two tests (Sale, 1990). To enable a comparison with reproducibility studies of the test performed on other populations (Collie *et al.*, 2003b), intraclass correlation coefficients for all measures were also calculated (Shrout and Fleiss, 1979; Benestad and

Laake, 2004). The Intraclass correlation coefficient is typically a value between 0 and 1, where a value of 1 indicates perfect reproducibility.

Paper II

The material for Paper II was also based on the data from the 2004 preseason baseline testing. The first test of the two consecutive neuropsychological assessments was regarded as a practise round, and all analyses were based on the second test. In addition, demographics and player characteristics were collected from the questionnaire completed by all participants.

The main effect variables here were the log 10 transformed mean reaction time data for all subtasks. From the patient history questionnaire, the total number of previous concussions, number of headings per match and lifetime heading exposure were chosen as independent variables. Lifetime heading exposure was estimated from the self-reported number of heading actions per match multiplied with the number of regular league matches played per team per season (N=26) and career duration estimated as the number of years above 16 years of age. The goaltenders were excluded from all the analyses using the heading exposure data.

Separate multiple regression analyses were created for these three independent variables and the seven different reaction time effect variables. The regression analyses were adjusted for possible confounding variables such as age, alcohol consumption, use of other central stimulants, previous number of surgical operations demanding full anaesthesia, exposure to solvents, learning difficulties, level of education, and neurological diseases. This was done by entering one variable at a time in the different regression analyses using a stepwise analytic model.

The association between previous concussions (yes/no) and the number of headings per match or lifetime heading exposure was investigated using a logistic regression model. Differences in neuropsychological performance between the least and most frequent headers were assessed by independent t-tests.

Finally, the received automated reports from the manufacturer of the test (Collie *et al.*, 2006a) were used as an indication as to how many of the footballers that performed within the normal range when compared to the general population.

Paper III

This paper focused on the baseline and follow-up results for the S100B samples collected for both seasons. The change in S100B concentration from baseline to follow-up for the Head Impact Group was compared to the results for the Match Control Group and the two training conditions (High Intensity Exercise Group and Heading Group). The null hypothesis that there was no difference between groups in the absolute or change in S100B serum concentration at any time point was tested using One-Way ANOVA with Bonferroni post-hoc p-value adjustments and pair-wise t-test comparisons.

All S100B concentrations presented in the text are back-transformed values from the log10 values used in the analyses.

Paper IV

In this paper, the change in neuropsychological performance from baseline to follow up for the Head Impact Group was compared to the Match Control Group. The data was collected from both seasons. In addition, the change from baseline 2004 to baseline 2005 was investigated and the results for the players who had experienced a head impact during the 2004 season were compared to players with no registered head impacts that particular season.

The main effect variable was a global change in neuropsychological test performance from baseline to follow-up for the head impact groups (Head Impact and Season Head Impact) compared to the controls (Match Control and Season Control respectively). The percent change for all six subtasks were included in a general linear model (Multivariate Analyse of Variance, MANOVA). If a significant difference was found, post-hoc pair-wise t-test comparisons with Bonferroni corrected p-values were performed to reveal significant differences between the examined groups for each of the six subtasks in the neuropsychological test battery. A within-person comparison was also performed to identify individual players with significant deteriorations from baseline to follow-up using the standardised regression-based reliable change index (RCIsrb) (Sawrie *et al.*, 1999; Erlanger *et al.*, 2003). In agreement with previous literature, a RCIsrb value below 1.64 (90th percentile, two-sided) on two or more tests was considered as a reduced neuropsychological performance (Rasmussen *et al.*, 2001; Lewis *et al.*, 2006).

Paired pre-post comparisons of the reaction time data within each group are presented for descriptive purposes only. The mean reaction time data were log10 transformed in the analyses to obtain a normal distribution. However, back-transformed data in ms are presented in the tables.

Power Calculations

Clinical relevant changes were set to a one standard deviation change from baseline mean for both the blood sample values and the neuropsychological test values. Sample size calculations revealed that these differences could be detected with samples sizes down to 17 in each group with the power set to 80% (β=0.8) and a significance level at 5% (α=0.05).

Results

Compliance

Due to the considerable turnover of players within each team in the pre-season period the exact number of the players in the A-squad in this period was difficult to assess. In *Table 5* the participation rate at baseline is calculated based on the players available at the pre-season testing. This figure is the most valid for the papers based on the baseline assessments (Paper I and II). In the prospective analyses presented in paper III and IV it would be more correct to use the number of players that were active during the respective seasons for calculating the baseline participation rate (League players in *Table 5*). A total of 326 players played in at least one regular match in Tippeligaen in 2004 and 334 players in 2005. However, since 205 of these were active in both seasons a total of 455 different players were active in Tippeligaen during the whole study period. Their mean age was 25.2 (18 to 34) years and 317 (79.1%) of the players were Norwegian or Scandinavian. This also means that the study covered a total of 660 "player seasons" (one player playing one season, 326 + 334, *Table 5*). Of these 660, preseason blood sampling was completed for 452 (68.3%) and the corresponding number for the neuropsychological tests was 462 (70.0%).

Table 5: *The compliance with the test protocol for the prospective league study*

	Pre-season Baseline			Season Follow up						
					Head Impact Group			Match Control Group		
	N*	Cog-Sport	S100B	League players[§]	N[†]	Cog-Sport	S100B	N	Cog-Sport	S100B
2004 cohort	300	271 (90%)	255 (85%)	326	105	17 (16%)	27 (26%)	53	47 (89%)	49 (92%)
2005 cohort										
Players from 2004	205	37 (18%) (Impact)[†] 107 (52%) (Control)[†]	141 (69%)	205	59	18 (31%)	17 (29%)	-	-	-
New 2005	181	133 (73%)	139 (77%)	129	64	9 (14%)	21 (33%)	-	-	-
Total 2005	386	277 (72%)	280 (73%)	334	123	27 (22%)	38 (31%)	-	-	-
Totals for both seasons	686	548 (80%)	535 (78%)	660	228	44 (19%)	65 (29%)	53	47 (89%)	49 (92%)

**In the pre-season period there was considerable turnover within each team, and thus the exact number of the players in the A-squad in this period is difficult to assess. Consequently, some players who were tested at baseline did not play any matches the following season. [§]The term league players represent all players who have been registered in the official match statistics for that particular season, including those who joined the teams after the baseline testing. [†]Head impacts identified on video review of the league matches.*

A total of 48 players were tested at baseline for the high-intensity and heading training sessions. Blood samples were collected for 35 (72.9%) of the players within one hour after the heading session (Heading Group) and for 36 (75.0%) of the players after the high-intensity exercise session (High-Intensity Exercise Group).

Video review was performed for 352 (95%) of the 371 regular league matches and television broadcasted cup matches that was played during the two follow-up seasons and a total of 228 head impacts were identified *(Table 5)*. This corresponded to an incidence of 19.6 head impacts per 1000 playing hours. Follow-up blood sampling was performed in 30% of these impacts (data used in Paper III) and neuropsychological follow-up test were conducted in 19% of the cases (data used in Paper IV). On the other hand, as presented in *Table 6,* only 13 (5.7%) of the 228 impacts were reported in as time-loss injuries to TISS, including 7 (3.1%) concussions (0.6 per 1000 playing hours).

Table 6: *Reported injuries and retrospectively classified concussions based on the Vienna concussion definition for the identified head impacts (N=228).*

	Head Impacts. Post-match follow-up status groups		
	Not followed up	Head Impact S100B (Paper III)	Head Impact CogSport (Paper IV)
N	149 (65.4%)	69 (30.3%)	44 (19.3%)
Reported time loss injuries to TISS (Total 13 [5.7%])	0	10 (14.5%)	11 (25.0%)
Concussion (Total: 7)	0	5 (50.0%)	6 (54.5%)
Facial fracture (Total: 3)	0	2 (20.0%)	3 (27.3%)
Other (Total: 3)	0	3 (30.0%)	2 (18.2%)
Loss of consciousness (LOC)	-	4 (5.8%)	5 (11.4%)
Post-traumatic amnesia (PTA)	-	2 (2.9%)	2 (4.5%)
Classified as concussions (Vienna definition)†	-	27 (39.1%)	22 (50.0%)
Taken out of play due to concussion	-	9 (33.3%)	11 (50.0%)

†Retrospective classification based on symptoms reported by the medical personnel or the players themselves.

The distribution of the general and specific severity assessments derived from the video analyses is presented for the different groups in *Table 7*. In general, the video analyses revealed that the impacts that appeared to be severe, and where the player did not return to play, were more likely to be followed up. On the other hand, for the specific severity assessments, no significant differences were evident, except for the striking body part. The followed-up groups had a lower proportion of hits by the upper extremity compared to the impacts that were not followed up. This was the case for the Head Impacts Groups used in both Paper III (S100B assessment) and Paper IV (CogSport assessment). Nevertheless, only 6

(5 in the S100B Head Impact Group) concussions were reported and 74.7% of the players in the Head Impact Group returned to play in the same match directly after the impact.

Table 7: *Distribution of risk factors identified on videotape for the head impacts which were not followed up and the head impacts that were followed up with post-match blood sampling, CogSport testing or either of the two. Distributions were compared using the Chi-square test.*

		Post-match follow-up status groups				
		Not followed up	S100B (Paper III)	RR (95%CI)	CogSport (Paper IV)	RR (95%CI)
N		149 (65.4%)	69 (30.3%)		44 (19.3%)	
General assessments						
Classification of the impact	Definite	117 (78.5%)	52 (75.4%)		35 (79.5%)	
	Doubtful	19 (12.8%)	4 (5.8%)		2 (4.5%)	
	Could not be assessed	13 (8.7%)	13 (18.8%)		7 (16.0%)	
Global impression of severity	Severe	20 (13.4%)	13 (18.8%)		13 (29.3%)*	2.1
	Not severe	127 (85.2%)	52 (75.4%)		30 (68.2%)	(1.2 - 3.6)
	Could not be assessed	2 (1.3%)	4 (5.1%)		1 (2.3%)	
Returned to play	No	9 (6.0%)	17 (24.6%)**	2.1 (1.4 - 3.1)	17 (38.6%)**	4.0 (2.5 - 6.4)
	Yes	138 (92.6%)	52 (75.4%)		27 (61.4%)	
Specific impact severity assessments						
Horizontal speed	High speed	26 (17.4%)	17 (25.8%)		12 (27.9%)	
	Low speed	70 (47.0%)	34 (51.5%)		21 (48.8%)	
	No relative speed	53 (35.6%)	15 (22.7%)		10 (23.3%)	
Head movement contribution	Both	19 (12.8%)	11 (15.9%)		8 (18.2%)	
	One player	18 (12.1%)	7 (10.1%)		6 (13.6%)	
	No head movement	104 (69.8%)	43 (62.3%)		26 (59.1%)	
	Could not be assessed	8 (5.4%)	8 (11.6%)		4 (9.1%)	
Location	Temporal/parietal	24 (16.1%)	16 (23.2%)		11 (25.0%)	
	Frontal	10 (6.7%)	6 (8.7%)		3 (6.8%)	
	Other	115 (77.2%)	47 (68.1%)		30 (68.2%)	
Striking body part	Head	33 (22.1%)	18 (26.1%)		15 (34.1%)	
	Upper extremity	60 (40.3%)	13 (18.8%)*	0.5 (0.3 - 0.8)	9 (20.5%)	
	Ball	5 (3.4%)	6 (8.7%)		3 (6.8%)	
	Other	51 (34.1%)	32 (46.4%)		17 (38.6%)	

**p≤0.05 and **p≤0.005 on Chi-Square. RR (95% CI) of being followed up was computed for this category versus the rest (e.g. the players who did not return to play were 2.1 times more likely to be followed up than those who returned to play)*

Reproducibility of the Neuropsychological Test

Of the 271 players who were tested at baseline prior to the 2004 season, 39 athletes experienced technical problems with one of the tests or did not fulfil the minimum requirements set by the computer program in order to exclude participants who clearly misunderstood the instructions or were not alert. However, repeated testing was performed on 232 athletes, and the results revealed excellent reproducibility for the reaction time measures,

while less optimal results were obtained for measures of accuracy and consistency (*Table 8*). In addition, a significant learning effect was found for all measures. This effect was most evident for the consistency and accuracy measures. A ceiling effect was present for the accuracy data for all tasks except Learning and Memory. These data also had the poorest coefficients of variation and intraclass correlation coefficients of the variables examined.

Table 8: *Reproducibility reported as the coefficient of variation and the intraclass correlation coefficient between test 1 and test 2 for the seven CogSport subtasks.*

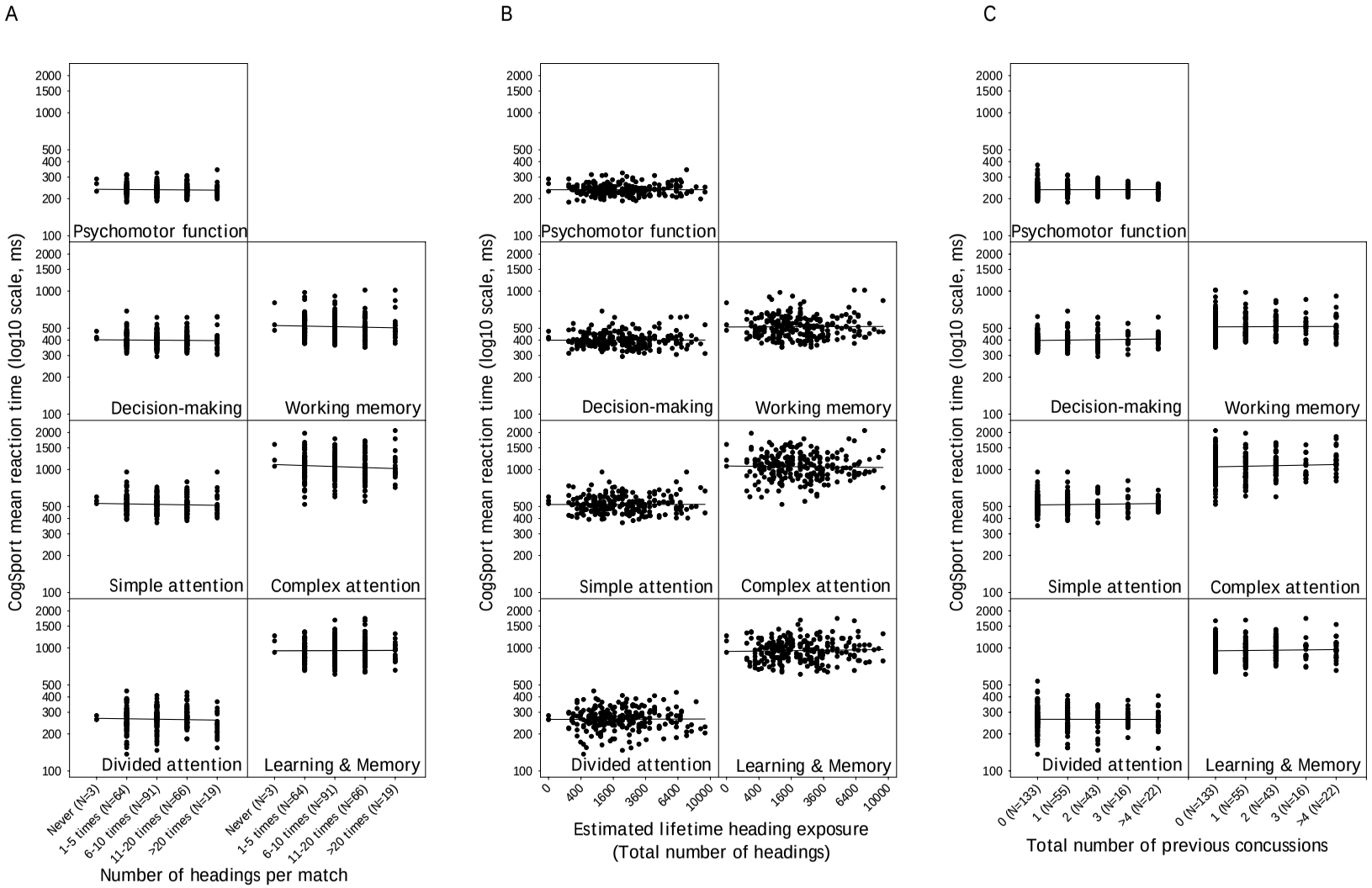
Subtask	Improvement* (%)	Coefficient of variation (%)	Intraclass correlation coefficient
Mean reaction time			
Psychomotor function	0.7	1.0	0.73 (0.67 to 0.79)
Decision-making	0.4	1.4	0.65 (0.57 to 0.72)
Simple attention	1.2	1.4	0.69 (0.61 to 0.75)
Divided attention	1.3	2.7	0.45 (0.34 to 0.55)
Working memory	2.7	1.8	0.71 (0.64 to 0.77)
Complex attention	2.0	1.8	0.69 (0.61 to 0.75)
Learning and Memory	1.1	1.3	0.79 (0.74 to 0.84)
Consistency (standard deviation)			
Psychomotor function	11.4	14.2	0.12 (-0.01 to 0.24)
Decision-making	5.1	9.2	0.39 (0.28 to 0.49)
Simple attention	3.6	7.0	0.35 (0.23 to 0.45)
Divided attention	5.9	6.5	0.32 (0.20 to 0.43)
Working memory	11.4	8.8	0.37 (0.25 to 0.47)
Complex attention	2.7	4.7	0.38 (0.27 to 0.49)
Learning and Memory	2.0	3.7	0.61 (0.52 to 0.69)
Accuracy (percent correct responses)			
Working memory	5.0	12.2	0.21 (0.09 to 0.33)
Complex attention	-1.1	12.4	0.24 (0.12 to 0.36)
Learning and Memory	3.8	10.4	0.31 (0.19 to 0.42)

**All improvements were significant, $p<0.03$. For each test, reproducibility results are shown for the mean and the corresponding standard deviation. Accuracy data are shown for the three most complex tasks only, due to the ceiling effect observed for the simpler tasks (Collie et al., 2006a).*

Effects of Heading Exposure and Previous Concussions

Of the 271 players who performed baseline neuropsychological testing prior to the 2004 season, a total of 137 players (50.6%) reported having had one or more previous concussions (55 players reported one previous concussion, 43 two, 17 three, and 22 more than four), and 112 of these players (81.8%) reported a football-related concussion. Defensive players reported to head the ball more frequently (74.0% with >11 headings per match), followed by attackers (48.8%). The manual count for the 2004 season, which included 18 players observed in two to four matches, showed that the average number of headings per player per match was 8.5 (range 0–26). This data further revealed that the players, at least the frequent headers,

Figure 7: *Relationship between the mean reaction time (log10, ms) and the number of headings per match (A), the estimated lifetime heading exposure (B) and the total number of previous concussions (C) for all seven CogSport subtasks. The subtasks are arranged vertically and from left to right according to their complexity from the top left (easiest) to the bottom right most difficult). Regression lines are shown as solid lines.*



slightly overestimated their number of headings per match. However, the correlation between the self-reported number of headings and the manual count was good (Spearman's rho=0.77, p=0.001), and the majority defined themselves in the same quartiles as those created by the observed values.

The multiple linear regression analyses did not reveal any relationship between the total number of previous concussions and neuropsychological performance for any of the seven subtasks *(Figure 7c)*. In addition, there was no relation between the number of headings per match or between estimated lifetime heading exposure and the neuropsychological test score for any of the subtasks *(Figure 7a and 7b)*. These results did not change if we excluded players with potential language problems (3%). There was also no difference in the neuropsychological test results of players with the lowest heading frequency (0–5 times per match) and those heading most frequently (>11 times per match). However, the estimated lifetime heading exposure was significantly associated with the number of previous concussions (logistic regression exponent=1.97 (1.03-3.75, p=0.039). Furthermore, the group who had experienced one or more previous concussion did not have a higher proportion of players with impaired neuropsychological test performance and their mean reaction time values were not significantly different from the footballers who allegedly never were previously concussed.

Only four players (1.5%) qualified as outliers for one or more subtasks when compared with the normal range as defined by the test manufacturers (that is, outside the 95% confidence interval of the normal population). An additional five players had too many errors with regard to the more complex tasks and their tests were reported as abnormal in the CogSport test reports. However, these players did not differ significantly from the others regarding previous concussions or heading exposure. Thus, 96.1 % of the footballers performed within the normal range as defined by the test manufacturers.

Minor Head Impacts and Serum S100B

In this paper, the serum concentration of S100B after a head impact was compared to the effect of heading, high-intensity exercise and playing a regular football match. Our main finding was that all conditions led to a transient moderate increase in S100B (*Figure 8*). The increase was higher for the two match conditions (Head Impact S100B and Match Control)

compared to the two training conditions, but there were no significant differences between the two match groups at any time point. In addition, the proportion of players above the cut-off for S100B was equally distributed between the two match groups. Even for the impacts that were retrospectively classified as concussions (N=26, 37.7%) based on their symptoms *(Table 6)*, the proportion of players with elevated S100B samples did not differ from their non-concussed colleagues (N=39, 56.5%, Missing: N=4).

The impacts occurred on average 56 (95% CI: 4.5 to 100) minutes prior to the end of the match while the B1 sampling was performed on average 29 (95% CI: 5 to 125) minutes after the match. The B1 sampling for the other groups was performed on average 23 to 33 minutes after the end of the activity (match or training session). Thus, for the Head Impact Group the time from the impact to the B1 sampling was on average 56 minutes longer than the time from the end of the match or training to the blood sampling for the control groups.

For the 13 time-loss injuries reported to TISS, blood samples were available in 9 (69.2%) of the cases. Although some of these injuries were concussions that kept the player out of training or match for more than 21 days, none of these samples were above the theoretical maximum serum level of what can be achieved by stress or exercise-induced disruption of the blood-brain barrier alone (Marchi *et al.*, 2004). In fact, the highest value measured in the whole follow-up study was 0.33 ng/mL, and this sample was drawn from a midfield player in the Match Control Group after a league match where he did not even head the ball.

For the two match groups (Match Control and Head Impact) conjoined, a total of 39 (34.2%) of the B1 samples scored equal to or slightly above the cut-off (≥0.012 ng/mL) but they were equally distributed between the Head Impact and the Match Control groups (Chi-square: $p = 0.48$). Only five B1 samples in the training group (7.0%) were equal to or above the cut-off. Although four out of these were within the High-Intensity group, the numbers were too small to test for any significant differences in the distribution.

The players in the Heading Group who reported the same number or more headings in the training session compared to a regular league match, had significantly higher Delta B1 (B1 ÷ baseline) values than the other players. However, this finding resulted from a significantly lower baseline serum level of S100B for the subgroup who reported the same or more frequent heading intensity *(Table 9)*. There was no significant difference in the serum concentration of S100B at B1 between the two subgroups. Within the High-Intensity Exercise

Group no differences were discovered with respect to the effect of the exercise intensity level *(Table 9)*.

Figure 8: *Mean S100B values in ng/mL for the Head Impact S100B, Match Control, Heading and High-Intensity Exercise groups at baseline (BL), one hour (B1) and twelve hours (B12) post impact/match/training. The error bars represent the 95% confidence interval of the mean.*

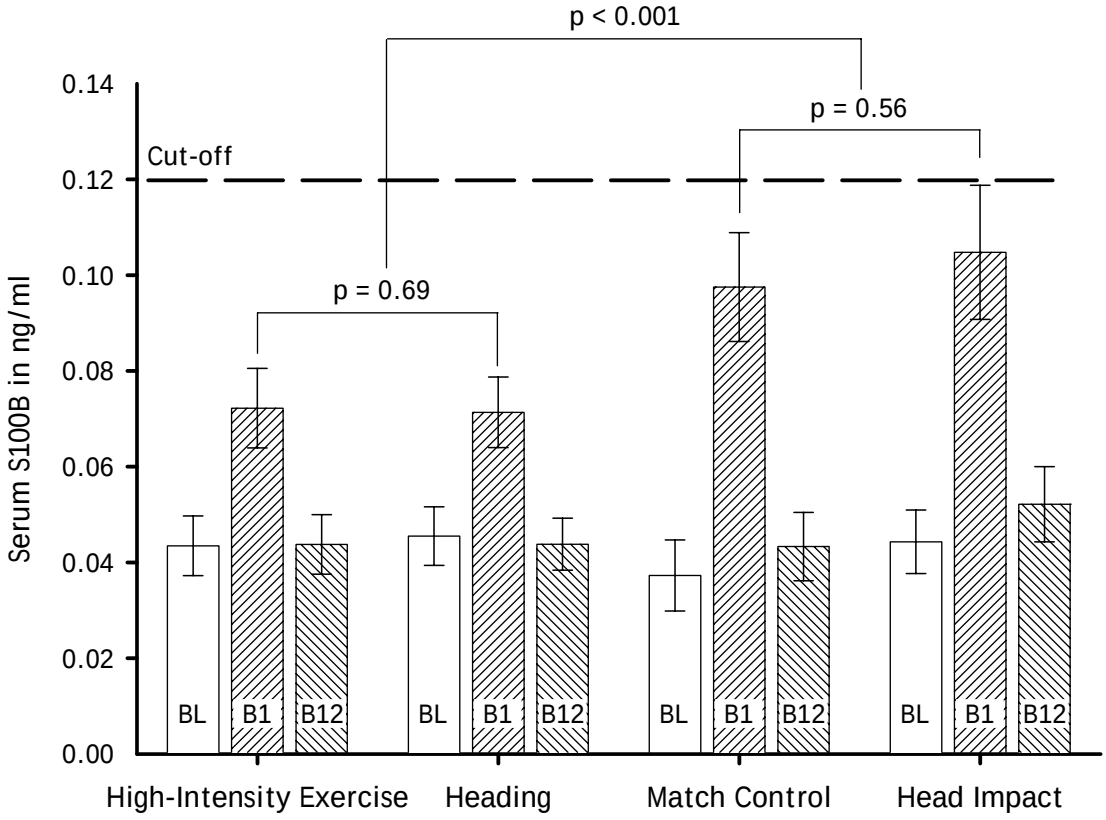


Table 9: *Serum concentration of S100B in ng/ml at all three test points for the High-Intensity Exercise Group and the Heading Group. Both groups are dichotomised according to self-reported level of fatigue or number of headings compared to a regular match.*

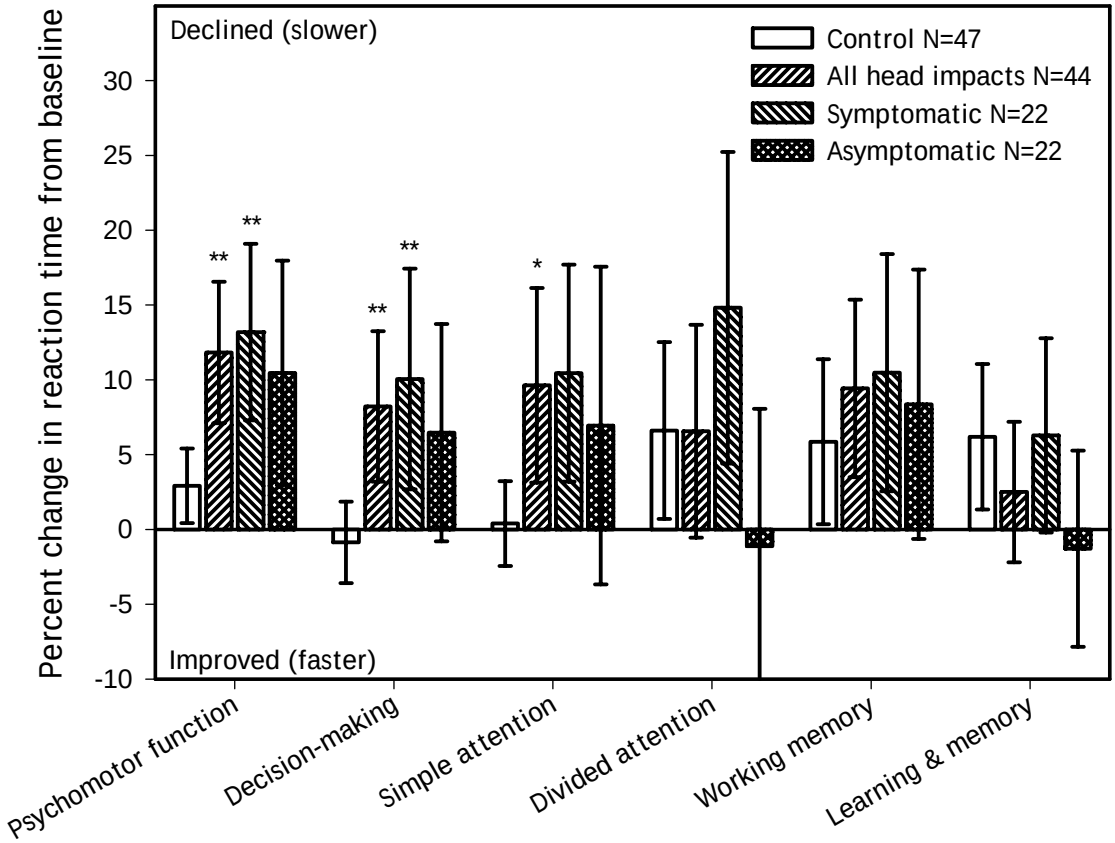
	High-Intensity Exercise Group			Heading Group		
	Level of fatigue vs. match			# of headings vs. match		
S100B sample	Less (N=19, 53%)	Same or more (N=17, 47%)	p	Less (N=10, 29%)	Same or more (N=25, 71%)	p
Baseline	0.043 (0.035 to 0.053)	0.045 (0.036 to 0.056)	0.82	0.061 (0.043 to 0.087)	0.039 (0.034 to 0.045)	0.009
One hour sample (B1)	0.070 (0.060 to 0.081)	0.075 (0.061 to 0.092)	0.57	0.078 (0.057 to 0.11)	0.066 0.060 to 0.072)	0.16
Twelve hour sample (B12)	0.041 (0.035 to 0.048)	0.047 (0.036 to 0.062)	0.40	0.052 (0.036 to 0.075)	0.041 (0.036 to 0.048)	0.20
Delta B1	0.025 (0.011 to 0.038)	0.032 (0.019 to 0.045)	0.73	0.016 (-0.005 to 0.036)	0.025 (0.020 to 0.031)	0.022

For the players in the Match Control Group, there was a trend towards a positive correlation between the number of headings in the respective match and serum S100B at B1 (Spearman's rho=0.28, p=0.056), but not for Delta B1 (Spearman's rho=-0.20, p=0.89). When the number of all other head accelerating events and the number of headings were added, a significant correlation with serum S100B at B1 was found (Spearman's rho = 0.36, p = 0.012), but still there was no correlation with Delta B1 (Spearman's rho = 0.025, p = 0.87).

Changes in Neuropsychological Performance

Neuropsychological testing was conducted the day after the head impact for a total of 44 cases (Head Impact Group). Global testing of the percent change in performance from baseline to follow up revealed a significantly reduced performance for the Head Impact Group compared to the Match Control Group (Wilks' lambda 0.82, p=0.008).

Figure 9: *Change (%) in reaction time from baseline to follow-up for the Head Impact Group and the Match Control Group. Data is also shown for symptomatic and asymptomatic players in the Head Impact CogSport Group. *p<.05 vs. the Match Control Group; **p<.01.*



As illustrated in *Figure 9*, the differences in neuropsychological performance between the groups were mainly apparent for the three simple subtasks, and significant differences were found for the Psychomotor function and the Decision-making tasks. The declines were more prominent among the players reporting to be symptomatic directly after the impact, but no significant differences were found between the symptomatic and the asymptomatic players in the Head Impact Group.

On an individual basis, there were significantly more players in the Head Impact Group with declined performance on two or more tests compared to the Match Control Group *(Table 10)*. A total of 66.6% (N=10) of these players reported having symptoms immediately after the impact or reported symptoms at the time of the test the following day. In addition, five players in the Head Impact Group scored below the 99th percentile of the predicted follow-up score on two or more tests. There was however, no association between deficits in the neuropsychological test results and the serum concentration of S100B. The proportion of attackers and central defenders was higher within the Head Impact Cogsport Group compared to the Match Control Group, but group demographics were comparable otherwise *(Table 11)*.

Table 10: *Reaction time data at baseline and follow up for the Head Impact and Control groups for the tests performed the day after the match. The number of players with a declined performance on each subtest is also presented.*

Task	Baseline (ms, 95%CI)	Follow up (ms, 95%CI)	Sign.†	Number of players with declined performance††
Prospective Match Study, both seasons				
Head Impact (N=44)				
Psychomotor function	228 (221 to 235)	251 (239 to 264)	< 0.001	10 (22.7%)
Decision-making	377 (367 to 388)	401 (381 to 422)	0.004	12 (26.7%)
Simple attention	496 (476 to 517)	530 (501 to 561)	0.005	14 (31.1%)
Divided attention	256 (239 to 275)	268 (250 to 287)	0.21	4 (8.9%)
Working memory	490 (460 to 522)	520 (486 to 556)	0.010	7 (15.9%)
Learning & Memory	903 (852 to 958)	923 (873 to 975)	0.37	0 (0.0%)
Declined performance on ≥ 2 tests				15 (34.1%)*
Match Control (N=47)				
Psychomotor function	231 (224 to 237)	236 (228 to 243)	0.082	5 (10.5%)
Decision-making	392 (377 to 407)	387 (373 to 401)	0.37	3 (6.4%)
Simple attention	505 (485 to 526)	506 (488 to 524)	0.95	2 (4.3%)
Divided attention	257 (246 to 270)	274 (260 to 288)	0.026	3 (6.4%)
Working memory	492 (467 to 518)	511 (484 to 540)	0.041	4 (8.5%)
Learning & memory	919 (867 to 974)	964 (906 to 1024)	0.032	4 (8.5%)
Declined performance on ≥ 2 tests				7 (14.9%)

*All the reaction time data are back-transformed from log10 values. †Paired samples t-test (baseline versus follow up). ††Declined performance was defined as a reliable change index (RCIsrb) below 1.65 (90th-percintile, see methods section).*A significantly higher proportion compared to the Control group (Chi-square test, p=0.033).*

Table 11: *Comparison of the Head Impact Groups and the Control groups at baseline for the prospective match study and the one year follow-up study (baseline 2004 versus baseline 2005).*

	Match case-control study			Baseline 2004 versus Baseline 2005		
	Head Impact (N=44)	Match Control (N=47)	p	Season One Head Impact (N=37)	Season One Control (N=107)	p
Age at incident	26.8 (25.7 to 27.9)	26.2 (25.0 to 27.5)	0.50	27.4 (25.9 to 28.9)	25.7 (24.9 to 26.6)	0.048
Audit† multiplied score (median, IQR)	4.0 (0.0 to 5.0)	4.0 (0.0 to 8.5)	0.50	3.0 (0.0 to 6.0)	4.0 (0.0 to 8.0)	0.82
Number of active seasons	7.1 (5.9 to 8.2)	5.7 (4.6 to 6.8)	0.08	6.5 (5.6 to 7.3)	5.7 (5.0 to 6.4)	0.14
Number of previous concussions (median, IQR)	1 (0 to 1)	0.0 (0 to 2)	0.92	1 (0 to 2)	1 (0 to 2)	0.98
Days from baseline to follow up	130 (110 to 149)	161 (150 to 172)	0.009	346 (340 to 352)	349 (346 to 352)	0.44
Number of headings per player per match	7.8 (6.1 to 9.5)	6.2 (4.9 to 7.4)	0.13	7.4 (6.0 to 8.8)	5.1 (4.2 to 5.9)	0.004
Playing at a position with an increased risk of head trauma††	32 (76.2%)	24 (55.8%)	0.048	26 (70.3%)	44 (41.1%)	0.002

The numbers in the brackets represents the 95% confidence interval of the mean or the inter quartile range (IQR). †Multiplied score of question 1-3 from the Alcohol Use Disorders Identification Test (AUDIT)by WHO (Saunders et al., 1993). ††Attackers and central defenders (Missing data on 6 players).

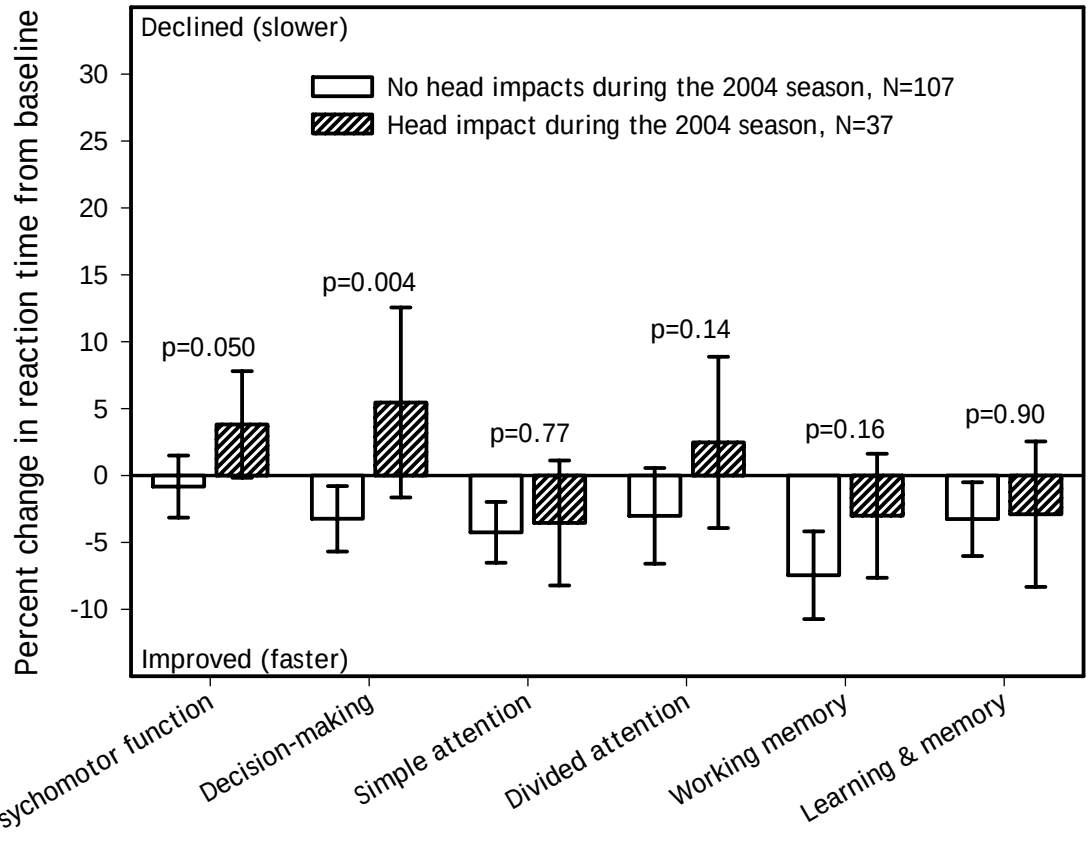
In 17 of the 44 impacts that were followed up, the footballer did not return to play. Eleven cases were due to concussions, as diagnosed retrospectively based on the symptoms reported by the medical staff or player. Six of these (54.5%) showed a decline in performance on more than one test (Fisher's exact test, p=.010 vs. the Match Control Group), but only three of these were reported to TISS as time-loss injuries (two concussions and one jaw contusion). Five players did not return to play after the incident because of other injuries (i.e. two jaw sprains and three facial fractures).

Among the remaining 27 players who returned to play (RTP Group), eleven reported playing with one or more symptoms. The RTP Group was significantly slower than the Match Control Group on the follow-up test (Wilks' lambda: .76, p=.004). The post-hoc analyses of each subtest revealed that only Psychomotor function was significantly different from the Match Control Group (% change: RTP 13.8 [SE 3.2], Match Control Group 2.9 [SE 1.3], p=.004). The proportion of players with reduced neuropsychological performance did not differ significantly between the RTP group (8 [28.6%]) and the Match Control Group (7 [14.9%], p=0.15).

A pre- to post-season comparison (baseline 2004 versus baseline 2005) of the neuropsychological performance for the players who had experienced one or more head impacts during the 2004 season (Season Head Impact Group, N=37) revealed

neuropsychological score changes that were significantly different from their non-injured colleagues (Season Control Group, N=107, *Figure 10*).

Figure 10: *Change (%) in reaction time from baseline 2004 to baseline 2005 for players with (Season Head Impact) and without (Season Control) a registered head impact during the 2004 season (N=144).*



The Season Head Impact Group included all head impacts, also those which were not followed up. The majority (N=31, 83.7%) of the players in this group had experienced only one head impact, and the mean time from the impact to follow up was 200 days (range 107 to 303). However, one player who experienced as many as 6 impacts was still within the normal range for all tests at follow up. Within the Season Head Impact Group there were 7 reported concussions that led to time-loss from training or matches, but only one of these had a deteriorated performance on two or more tasks. This player was, however, below the 99th percentile of the predicted scores and had sustained two concussions during the 2004 season, each keeping him out of training and matches for more than 21 days.

Only four players (10.8%) within the Season Head Impact Group showed a declined performance from one year to the next on two or more subtasks. The corresponding number

for the Season Control Group was 6 (5.7%) but this difference did not reach significance on the Chi-square test (p=0.290). Furthermore, all the baseline tests performed in 2005 for the Season Head Impact Group were within the normal range as defined by the manufacturer of the test.

Discussion

Compliance with the Test Protocol

Baseline testing

Based on the official player statistics, the total number of players in Tippeligaen was approximately 330 each season. Hence, a realistic estimate of the response rate would be close to 80%. However, the exact response rate within this group is difficult to estimate, due to the considerably turnover of players in the professional football market, especially in the pre-season period. This is illustrated by the fact that among the 271 players who completed a baseline neuropsychological test prior to the 2004 season, 36 (13.3%) of them ended up not even playing a single match the following season, and only 144 returned for pre-season baseline testing the next year. Although a few players refused to perform a new baseline test prior to the 2005 season, the most common cause for not participating was that the players were no longer playing in Tippeligaen and had been replaced by new players during the course of the season. Thus, the baseline assessments covered about 70% of the players who went on to play matches.

Nevertheless, the footballer sample in this study is by far the largest sample investigated so far. The main reason for not participating at baseline was that the player was not present at the training camp at La Manga at the time of the testing, and only a handful of the players who were available for baseline testing refused to participate. Although these players had no evident common characteristics, we experienced that when a player with a dominant position in the team refused to participate, his attitude would easily spread to two or three other team members. However, no other selection bias is suspected. Hence, the cohort investigated in this study is considered to be representative for the general population of professional football players in Norway.

Follow up of the Minor Head Impacts

The incidences of minor head impacts and concussions that were identified in the prospective league study were consistent with the incidences previously reported for professional football

both in Norway (Andersen *et al.*, 2004a) and internationally (Fuller *et al.*, 2005). Thus, the included head impacts seem to be representative for the minor head impacts that occur in competitive football.

However, as presented in *Figure 7*, follow-up blood sampling and neuropsychological testing was only performed for about 20% of these impacts. This problem with compliance with the study protocol was identified already after the first season. To increase the compliance for the second follow-up season, additional local bioengineers or physicians were recruited for each arena to serve as objective live observers. Their focus at the match arena was to identify minor head impacts during the match, to perform the 1 hour blood sampling and arrange for the follow-up testing the following day with help from each team's own medical personnel. In addition, all teams were contacted the day after as usual if a head impact was identified on the video review of the match.

Still, these efforts did not increase the compliance significantly. Several different reasons for this were identified, but the by far most significant cause was that the players themselves refused to be tested. The fact that a head "impact" and not a head "injury" was the qualifying criteria for a follow-up test would naturally result in the inclusion of both perceived and actual trivial impacts. Due to the liberal inclusion criteria, the players regarded most of these impacts as trivial and were therefore reluctant to be tested. This is consistent with the results from the video analyses showing that the impacts giving the impression of being severe, and where the players did not return to play, were somewhat more likely to be followed up. Still, we managed to test approximately 30% of the players who *did* return to play. Also more than 50% of the followed-up impacts were initially asymptomatic and thus not diagnosed as concussions according to the Vienna definition. Only about 13% followed-up head impacts were reported to TISS as concussions. Further on, only five episodes of loss of consciousness and two episodes of post-traumatic amnesia were identified, and the vast majority of the players in the followed-up group did return to play after the impact.

Both the cases and the controls in this study were tested after playing a regular league football match at the same level. This is in contrast to the previous retrospective football studies, where the footballers have been compared to controls from other populations (Tysvaer and Lochen, 1991; 1992; Matser *et al.*, 1998; 1999; 2001; Downs and Abwender, 2002). Although there was a higher proportion of attackers and central defenders in the Head Impact Group, compared to the Match Control Group, no significant differences were found for the live

counted number of headings per player per match between the groups. Hence, the main difference between the cases and controls in our study was the head impacts.

Nevertheless, the low compliance with follow-up testing represents the main limitation of this study, and the question is to what extent the followed-up impacts are representative for all the minor head impacts occurring during the course of the matches. The answer is that they were not fully representative. But the vast majority of the followed-up incidents were initially considered as benign and to some extent trivial, with no symptoms or signs present. Apart from the study by Moriarity *et al*. (2004) where neuropsychological changes in amateur boxers were assessed after a competition, this study is the first to include head impacts that were not initially diagnosed as concussions in a prospective assessment of neuropsychological changes after head traumas in sports (Warden *et al.*, 2001; Collins *et al.*, 2003a; Lovell *et al.*, 2004; Moriarity *et al.*, 2004; Pellman *et al.*, 2004a; Gosselin *et al.*, 2006; Collie *et al.*, 2006b). Thus, the assessment of these minor impacts provides new and valuable information with respect to acute nervous tissue injury and the neuropsychological effect of sub-concussive minor head traumas. However, the material is not large enough to enable further analyses of the effects of different injury mechanisms including impact speed, point of impact to the head, striking object, awareness, etc. Although we did manage to do some subgroup analyses based on symptoms, return to play (yes or no) and previous head impacts, the limited size of the material must be taken into consideration when interpreting the neuropsychological results from these analyses. And further on, the limited size of the material restricted any further subgroup analyses.

Reproducibility of the Neuropsychological Test

The assessment of the translated version of the computerised neuropsychological test battery (CogSport) showed excellent reproducibility for the reaction time measures. The measures of consistency and accuracy were less reliable and consequently deemed not to be suitable as outcome measures. These results are in accordance with the reproducibility studies performed by the CogSport group itself (Collie *et al.*, 2003a; Collie *et al.*, 2003b). In their material the reproducibility for the reaction time measures was still high when retested after one week.

Still, this current study did find significant improvements between test 1 and 2 on all subtasks of CogSport. This was most evident for the consistency and the accuracy data, but also the

reaction time measures did show a significant learning effect. However, the improvements for the reaction time data were small, ranging from 0.4% to 2.7%, and a regression towards the mean was evident (Paper III). Basically, this refers to the fact that the extreme cases tend to come closer to the mean with repeated testing, which is a familiar statistical phenomenon, and similar effects have been described in the application of other neuropsychological instruments as well (Erlanger, 2001).

The vast majority of the learning effect has been shown to occur between the 1st and 2nd administration of the test (Falleti *et al.*, 2003; Collie *et al.*, 2003a). Hence, it is proposed that a dual administration of the baseline test, where the first is discarded, would largely tease out the practise effect. In conclusion, the reaction time measures were the most reproducible and the least vulnerable to the practice effect. Hence, they are therefore recommended as primary outcome measures of the test.

Effects of Heading Exposure and Previous Concussions on Neuropsychological Performance

In general, the baseline investigations performed for this current study were based on the same methodology as the previous studies in the field, including retrospective recall of concussion history, self-reported heading frequency, and cross-sectional neuropsychological testing (Tysvaer and Lochen, 1991; 1992; Matser *et al.*, 1998; 1999; 2001; Downs and Abwender, 2002; Witol and Webbe, 2003). However, in contrast to the previous studies a computer-based neuropsychological test was used in this current study. There is no evidence suggesting that the computerised tests used in our study are inferior to the conventional tests used in the preceding studies (Bleiberg *et al.*, 1998; Collie *et al.*, 2003b), rather the other way around. Nevertheless, we were not able to reproduce the previous findings of cognitive deficits among professional footballers, and no association between neuropsychological performance and the number of previous concussions or heading exposure was found. However, there are some differences that could have contributed to the apparent discrepancies between the current findings and the results from the previous studies.

First, it must be kept in mind that not all previous studies have found evidence of impaired neurocognitive performance in football players (Guskiewicz, 2002). Second, critical reviews of these previous studies have raised several concerns, especially related to the methods and

control group selection used, concluding that the evidence behind their conclusions is sparse (Kirkendall *et al.*, 2001; Rutherford *et al.*, 2003). The gold standard is that participants should differ only on the variable under examination. Our approach was to use the footballers themselves as controls since both heading frequency and concussion risk and history varies considerably within this group according to the players' physical characteristics, playing style, technique and playing position (Andersen *et al.*, 2004b; Fuller *et al.*, 2005). However, the neuropsychological performance for the group of players with previous head injuries was not different from their non-injured teammates, and in addition, the proportion of players with impaired neuropsychological performance was the same between these groups.

Still, age may be the most important difference between the current study and the studies that have found the largest neurocognitive deficits related to concussion and sub-concussive blows in sports (Roberts, 1969; Kaste *et al.*, 1982; Tysvaer and Storli, 1989; 1991; 1992; Jordan *et al.*, 1997). The athletes assessed in these studies were significantly older than our footballers. Thus, the discrepancy between the absence of neuropsychological deficits in this current study and the high frequency of such in the work of Tysvær, might partly be due to effects related to aging. However, this is not the case for the other studies reporting cognitive deficits among football players where the players examined were in the same age group as in this current study (Matser *et al.*, 1998; 1999; 2001; Downs and Abwender, 2002; Witol and Webbe, 2003). The deficits reported in these studies on younger athletes were, however, much more subtle and thus more vulnerable for methodological irregularities, such as type 1 statistical errors (Rutherford *et al.*, 2003).

In conclusion, neuropsychological testing of more than 270 professional football players did not reveal any evidence of impairments when compared to normative control data. Half of the footballers had experienced one or more previous concussions, but no effect of these concussions on the neuropsychological performance could be detected. The heading frequency was associated with the number of previous concussions, but not with neuropsychological performance.

Minor Head Impact and Serum S100B

Minor head impacts led to a transient increase in the serum concentration of S100B that exceeded values seen after high intensity training or heading exercises, but did not differ

significantly from the increase caused by playing a football match alone. Apart from a small study showing comparable increases in a group of 10 boxers assessed before and within 15 minutes after a bout in the German amateur boxing championship (Otto *et al.*, 2000), no other studies have measured S100B in athletes after minor head impacts that were not initially diagnosed as concussions. However, several studies have assessed S100B values in minor head trauma patients on admission to the hospital and compared the values with outcome and findings on neuroimaging studies (CT/MRI, *Figure 3)*. The mean S100B value for the Head Impact Group was close to the cut-off used to screen for CT admissions in hospitals, but well below the values for the minor head trauma cases with pathological CT/MRI and also lower than the values for the other hospital admitted minor head trauma cases with normal CT/MRI.

Nevertheless, there are a few concerns that must be borne in mind when interpreting these results. First, approximately 35% of the players who had played a competitive match with or without experiencing a head impact, scored above the assigned cut-off. The values were comparable to the increases seen after non-contact activities (Otto *et al.*, 2000; Dietrich *et al.*, 2003; Stalnacke *et al.*, 2003), and no values exceeded levels thought to represent true neuropathology (Korfias *et al.*, 2006). Nevertheless, there was a correlation between the S100B values and the number of head accelerating events during the match, but there was no correlation between the S100B values and the neuropsychological performance. In the literature there is an agreement that the negative predictive value of the S100B measurements with respect to injury-related lesions on CT/MRI is close to 100% when the cut-off level is set to 0.12 ng/ml. Thus, for 60% of the head impact cases, the chance of having a visible lesion on a CT/MRI scan is close to 0.

The second concern is related to the interval from the impact to the blood sampling. The biological half-life of S100B in serum has been reported to be as short as 25 minutes (Jonsson *et al.*, 2000), and consequently an increase caused by the head impact would decrease substantially during the time from the impact until the end of the match. On the other hand, the time from the impact to the sampling of S100B was comparable to the reported time frames in the studies assessing hospital admitted patients with minor head traumas (Biberthaler *et al.*, 2002; Mussack *et al.*, 2002a; Biberthaler *et al.*, 2006). Still, as previously addressed, the values for the Head Impact Group were significantly lower *(Figure 3)*.

Hence, the head impacts did not have any additive effect on the S100B concentration when compared to playing a football match only. In addition, the values measured within three

hours after the impact were far from the levels seen in hospitalised minor head trauma patients with pathological CT/MRI scans. Consequently, there is no evidence suggesting that the head impacts experienced by these footballers caused any nervous tissue injury.

S100B and Football Play

We found an increase in serum S100B after playing a regular match without experiencing any head impacts. In addition, a somewhat smaller increase was found after a high-intensity exercise without heading. These findings correspond well with the results for the sports studies presented in the meta-analysis of S100B *(Figure 3)*. Playing a competitive match is associated with high levels of stress, adrenaline and physical intensity, which it is difficult to mimic in a regular training session. This was reflected in the post-training questionnaire, where 53% of the players reported a lower level of fatigue after the training session compared to a league match. Hence, the higher B1 values for the match groups compared to training groups in our study could be due to different level of exertion only. These results support the idea that the serum concentration of S100B can be altered be physical activity only. Consequently, S100B is not ideal as a screening tool for potential neuropathology after minor head traumas in sports involving high-intensity physical activity.

S100B and Heading

In our heading exercise session, the idea was to minimize the effect of physical activity and subsequently tease out the effect of heading alone. However, after correcting for the difference in the S100B baseline values within the Heading Group, we could not detect any relationship between S100B and perceived heading intensity. Furthermore, for the Match Control Group we found no correlation between the observed number of headings and head accelerating events and the Delta B1 values as previously reported in studies of Swedish footballers (Stalnacke *et al.*, 2004; Stalnacke *et al.*, 2006). Yet, a closer examination of the baseline levels for the upper quartile compared to the lower quartile with respect to the number of headings in the match, revealed a trend towards higher baseline levels for those who headed more frequently and consequently, this could cause a subsequent bias of the delta values for our Match Control Group. A plausible explanation could be that the baseline samples were collected during a training camp where the players had two or three training sessions per day, and although the baseline blood sampling was performed in the morning

before training, there could be some effects left from the training sessions the day before for the most frequent headers.

In contrast to our results from the heading session, Mussack *et al*. (2003) found that an exercise session with repetitive controlled headings led to a higher transient increase in serum S100B than an exercise session only. However, this difference could very well be due to the fact that our footballers were significantly older and most likely much more experienced headers than the young players who were assessed in the study by Mussack *et al*.

Nevertheless, the heading exercise did cause a transient increase in S100B, even when the physical activity component was reduced to a minimum. However, the magnitude of the increase was well below the values measured after minor head traumas and not distinguishable from the increases seen after high intensive physical activities. Still, the significantly higher values for the Match Control Group might suggest an additive effect of heading and physical activity. As a consequence, the interpretation of an increased S100B value after a head impact in a match is even more difficult. Nevertheless, these values were as illustrated in *Figure 3,* far from levels seen in patients with positive CT/MRI scans and thus there are no evidence suggesting that controlled heading causes any injury to the nervous tissue.

Change in Neuropsychological Performance

This study is the first to prospectively identify neuropsychological changes after head impacts during regular football matches irrespective of whether the impacts were initially diagnosed as concussions or not. On the group level, the largest decline in reaction time from baseline to follow up for any test was approximately 12% (Psychomotor function). Both the magnitude and the pattern of the deficits were comparable to the results reported for other concussed athletes (Makdissi *et al.*, 2001; Erlanger *et al.*, 2001; Iverson *et al.*, 2003; Collins *et al.*, 2003b; Lovell *et al.*, 2004; Moriarity *et al.*, 2004; Bleiberg *et al.*, 2004; Pellman *et al.*, 2004a; Collie *et al.*, 2006b). However, a comparison of the raw data shows that the footballers in the Head Impact Group were generally faster than most of the initially concussed athletes in the other studies on both the baseline and the follow-up assessments. However, the percent change from baseline to follow up was similar. Nevertheless, in other studies, where the deficits also were limited to the Psychomotor function and Decision-making only, the authors

have concluded that these athletes should be considered to have acute cognitive impairments until proven otherwise (Moriarity *et al.*, 2004).

Symptomatic Versus Asymptomatic Players

It should be noted that both the symptomatic and the asymptomatic players after head impacts demonstrated a reduced neuropsychological performance compared to controls (*Figure 9*). This is in contrast to the results from the previously mentioned study by Moriarity *et al*. (2004). They only identified deficits in boxers who presented neurological symptoms and signs to make the referee stop the match to prevent further injury. Except for this study, no other prospective studies have assessed athletes after minor head impacts that were not initially diagnosed as concussions.

On the other hand, several studies have assessed initially concussed athletes where the symptoms have resolved after a few minutes or by the time of testing (Warden *et al.*, 2001; Collins *et al.*, 2003a; Lovell *et al.*, 2004; Pellman *et al.*, 2004a; Gosselin *et al.*, 2006; Collie *et al.*, 2006b). In coherence with the findings in our study, there seems to be an agreement that the largest deficits in neuropsychological performance are found among the players being symptomatic at the time of the test (Lovell *et al.*, 2004; Pellman *et al.*, 2004a; Collie *et al.*, 2006b). Nevertheless, other, studies have revealed electrophysiological changes (Gosselin *et al.*, 2006) as well as neuropsychological deficits (Warden *et al.*, 2001) among concussed athletes where the symptoms have allegedly resolved. Still, our study is the first to demonstrate acute neuropsychological deficits after minor head impacts where the player did not report any acute concussive symptoms.

Long-Term Effects

The comparisons of the baseline from 2004 to baseline 2005 revealed a reduced neuropsychological performance for the players who had experienced one or more head impacts during the 2004 season that were significantly different from their uninjured colleagues. The Season Head Impact group included all head impacts, also those that were not followed up, and a selection bias is therefore unlikely. The main difference between the groups was found for the Decision-making task (*Figure 10*).

Neuropsychological tasks measuring choice reaction time comparable to the Decision-making task in the CogSport battery have proved to detect deficits 3-10 months after closed head

traumas in patients with allegedly good outcome (Stuss *et al.*, 1985; Hugenholtz *et al.*, 1988; Stuss DT *et al.*, 1989). However, these previous studies consisted of cases initially hospitalised for their injury and thus represented a more severe spectrum of minor head traumas. In comparison, within the Season Head Impact Group there were 7 reported concussions that led to time loss from training or matches, but only one of these had a deteriorated performance on two or more tasks.

Not surprisingly, the Season Head Impact Group had a higher proportion of frequent headers, and players playing in positions with an increased risk of sustaining head impacts. Since there were no registration of head impacts from the end of the season in late October 2004 until the follow-up testing (preseason baseline) in February/March 2005, we *cannot* exclude that these players had experienced unreported minor head impacts in a match or during training close to the follow-up test which could have influenced their performance. On the other hand, this skewness in risk of head traumas between the two groups would have been present prior to the baseline testing in 2004 as well, and no significant differences between the two groups were found at that time.

Comparisons of individual change from baseline to follow up have been suggested as more sensitive than cross-sectional control group comparisons for detecting head injury related neuropsychological effects (Sundstrom *et al.*, 2004). Within the Season Head Impact Group, there were only 4 (10.8%) players who showed a declined performance on two or more subtests. Moreover, all the 37 follow-up tests completed by the players in the Season Head Impact Group were within the normal range as defined by the manufacturer. Consequently, the clinical significance of the deficit demonstrated for the Season Head Impact Group compared to the Season Controls is not known.

Clinical Implications

A total of 28 footballers in our study returned to play directly after the impact (RTP Group). Even though these were allegedly asymptomatic and considered fit to play the rest of the match, one third reported at the time of the testing that they indeed had experienced symptoms of concussion directly after the impact and an additional four players experienced a delayed onset of such symptoms. The RTP Group also demonstrated a declined neuropsychological performance compared to controls. These findings emphasise the

perception that concussive symptoms are often not recognised by the players (Delaney *et al.*, 2002), and that, if recognised, only half of the players report their symptoms to others (McCrea *et al.*, 2004). This is also reflected by the large discrepancy between the number of concussions reported to TISS and the concussions classified retrospectively based on the symptom self-report from the 69 followed-up impacts (*Table 6*). If the Vienna concussion definition had been applied, a total of 27 of these would be diagnosed as concussed. This represents 11.8% of all head impacts identified on video during the follow-up period and thus, the corresponding concussion incidence for the players in Tippeligaen would be at least 2.3 per 1000 playing hours, which is up to four times higher than the previously reported incidences (Delaney *et al.*, 2002; Covassin *et al.*, 2003; Andersen *et al.*, 2004a; Fuller *et al.*, 2005; Hootman *et al.*, 2007; Dvorak *et al.*, 2007b).

On the other hand, meta-analyses of previously published studies within the field have not been able to identify neuropsychological deficits attributable to minor head traumas beyond 7 days post impact for the sports-related concussions (Belanger and Vanderploeg, 2005), and 3 months for the minor head trauma population at large (Belanger *et al.*, 2005). This is in line with our results from the baseline investigation (Paper II), where no significant effect of previous concussions on neuropsychological performance was found, and the results from the change in baseline performance from one year to the next, do not alter this perception.

Nevertheless, sub-concussive head impacts in football caused acute impairments in neuropsychological performance that differed significantly from the effect of playing an elite football match. Although the largest deficits were seen in the symptomatic players, both the asymptomatic players and the players who returned to play also showed significant deficits compared to controls. However, this current study does not provide any evidence suggesting that these acute impairments develop into more chronic brain impairments such as chronic traumatic brain injury. Nevertheless, the finding does emphasise the need for an increased awareness of concussion signs and symptoms not only among the team's medical personnel, but also among the players themselves.

Conclusions

A translated version of the computerised neuropsychological test battery (CogSport) showed excellent reproducibility in our large cohort of Norwegian professional football players. The reaction time measures proved to be the most reliable for all subtasks tested and were therefore recommended as primary outcome measures. However, a small but significant practise effect was found, and dual baseline testing with rejection of the first test is advised to minimise these effects.

The neuropsychological testing of more than 270 professional football players did not reveal any evidence of impairments, even when compared to normative controls. Half of the footballers had experienced one or more previous concussions, but no effect of these concussions on the neuropsychological performance was found. The heading frequency was associated with the number of previous concussions, but not with neuropsychological performance.

Both football training and football matches cause a transient increase in serum S100B up to the cut-off level for what is considered as pathological values. The S100B values are, however, below the level for hospital admitted patients with minor head trauma, and minor head impacts do not cause an additional increase in the S100B level beyond what is measured after a regular match. Thus, there is no evidence suggesting that there is significant brain tissue injury after these minor head impacts in football. However, the S100B sample may not be an ideal marker for brain injury in athletes due to the increases seen after physical activity alone.

Signs of reduced neuropsychological performance were found after minor head impacts in football, even in allegedly asymptomatic players and in players who were not removed from play. However, the followed-up impacts represented the more severe spectrum of the minor head impacts in football. Still, only six of these 44 impacts were reported as concussions. In addition, individual pre-season test performance was somewhat reduced from one year to the next in footballers who had experienced one or more head impacts during the season, although all tests were normal when compared to normative data. Consequently, the clinical significance of this finding is uncertain.

Future Research

This study has demonstrated acute neuropsychological changes caused by minor head impacts in football comparable to what is seen after concussions, even in the cases were the player reported no symptoms and continued to play the rest of the match. Nevertheless, even after a verified concussion, among athletes the neuropsychological deficits have been reported to resolve within a few days (Belanger and Vanderploeg, 2005), and there is no reason to believe that the concussive or sub-concussive impacts observed in this study will progress differently.

Other studies have indicated that the brain might compensate for the functional deficits caused by neurotrauma and that symptoms only will emerge with increasing age (Mortimer *et al.*, 1985; Ronnlund *et al.*, 2005; Sundstrom *et al.*, 2006). The latest research in this field also suggests that this vulnerability is attached to a genetic disposition (APOE ε4) (Jordan *et al.*, 1997; Sundstrom *et al.*, 2004; Teasdale *et al.*, 2005; 2006). In conclusion, the questions related to potential cumulative effects of these impacts are still unresolved.

This study, based on the baseline data on 404 football players with normal neuropsychological test performance, represents a unique opportunity to examine the long-term effects of football play. Many of them will continue to play football in different teams in Tippeligaen for several years ahead, and the teams' medical personnel will continue to report time-loss injuries to TISS. Consequently, this represents an opportunity for a five and ten year follow-up study assessing the development in neuropsychological performance for the footballers. One might also consider performing APOE-genotyping to identify if this is a contributing factor to the neurocognitive development in football players, although this raises some ethical issues. In addition, a control group of elite athletes from non-contact sports should be added as an additional control group. Baseline data has already been collected from a group of Norwegian elite swimmers and orienteerers for this purpose.

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Paper I - IV

Paper I

SUPPLEMENT

Reproducibility of computer based neuropsychological testing among Norwegian elite football players

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Background: Head injuries account for 4–22% of all football injuries. The rate of brain injuries is difficult to assess, due to the problem of defining and grading concussion. Thus computerised testing programs for cognitive function have been developed.

Objective: To assess the reliability of a computerised neuropsychological test battery (CogSport) among Norwegian professional football players.

Methods: Norwegian professional football league players (90.3% participation) performed two consecutive baseline Cogsport tests before the 2004 season. CogSport consists of seven different subtasks: simple reaction time (SRT), choice reaction time (ChRT), congruent reaction time (CgRT), monitoring (MON), one-back (OBK), matching (Match) and learning (Learn).

Results: There was a small but significant improvement from repeated testing for the reaction time measurements of all seven subtasks (SRT: 0.7%, ChRT: 0.4%, CgRT: 1.2%, MON: 1.3%, OBK: 2.7%, Match: 2.0%, Learn: 1.1%). The coefficient of variation (CV) ranged from 1.0% to 2.7%; corresponding intraclass correlation coefficients ranged from 0.45 (0.34 to 0.55) to 0.79 (0.74 to 0.84). The standard deviation data showed higher CVs, ranging from 3.7% (Learn) to 14.2% (SRT). Thus, the variance decreased with increasing complexity of the task. The accuracy data displayed uniformly high CV (10.4–12.2) and corresponding low intraclass correlation coefficient (0.14 (0.01 to 0.26) to 0.31 (0.19 to 0.42)).

Conclusion: The reproducibility for the mean reaction time measures was excellent, but less good for measures of accuracy and consistency. Consecutive testing revealed a slight learning effect from test 1 to test 2, and double baseline testing is recommended to minimise this effect.

Football is the only contact sport that exposes a large number of participants to purposeful use of the head for controlling and advancing the ball.[1] Based on a series of cross-sectional studies using neurological examinations, neuropsychological tests, computed tomography scans and electroencephalographic examinations on active and older retired Norwegian football players, Tysvaer[2] postulated that heading the ball could lead to chronic brain injuries as seen in boxing. Since then, several cross-sectional studies have indicated that football can cause sustained measurable brain impairment,[3–6] although not all studies have reported such a relation.[7 8]

Head injuries account for 4–22% of all football injuries[2] with a reported incidence during matches of 1.7 injuries per 1000 player hours.[9] However, this figure incorporates all types of head injury, including facial fractures, concussions, lacerations, and eye injuries. The incidence of concussion has been estimated to be 0.5 injuries per 1000 match hours[9] but is difficult to assess, due to the problem of defining and grading concussions.[1 10] When using the traditional diagnostic criteria for concussions, which require loss of consciousness or amnesia, only a fraction of these are recognised as concussions. Trauma to the neck and/or head that is sufficient to cause facial fractures or lacerations, will potentially also cause damage to the brain, although this is easily overlooked because of the more visible injuries. Although most athletes with head injuries recover uneventfully following a single episode of concussion, repetitive mild head trauma may be implicated in the development of cumulative cognitive deterioration.[1] Accurate monitoring of symptom resolution and cognitive recovery is therefore important to ensure the athlete's safety and indicate whether the player should return to play or not.

The change of paradigm in the diagnosis and management of concussion has evoked the need for new diagnostic instruments within sports related head injuries. One item in such tests is deterioration in cognitive test performance.[11] In the sports arena, changes in cognition following a concussion injury are conventionally determined by administering a battery of neuropsychological tests during the preseason to establish a baseline for comparison after an injury. In studies using such a design, any changes from baseline are considered to be a consequence of the concussion injury.

In the past decade, computerised cognitive function testing programs have been developed—for example, CogSport (CogState Ltd, Melbourne, Australia), ImPACT (ImPACT Inc., Pittsburgh, PA), ANAM (Automated Neuropsychological Assessment Metrics; developed by the US Department of Defense), CRI by HEADMINDER (concussion resolution index; Headminder Inc., New York). The conventional paper and pencil tests were designed primarily for assessment of cognitive dysfunction caused by neuronal or psychiatric disorders and not for the assessment of mild changes in cognitive function over time.[12] Therefore, these tests often have poor psychometric properties for serial studies including a limited range of possible scores, floor and ceiling effect(s), learning effects, and poor test–retest reliability.[13 14] Computerised testing using infinitely variable test paradigms may overcome these concerns.[15]

Makdissi *et al*[16] compared the sensitivity of the CogSport test and conventional paper and pencil tests to detect cognitive changes following mild concussion in a cohort of elite players from the Australian Football League by comparing baseline tests with post-injury tests. Their data suggested that computerised tests may be particularly sensitive to the cognitive consequences of sports related concussions, and

Table 1 Description of the seven CogSport subtasks and their assumed corresponding cognitive function

Test	Description	Cognitive function
Simple reaction time	A single card was presented face down in the centre of the screen. The was player instructed to press ''yes'' whenever the card turned face-up. Fifteen trials were presented and the test was repeated three times; at the beginning, in the middle, and at the end of the battery. All other tests were presented just once	Motor function
Choice reaction time	This test used the same stimuli as above, but the player was now instructed to indicate whether the card was red by pressing ''yes'' or black ''no''	Decision making
Congruent reaction time	Two cards were presented and the player had to indicate if they were same colour or not by pressing ''yes'' or ''no''	Simple attention
Monitoring	Five cards moved simultaneously on the screen and the player was instructed to press ''yes'' as soon as one card moved outside a predefined area	Divided attention
One-back	The player was instructed to indicate whether a new card was identical to or different from the last by pressing ''yes'' or ''no''	Working memory
Matching	Six card pairs were presented at the top of the screen and the player had to decide whether a pair presented at the bottom of the screen matched any of the above	Complex attention
Learning	*Incidental learning*: this followed immediately after the matching task, and was identical to that task except that the six pairs were turned face down *Associate learning*: similar to the matching task, however, the pairs were turned face down when the player correctly indicated a matching pair presented at the bottom of the screen	Learning and memory

also that conventional neuropsychological tests do not show this sensitivity in athletes with mild concussion. Similar findings have recently been reported in studies on high school athletes with head injuries using ImPACT.[17–19] Computer based cognitive tests have many advantages over paper and pencil tests that may allow them to detect subtle impairments such as those expected to occur in mildly concussed athletes.[20] In general, repeated tests of healthy adults in different age groups have shown that computer based tests are reliable[20 21]; although there is a learning effect between test 1 and 2, this effect seems to decrease after the first two tests.[22]

The test properties of the CogSport test, a computer based neuropsychological evaluation tool widely used in football concussion management, have not been assessed by independent researchers, nor has it been examined among elite athletes. Therefore, the objective of this study was to evaluate the CogSport test by investigating the reproducibility of two consecutive baseline tests in a cohort of elite football players.

METHODS

We invited all the 14 clubs of the Norwegian professional male football league (Tippeligaen) with their A-squad contract players (about 300) to participate in the study; 289 players (90%) agreed to take part. Written informed consent was obtained from all participants and the project was approved by the Regional Ethics Committee for Southern Norway.

Neuropsychological testing

The teams meet for the La Manga Cup and pre-season training camp in February/March every year at the Norwegian Football Association training centre in La Manga, Spain. We conducted testing among 13 of the 14 teams of Tippeligaen at La Manga prior to the 2004 season in a test lab set up in the residential complex, Los Lomas II. Trained personnel administered and supervised the neuropsychological testing, and the tests were completed by the players in groups of three in the same quiet room to allow efficient data collection. The last team was tested at its home field in Norway two weeks later under similar standardised conditions. There is no time difference between Spain and Norway and the testing was performed at the same time of day with the same person instructing and supervising the test for each team.

We used the computer based neuropsychological test CogSport (versions 2.2.0 and 2.2.1). Norwegian speaking players were tested with the Norwegian language version of the test, where instructions for each subtask were in Norwegian, and the rest of the players used the English language version. The test has been described in detail elsewhere.[13 23 24] The stimulus for all tasks consists of playing cards and responses are given using the keyboard. The **d** key indicates ''no'' and the **k** key ''yes'' (vice versa for left handed players). These are the only keys used throughout the whole test.

The CogSport test battery includes seven subtasks testing different cognitive brain functions (table 1). All subtasks

Table 2 Comparison between the results from test 1 and test 2 for the main CogSport outcome measures

Subtask	Mean difference (95% CI)	Improvement (%)	p
Simple reaction time	−0.016 (−0.020 to −0.012)	−0.7	<0.001
Choice reaction time	−0.009 (−0.0158 to −0.003)	−0.4	0.004
Congruent reaction time	−0.034 (−0.040 to −0.027)	−1.2	<0.001
Monitoring, reaction time	−0.031 (−0.043 to −0.0194)	−1.3	<0.001
One-back, reaction time	−0.074 (−0.083 to −0.066)	−2.7	<0.001
Matching, reaction time	−0.062 (−0.072 to −0.0519)	−2.0	<0.001
Learning, reaction time	−0.032 (−0.039 to −0.025)	−1.1	<0.001
One-back, accuracy	0.066 (0.036 to 0.096)	5.0	<0.001
Matching, accuracy	−0.014 (−0.044 to 0.016)	−1.1	0.300
Learning, accuracy	0.039 (0.019 to 0.058)	3.8	0.001

Data are the mean difference of the $\log_{10}$ of the reaction times (ms) and arcsine of the per cent correct responses for the accuracy data for test 1 and 2 with the corresponding 95% confidence intervals (CI) in parenthesis.
Test results were compared using paired Student's *t* test.

include between 15 and 40 trials, and the data are reported by the CogSport program as mean reaction times with corresponding standard deviations for all subtasks, accompanied by accuracy data for all tasks except simple reaction time and monitoring. Anticipatory responses (reaction times <100 ms) and abnormally slow responses (reaction times >3500 ms) are recorded as errors and excluded from the analyses. Accuracy data are calculated as the number of true positive responses divided by the number of trials.

The computer program sends a test report by e-mail to the test supervisor with basic analyses of the result. In addition, the test report includes an estimate of whether the player's performance meets the minimum requirements of the test with regard to alertness throughout the test and the plausibility of whether they understood the instructions or not. This built-in decision is based on the variability of performance on simple reaction time and a threshold value for accuracy on the three final tasks. If a player has more than 40 incorrect responses on one task, the test is stopped.

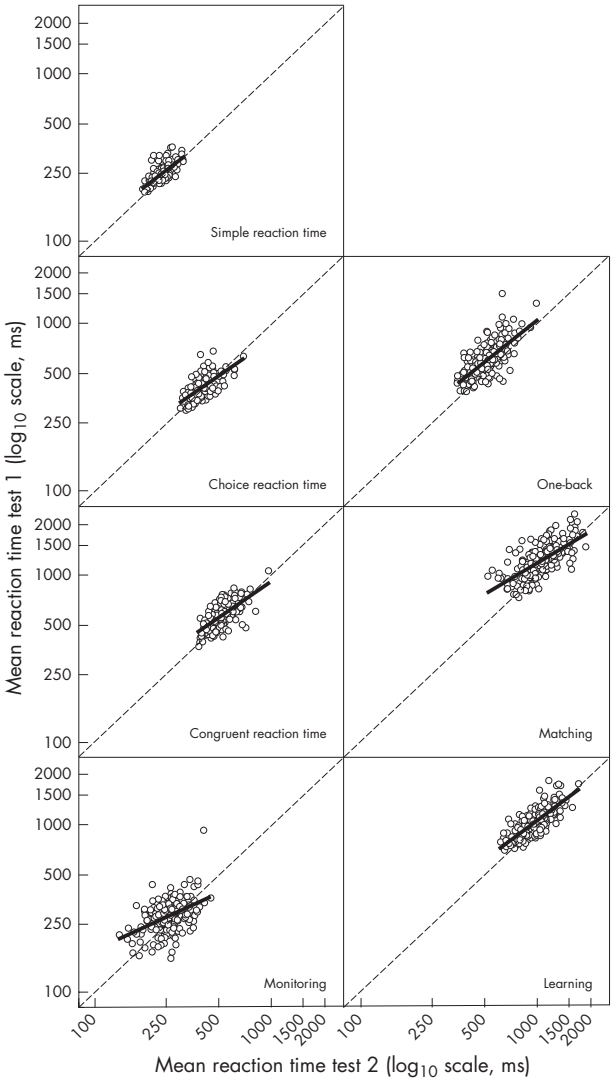

Figure 1 Reproducibility of mean reaction time (log_{10}, ms) for five CogSport subtasks; test 1 plotted against test 2 (n = 232). The hatched line is the identity line (x = y). Regression lines (dotted) have been added to illustrate whether there were systematic differences between test 1 and test 2. The subtasks are arranged vertically and from left to right according to their complexity from top left (easiest) to bottom right (most difficult).

Data analysis

Reliability and correlation studies of CogSport on young adults recommend the mean reaction time for all seven subtasks and accuracy data from the three final tasks (one-back, matching, learning) as the main outcome measures.[20] Our data analysis therefore focused on these 10 measures. Before all calculations, the mean reaction times and standard deviation data were log_{10} transformed and the accuracy data were arcsine transformed to obtain a more normal distribution.[20]

Reproducibility analyses were performed using the method error (ME), calculated as the standard deviation (SD) of the mean difference between test 1 and 2 divided by the square root of the number of tests performed: ME = SDmean diff/$\sqrt{2}$.[25] From the ME we calculated the coefficient of variation (CV), which quantifies the variation between each measurement as a percentage of the joined mean: CV = ME/[(X_1mean + X_2mean)/2]. These calculations were done for all outcome measures supplied by the test. We also calculated the intraclass correlation coefficient for the same measures. The intraclass correlation coefficient is defined as the ratio of the ''true'' variance, or the variance between subjects (S^2_b), relative to the total variance given by the variance between subjects adding the variance within subjects (S^2_w).[26] The intraclass correlation coefficient ranges from 0 to 1, and from the equation it its simplest form (S^2_b /(S^2_b + S^2_w)), we see that when the variation within the subjects (that is, a player's test score on two consecutive tests) moves towards 0, the intraclass correlation coefficient approaches 1 indicating good reproducibility.

We used SPSS version 11 for the statistical analyses and its two way random single measure model for calculating the intraclass correlation coefficients. Paired Student's *t* tests were used to investigate significant differences and any directional trends between the groups.

RESULTS

Demographics

Of the 289 players (96.3%) who agreed to participate in the study, 18 did not report for testing, leaving us with 271 (90.3%) players who underwent two consecutive neuropsychological tests. However, due to technical problems with some tests (unrelated to test performance), the number of players with dual tests decreased to 247. In addition, 15 tests did not fulfil the minimum requirements set by the computer program and therefore could not be included in the analyses. Thus, a total of 232 players (83% Norwegians, 8% Scandinavians (with no problems in understanding Norwegian), and 9% from other countries (mainly European)) were included in the study. The mean (SD) age of the investigated group was 25.7 (4.6) years (range 17–35); 87.5% were right and 12.5% left handed; 62.9% had completed secondary education (that is, high school), and 36.6% had a tertiary level of education (that is, college or beyond). The demographic characteristics of excluded group did not differ significantly in any way from the included group.

Reproducibility

There was a significant improvement in the CogSport subtasks from test 1 to test 2, ranging between 0.4% and 2.7% for the log_{10} transformed reaction time measures (table 2, fig 1). The improvement in reaction time was slightly higher for the more complex tasks compared with the simpler ones (table 2). The accuracy data for the more complex subtasks (one-back and learning) also indicated a better performance (higher percentage of correct responses) in test 2, except for matching (table 2, fig 2).

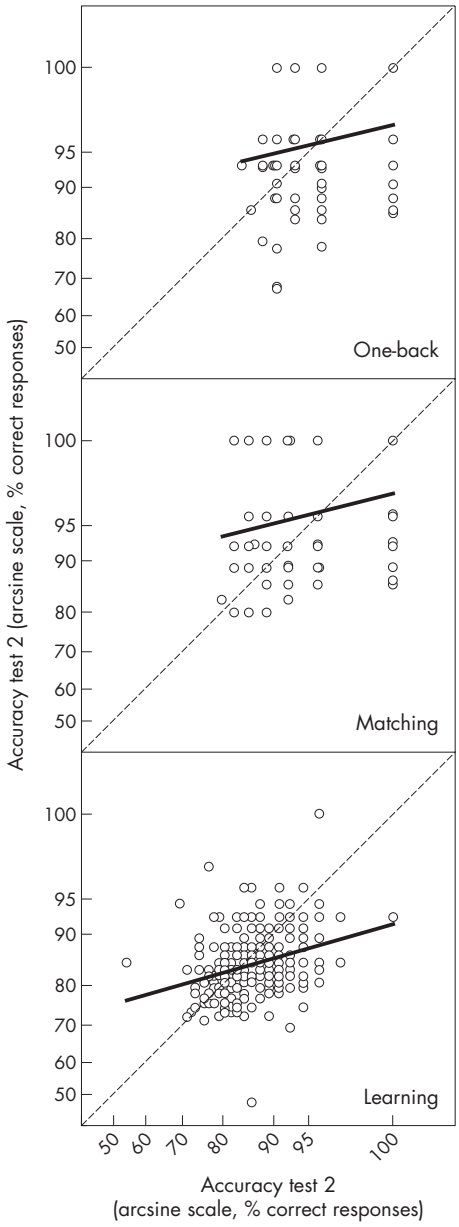

Figure 2 Reproducibility of accuracy (arcsine of % correct responses) for three CogSport subtasks; test 1 plotted against test 2 (n = 232). See fig 1 for further details.

The reproducibility tests resulted in a CV ranging from 1.0% to 2.7% for the reaction time measures (table 3). A closer look at fig 1 reveals higher variability for subjects with slower reaction times and Bland–Altman plots (not shown) were used to examine this phenomenon more closely. They uniformly indicated a somewhat increasing difference in favour of test 2 with increasing reaction time. Thus, a poor performance on test 1 indicated a larger improvement on test 2. The intraclass correlation coefficients were also generally high for the reaction time measurements. All but one task, monitoring (0.45 (0.34 to 0.55)), resulted in intraclass correlation coefficients above 0.65 (up to 0.79 for the most complex task, learning, thus indicating good reproducibility; table 3).

The accuracy data for the three more complex tasks, one-back, matching, and learning, showed poorer reproducibility. The CV ranged from 10.4% to 12.4% and the intraclass correlation coefficient from 0.31 to 0.14 (table 3).

Table 3 Reproducibility reported as the coefficient of variation and the intraclass correlation coefficient between test 1 and test 2 for the seven CogSport subtasks

Subtask	Coefficient of variation (%)	Intraclass correlation coefficient
Mean reaction time		
Simple reaction time	1.0	0.73 (0.67 to 0.79)
Choice reaction time	1.4	0.65 (0.57 to 0.72)
Congruent reaction time	1.4	0.69 (0.61 to 0.75)
Monitoring	2.7	0.45 (0.34 to 0.55)
One-back	1.8	0.71 (0.64 to 0.77)
Matching	1.8	0.69 (0.61 to 0.75)
Learning	1.3	0.79 (0.74 to 0.84)
Standard deviation		
Simple reaction time	14.2	0.12 (−0.01 to 0.24)
Choice reaction time	9.2	0.39 (0.28 to 0.49)
Congruent reaction time	7.0	0.35 (0.23 to 0.45)
Monitoring	6.5	0.32 (0.20 to 0.43)
One-back	8.8	0.37 (0.25 to 0.47)
Matching	4.7	0.38 (0.27 to 0.49)
Learning	3.7	0.61 (0.52 to 0.69)
Accuracy		
Choice reaction time	11.4	0.14 (0.01 to 0.26)
Congruent reaction time	11.1	0.23 (0.11 to 0.35)
One-back	12.2	0.21 (0.09 to 0.33)
Matching	12.4	0.24 (0.12 to 0.36)
Learning	10.4	0.31 (0.19 to 0.42)

For each test, reproducibility results are shown for the mean and the corresponding standard deviation. Accuracy data are shown for the tasks requiring a ''yes'' or ''no'' response.

Additionally, as indicated in fig 2, one-back and matching tasks suffered from a ceiling effect with many participants managing 100% correct responses.

Measures of consistency, as given by the standard deviations of the mean reaction times for each subtask, were subject to greater variability than the mean result and inversely related to the complexity of the task. The CV for the standard deviation ranged from 14.2% for simple reaction time to 3.7% for learning, the most complex task (table 3). In the same way, the corresponding intraclass correlation coefficients increased with increasing task complexity, ranging from 0.12 for simple reaction time to 0.61 for learning (table 3).

DISCUSSION

This is the first study to examine the test properties of a computer based neuropsychological test battery performed by an independent research group. The main finding was that the day to day reproducibility for the mean reaction time measures was excellent in a large cohort of professional football players, but that the accuracy and consistency measures were less reliable. We also observed a slight learning effect from the first to the second test. Thus our results are in accordance with those of recent studies examining the reliability of computerised neuropsychological tests among healthy young adults and elderly people.[20] Collie *et al* assessed the reliability of CogSport by serial testing at a one hour and a one week interval 60 young volunteers recruited through advertisements around university campuses in Melbourne, Australia.[20] Elite athletes are select individuals, who may differ from this group in many different ways, including background characteristics such as education level and socioeconomic status. However, even more important is that superior neurocognitive skills may be one of the selection criteria to become an elite footballer. In fact, a closer look at the reaction time data of Collie *et al*'s 60 volunteers reveals that they were considerable slower than the footballers on all subtasks. The reproducibility of the CogSport test on elite athletes has not been thoroughly investigated before. The apparent difference between regular

What is already known on this topic

- Computerised neuropsychological testing programs have been proved to be sensitive and reliable in the evaluation of cognitive function after concussions in sport
- Dual baseline testing is recommended to minimise learning effects

What this study adds

- The computerised test battery (CogSport) showed excellent reproducibility in a large cohort of professional Norwegian football players using a translated version of the test
- The reaction time measures proved to be the most reliable for all subtasks tested, and these are therefore recommended as primary outcome measures

controls and elite athletes illustrates the need to develop appropriate reference data in populations of elite athletes, and supports the practice of individual baseline testing in the elite as a basis for the management of concussion.

The CV ranged from 1.0% to 2.7% for the mean reaction time measures and all values under 5% must be considered as good. Collie *et al*,[20] in their study on 60 healthy non-athletic young volunteers, reported intraclass correlation coefficients for the reaction time measurement higher than 0.69 for all of the four tested subtasks. Except for simple reaction time, the results were similar when comparing the test–retest results with both the one hour and the one week interval between the tests. The intraclass correlation coefficient for the mean reaction time measures from our material were within the same range. Reaction time measures have been shown to provide the most sensitive index of cognitive changes following a head injury,[27] which in part is due to the fact that they are highly reproducible, as indicated in both our study and previous studies on other study populations.[16 20 22 28] In contrast, of the consistency measures only the standard deviations for the most complex tasks (matching and learning) were within this limit. Although there was a uniform trend of less variation on test 2, the reproducibility data imply that these measures are unlikely to be helpful for follow up evaluations. The simpler tasks were the least consistent and one may speculate that the lack of complexity in these tasks causes the player to lose focus during the task. In the Cogsport testing program, simple reaction time testing is repeated three times during the session, which may exaggerate this effect.

In our study, the accuracy data showed inadequate reproducibility and the highest improvement from test 1 to test 2. The ceiling effect found on both one-back and matching may also make these less suitable as outcome measures, even with a dual baseline setting. Previous analyses using this computerised battery have shown ceiling effects for all accuracy data except matching and learning,[29] but our results indicate that this is also the case for matching.

It should be noted that intraclass correlation coefficients must be interpreted with caution. From the simplified equation for the intraclass correlation coefficient ($S^2_b/(S^2_b + S^2_w)$) it is evident that data of a homogeneous group (that is, where the between-subjects variability (S^2_b) is small compared with the within-subjects variability (S^2_w)) will produce a poorer intraclass correlation coefficient than data of a heterogeneous group (that is, with high between-subject variability with respect to the within-subject variability), even if within-subject variability is exactly the same for the two groups. It is therefore recommended not to compare directly the intraclass correlation coefficients from different study populations without knowing the variance within the tested groups.[30] We have therefore, as recommended,[25] also presented the test–retest coefficients of variation, which are independent of test result range and therefore can be compared directly between studies. It should be noted that, compared with the performance data reported by Collie *et al*,[20] our footballers displayed both faster mean reaction times and a more homogeneous performance. When this is taken into consideration, a comparison of the test–retest intraclass correlation coefficients with Collie *et al* indicates that the reproducibility of the mean reaction time measures may be even better among elite footballers than non-athletic controls. In a one year follow up of 84 elite Australian Rules footballers, the test–retest coefficients of variation were not reported.[31]

In our group of professional football players, there was a significant improvement from test 1 to test 2 for the mean reaction time measures on all subtasks of CogSport. Collie *et al* found a similar practise effect when a group of elderly volunteers (mean age 64 (8) years)) performed four consecutive CogSport™ tests in three hours.[22] Whereas our professional football players tended to display a more pronounced practise effect when the tasks became more complicated, Collie *et al*'s elderly volunteers showed an opposite trend. More relevant is a comparison with elite Australian Rules footballers, and, as mentioned above, 84 of these were tested after an injury-free season (the exact timeframe was not stated) without displaying any significant differences in performance since baseline for any of the subtasks of CogSport (for the final two tasks, matching and learning, accuracy data were presented instead of mean reaction times). A practise test was conducted before the baseline test, but it is not clear if this was done for the follow-up as well (either in full or shortened).

Since we performed only two tests, we are not in a position to say whether the practise effect will decrease with further testing. However, Falleti *et al* followed 26 young volunteers who performed four different baseline CogSport tests on three different days, where the first two tests were performed on the same day with a two hour break in between, and the first was discarded. In the three remaining baseline tests (time intervals not stated) there were no differences in performance on reaction time or accuracy measures.[23]

Another aspect of the mean reaction time measurements, which became evident on Bland–Altman plots, was that the improvement from test 1 to 2 was not evenly distributed. The players with the slowest mean reaction times improved the most, and on some subtasks those with the fastest mean reaction times were actually slower on test 2. Such regression towards the mean has also been described by Erlanger on simple and choice reaction time measures from a similar computerised neuropsychological test package from HEADMINDER.[32]

Due to the practise effect, we agree with previous studies conducted on other populations that the test requires a dual baseline, where the first test is discarded.[22 23] Whether this procedure should be used in follow up testing if more than a couple of weeks have passed since the baseline testing, needs further investigation. One problem with a dual baseline tests is that the test becomes more time consuming and there is a risk is that the player will lose their focus. A large study of patient with head injuries found that effort explained 53% of

the variance in neuropsychological test performance (in comparison, educational level accounted for only 11% and age only 4%).[33] It has to be noted that the group used the old paper and pencil test, which implies a different testing setting. The results can therefore not be transferred directly to computerised testing. Nevertheless, the issue of including some kind of effort measure when conducting a neuropsychological test was recently stressed at the Second International Symposium on Concussion in Sport in Prague.[34]

In conclusion, the reproducibility for the mean reaction time measures was excellent in the cohort on professional footballers included in the present study. However, the accuracy and consistency measures were less reliable, and may therefore be less sensitive as outcome measures in post-concussion management. Consecutive testing revealed a slight learning effect from test 1 to test 2, and dual baseline testing with rejection of the first test is recommended to minimise this effect.

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Competing interests: none declared

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Paper II

SUPPLEMENT

Effects of heading exposure and previous concussions on neuropsychological performance among Norwegian elite footballers

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Background: Cross-sectional studies have indicated that neurocognitive performance may be impaired among football players. Heading the ball has been suggested as the cause, but recent reviews state that the reported deficits are more likely to be the result of head injuries.

Objective: To examine the association between previous concussions and heading exposure with performance on computer based neuropsychological tests among professional Norwegian football players.

Methods: Players in the Norwegian professional football league (Tippeligaen) performed two consecutive baseline neuropsychological tests (Cogsport) before the 2004 season (90.3% participation, n = 271) and completed a questionnaire assessing previous concussions, match heading exposure (self-reported number of heading actions per match), player career, etc. Heading actions for 18 players observed in two to four matches were counted and correlated with their self-reported values.

Results: Neither match nor lifetime heading exposure was associated with neuropsychological test performance. Nineteen players scored below the 95% confidence interval for one or more subtasks, but they did not differ from the rest regarding the number of previous concussions or lifetime or match heading exposure. The number of previous concussions was positively associated with lifetime heading exposure (exponent (B) = 1.97(1.03–3.75), p = 0.039), but there was no relation between previous concussions and test performance. Self-reported number of headings correlated well with the observed values (Spearman's $\rho = 0.77$, $p < 0.001$).

Conclusion: Computerised neuropsychological testing revealed no evidence of neuropsychological impairment due to heading exposure or previous concussions in a cohort of Norwegian professional football players.

Heading in football was previously considered to be ludicrous and ''not football''. However, it has developed to become not only a natural feature of the game, but also an important part of defensive and offensive play.[1] Today football is the only contact sport exposing a large number of participants to purposeful use of the head for controlling and advancing the ball. In 1992, on the basis of a series of cross-sectional studies using neurological examinations, neuropsychological tests, computer tomography scanning, and electroencephalography in active and older retired Norwegian football players, Tysvaer proposed that, as seen in boxing, heading in football could lead to chronic brain injury.[2] Following Tysvaer's study, several other cross-sectional studies indicated that head injuries sustained during football can cause continued and measurable brain impairment.[3–7] Nevertheless, not all studies have found such a relation[8] and several concerns have been raised about the methodology and design used in previous studies.[1]

In a recent review, Kirkendall *et al* state that to date it appears that heading is not likely to be a significant factor, but that any deficits are more likely to be the result of accidental head impacts that occur during the course of the matches.[9] Estimations carried out by Schneider and Zernicke indicate that the linear forces associated with controlled heading are probably not sufficient for brain injury[10]; in comparison, in boxing a punch can generate four to five times more force to accelerate the head than heading a football.[11] Even so, computer simulation of headings has revealed an unacceptably risk of head injury because of the angular acceleration caused by frontal and lateral heading impacts with medium velocities.[10] This finding emphasises the importance of correct heading technique as the simulations did not take into account the fact that the skill of heading involves bracing the neck muscles to minimise the acceleration of the head.[1]

Among injuries related to football, 4–22% are head injuries.[2] The reported incidence during matches—1.7 injuries per 1000 player hours[12]—incorporates all types of head injury including facial fractures, contusions, lacerations, and eye injuries. The estimated incidence of concussion—0.5 injuries per 1000 match hours—probably represents a minimum estimate[12] due to the problem of defining and grading concussions.[9 13] Although most athletes with head injuries recover uneventfully following a single concussive episode, repetitive mild head trauma may be implicated in the development of cumulative cognitive deterioration.[9 14] Based on paper and pencil tests, cumulative effects of repeated concussions have been found to cause deterioration in neuropsychological function among athletes in other sports such as American football[15 16] and boxing,[17] as well as in non-athletes.[18]

The consensus at the first International Conference on Concussion in Sport, held in Vienna in 2001, recognised neuropsychological tests as one of the cornerstones of concussion evaluation,[19] and emphasised the benefits of the computerised cognitive function testing programs that have been developed during the past decade—for example, CogSport (CogState Ltd, Melbourne, Australia), ImPACT (ImPACT Inc., Pittsburgh, PA), ANAM (Automated Neuropsychological Assessment Metrics; developed by the

US Department of Defense), and CRI (concussion resolution index; HeadMinder Inc., New York, NY).

Conventional paper and pencil tests were designed primarily for assessment of cognitive dysfunction caused by neuronal or psychiatric disorders and not for the assessment of mild changes in cognitive functions over time.[20] These tests have therefore often poor psychometric properties for serial study, including limited range of possible score, floor and ceiling effects, learning effects, and poor test–retest reliability.[21] Computerised testing, using infinitely variable test paradigms, may overcome these concerns and is therefore recommended for monitoring consequences of concussion in sport.[19] Studies suggest that computerised tests may be particularly sensitive to the cognitive consequences of sports related concussions, and also that conventional paper and pencil tests do not share this sensitivity.[22–25] In addition, computer based neuropsychological tests have demonstrated sensitivity to cognitive changes caused by fatigue,[26] alcohol,[26] early neurodegenerative diseases,[27] coronary surgery,[28] and childhood mental illnesses.[29]

Studies indicating impaired neuropsychological performance due to heading exposure and/or previous concussions in football were based on *conventional* paper and pencil neuropsychological tests.[2–7] Therefore the present study sought to investigate whether these impairments could be reproduced among professional Norwegian footballers when assessed by the new and more sensitive computer based neuropsychological tests. To that end, we examined the association between previous concussions and heading exposure with computer based neuropsychological test performance among professional Norwegian football players.

METHODS

Participants

The Norwegian professional men's football league (Tippeligaen) has 14 clubs. We invited all the clubs with their A-squad contract players (about 300) to participate in the study. A total of 289 players (96.3%) agreed to take part. The Regional Ethics Committee for Southern Norway approved the project and we obtained written informed consent from all the participating players.

Every year in February/March, the teams meet at the Norwegian Football Association training centre at La Manga, Spain, for the La Manga Cup and pre-season training camp. We collected data on 13 of the 14 Tippeligaen teams at La Manga prior to the 2004 season in a test lab set up within the residential complex, Los Lomas II. Data from the fourteenth team were collected at their home field in Norway two weeks later under similar standardised conditions as in La Manga. There is no time difference between Spain and Norway and the testing was done at the same time of day with the same persons instructing and supervising the tests for each team.

Questionnaire

The players were asked to complete a two-page questionnaire regarding age, nationality, education level, player position, seasons in the Tippeligaen and lower division leagues, highest level of education, and history of exposure to solvents, general anaesthesia, headache, migraine, epilepsy, depression, hyperkinetic activity disorders, or learning disabilities. Education level was measured on a seven-point scale (1 = primary/elementary school and 7 = six years of university education). The questionnaire also asked for an estimate of their typical number of heading actions per match (never, 1–5 times, 6–10 times, 11–20 times, and >20 times per match), the number of previous concussions while involved in football activity and the number of non-football concussions, in addition to the time since their last concussion. We defined concussion as loss of consciousness and/or amnesia after a head injury.

The questionnaire also included an abbreviated version of the World Health Organization's AUDIT form for assessing alcohol consumption[30]: ''How often do you drink alcohol?'' (never, monthly, 2–4 × per month, 2–4 × per week, >4 × per week); ''How many units do you drink on a typical 'drinking day'?'' (1–2, 3–4, 5–6, 7–9, ⩾10); ''How often do you drink more than 6 units?'' (never, monthly, 2–4 × per month, 2–4 × per week, >4 × per week); and a question assessing the use of other central stimulants (''Do you use any other central stimulant drugs?'' (never, monthly, 2–4 × per month, 2–4 × per week, >4 × per week)). The highest possible AUDIT score is 13. In addition, the players recorded their symptoms and signs on a 20-item post-concussion symptom scale (PCSS; 0–120) validated for use in evaluating concussions in sport.[23]

The players were assured that the information would be treated in a confidential way and not released to their club, and the second part of the questionnaire, which contained the PCSS and other sensitive questions, was anonymous with just a reference number to track player identity. To validate the self-reported number of headings per match, we randomly selected four different matches from the whole season involving one team playing against four different opponents, and the same person manually counted the heading action of each player, either live or from video review.

Neuropsychological testing

The neuropsychological tests were administered and supervised by trained personnel. The players undertook the tests in groups of three in the same quiet room to allow rapid data collection. We used the computer based neuropsychological test CogSport (versions 2.2.0 and 2.2.1). Norwegian speaking players were tested with the Norwegian language version of the test, where instructions for each subtask were in Norwegian, and all others used the English language version. The test is described in detail elsewhere.[21 26 31] The stimulus for all tasks consists of playing cards with responses given using the keyboard, with the **d** key indicating ''no'' and the **k** key ''yes'', or vice versa for left handed players. No other keys were used.

The CogSport test battery includes seven subtasks testing different cognitive brain functions:

- Simple reaction time (motor function)
- Choice reaction time (decision making)
- Congruent reaction time (simple attention)
- Monitoring (divided attention)
- One-back (working memory)
- Matching (complex attention)
- Learning (learning and memory)

All subtasks include between 15 and 40 trials, and for all subtasks the data are reported by the CogSport program as the mean reaction time with corresponding standard deviation, accompanied by accuracy data for all tasks except simple reaction time and monitoring. Anticipatory responses (reaction times <100 ms) and abnormally slow responses (reaction times >3500 ms) are recorded as errors and excluded from the analyses. Accuracy data are calculated as the number of true positive responses divided by the number of trials. The test was stopped if a player had more than 40 incorrect responses on one task. Since previous studies on CogSport have indicated a slight learning effect between the first two tests performed, in this study two consecutive tests

Table 1 Characteristics of the participating players. Results for all players are divided in two groups based on (*a*) previous concussion history (n = 270) and (*b*) headings per match (n = 153)*

Variable	Previous concussions		Headings per match†	
	Yes (n = 133)	No (n = 137)	>11 (n = 85)	0–5 (n = 68)
Age (years)	25.1 (4.5)	26.2 (4.7)	26.0 (4.7)	25.3 (4.9)
Playing experience in Tippeligaen (years)	2.8 (2.4)	3.3 (2.4)	3.1 (2.4)	3.2 (2.4)
PCSS score (0–120)	3.8 (6.7)	4.0 (6.2)	3.5 (6.2)	4.8 (7.1)
Total number of concussions	2.0 (1.1)	–	1.4 (1.4)	0.7 (0.9)
Alcohol intake (AUDIT score; 0–13)	5.3 (2.7)	5.1 (2.3)	5.1 (2.5)	5.1 (2.3)
Other stimulants (yes)	1.5	1.5	2.4	0‡
Exposure to solvents (yes)	3.9	8.1	2.4	7.4
General anaesthesia (yes)	49.2	58.1	49.4	55.9
Headache (monthly or weekly)	6.3	6.7	2.4	5.9
Migraine (yes)	5.3	9.6	5.9	4.4
Epilepsy (yes)	0	0.7	0	0
Depression (yes)	1.5	1.5	0	2.9
Hyperkinetic activity disorders (yes)	1.5	1.5	0	0
Learning disabilities	3.8	2.2	2.4	1.5
Highest education level				
Primary school or less (⩽9 years)	6.1	6.7	0	2.9
Secondary school (high school)	68.7	59.0	62.4	69.1
Tertiary education (college)	25.2	34.3	37.6	26.5
Nationality				
Norwegian	82.6	83.1	82.4	83.8
Other Scandinavian	6.1	8.1	8.2	5.9
Other European	8.3	5.9	5.9	7.4
Non-European	3.0	3.0	3.6	3.0
Playing position				
Goalkeeper	10.4	9.8	–	–
Defensive player	13.4	25.0	43.5	2.9
Wingback	16.8	15.9	10.6	13.2
Central midfielder	19.2	18.2	8.2	22.1
Other midfielder	10.4	6.8	3.5	19.1
Wing	10.4	10.6	3.5	25.0
Attacker	17.6	12.1	22.4	10.3
Unknown	1.6	1.5	8.2	7.3
Heading frequency (per match)				
Never	1.7	0.8	–	4.4
1–5 times	29.4	23.6	–	95.6
6–10 times	39.5	35.8	–	–
11–20 times	23.5	30.1	77.6	–
>20 times	5.9	9.8	22.4	–

*Results are shown as the mean (SD) or percentage of valid responses within the group.
†Excluding goalkeepers.
‡Data missing for five athletes.

were performed and the first was discarded unless the second was subject to technical problems.

Statistical analysis

We used the measures of mean reaction time for all seven subtasks as the main dependent variables, as these measures have shown the highest reproducibility and sensitivity.[32 33] Prior to all calculations, the mean reaction times and standard deviations were $\log_{10}$ transformed to obtain a more normal distribution.[34]

From the patient history questionnaire we chose the total number of previous concussions, number of heading actions per match and lifetime heading exposure as independent variables. We estimated lifetime heading exposure as: the self-reported number of heading actions per match × the number of regular league matches played per team per season (n = 26) × (age in years − 16). For example, for a 28 year old player reporting 10 heading actions per match, the estimated lifetime heading exposure was 3120 (10 × 26 × 12).

We performed multiple regression analyses for the main dependent variables (mean reaction time for the seven subtasks) and the independent variables (previous concussions, lifetime heading exposure, heading frequency). A number of potential confounding variables (age, alcohol consumption, use of other central stimulants, previous narcosis, exposure to solvents, learning difficulties, level of education, and neurological diseases) were entered in the model using backward methodology. Logistic regression was performed for the association between previous concussions (yes or no) and the two heading exposure variables. To increase the power of the logistic regression we rearranged the number of heading actions per match to form the three categories: ''0–5 times'', 6–10 times'', and ''>11 times'' . The lowest and the highest two categories of heading frequency (''0–5 times'' *v* ''>11 times'') and total number of previous concussions (''never concussed'' *v* those with three previous concussions or more) were examined for differences in neuropsychological performance using independent sample *t* tests. A Bland–Altman plot was constructed to examine the association between self-reported and manually counted number of headings per match, in addition to a non-parametric correlation test (Spearman's ρ). We set the level of significance as $p<0.05$, and we did not make any corrections for multiple testing (for example, Bonferroni). SPSS (version 11) was used for all statistical analyses.

RESULTS

Of the 289 players consenting to take part, 18 did not report for neuropsychological testing and were excluded, resulting in a final sample of 271 players. A total of 137 players (50.6%) reported having had one or more previous concussions (55 reported one previous concussion, 43 two, 17 three, and 22 more than four) and 112 players (41.3%) reported a football related concussion—20.8% having experienced a concussion within the previous year (one player did not report his concussion history). The participating players' characteristics are shown in table 1. Based on the country of origin and observations of the test supervisors, we identified 3% with language problems that could potentially bias the test performance.

When goalkeepers were excluded, 1.2% (n = 3) reported that they never headed the ball, 26.1% (n = 65) headed 1–5 times, 37.1% (n = 91) 6 –10 times, 26.9% (n = 66) 11–20 times, and 7.8% (N = 19) >20 times per match (table 1). Defensive players reported to head the ball most frequently (54.0% in the 11–20 category, 20.0% in the >20 category),

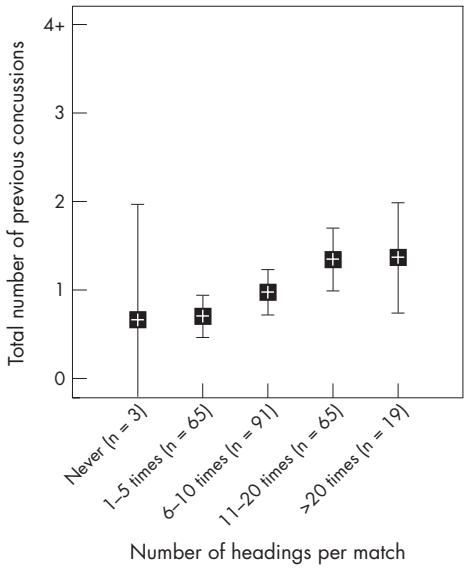

Figure 1 Self-reported number of headings per match and total number of previous concussions (n = 243). The results are shown as means with 95% confidence intervals. Goalkeepers are excluded.

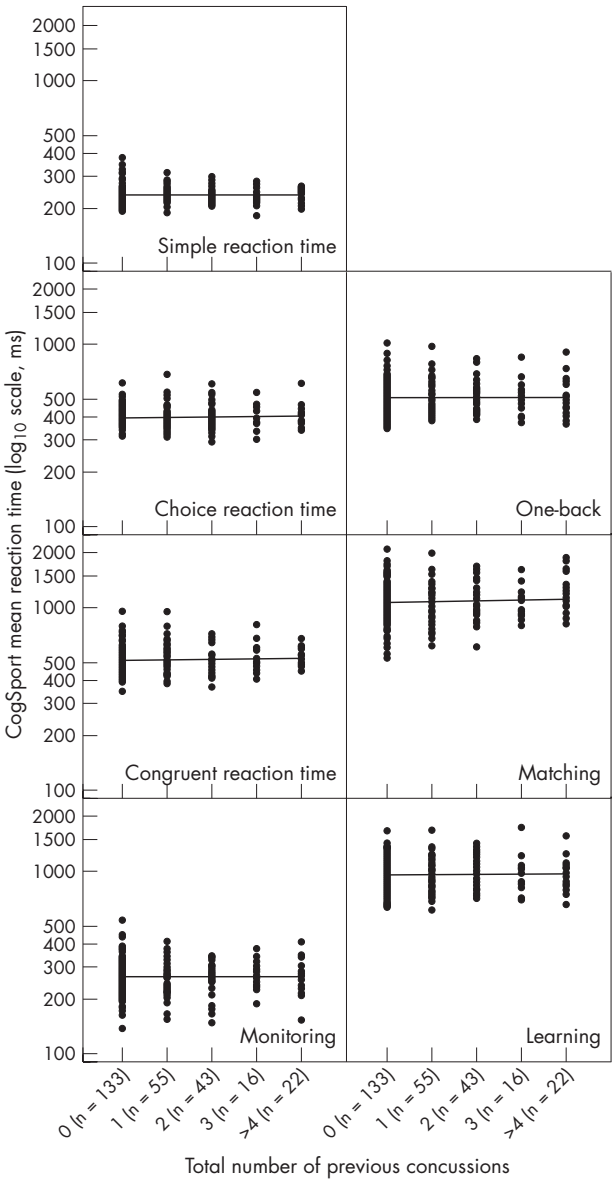

Figure 2 Relation between total number of previous concussions and mean reaction time (log_{10}, ms) for the seven CogSport subtasks (n = 269). The subtasks are arranged vertically and from left to right according to their complexity from top left (easiest) to bottom right (most difficult). Regression lines are shown as solid lines.

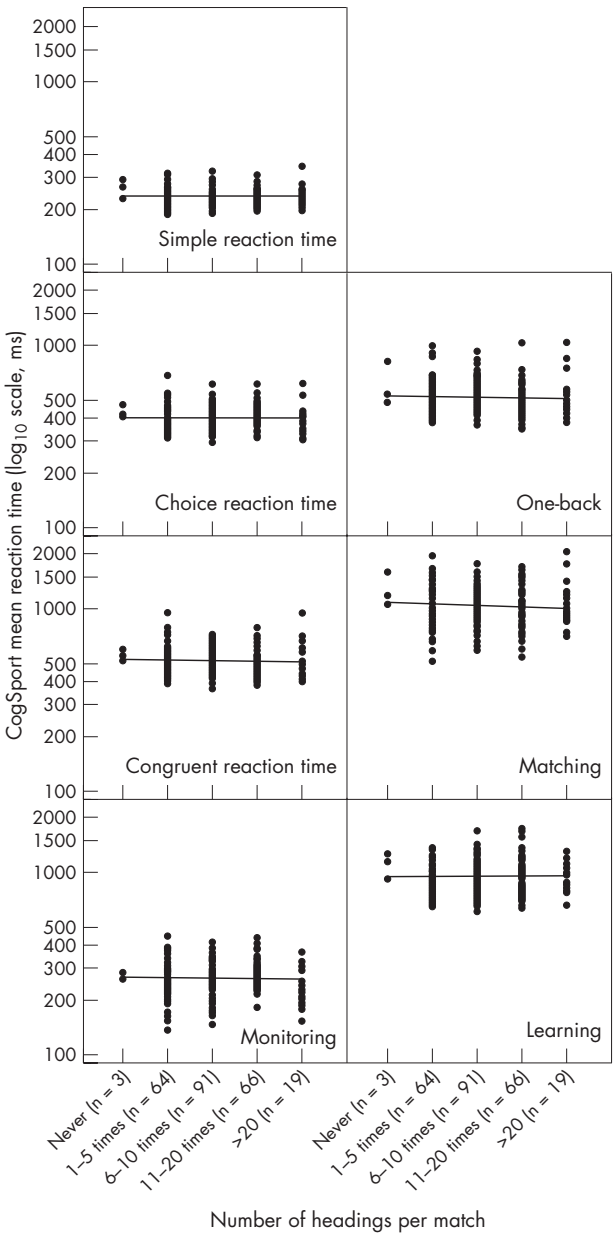

Figure 3 Relation between self-reported heading frequency and mean reaction time (log_{10}, ms) for the seven CogSport subtasks (n = 243). Goalkeepers are excluded.

followed by attackers (38.5% in the 11–20 category, 10.3% in the >20 category). The manual count, which included 18 players observed in two to four matches, showed that the number of headings per player per match averaged 8.5 (range 0–26). Data on these 18 players revealed a slight overestimation of the number of headings per match compared with the self-reported figures, at least for the frequent headers. However, the correlation between the self-reported number of headings and the manual count was good (Spearman's ρ 0.77, $p<0.001$), and the majority defined themselves in the same quartiles as those created by the observed values.

The estimated lifetime heading exposure was significantly positively associated with the number of previous concussions on logistic regression (exponent (B) = 1.97(1.03–3.75), $p = 0.039$) and the self-reported number of headings per match showed the same trend (fig 1, exponent (B) = 1.67, $p = 0.12$) between the medium frequency (6–10 headings) and the high frequency heading group (>11 headings).

However, the multiple linear regression analyses did not reveal any relation between the total number of previous concussions and neuropsychological performance on any of the seven subtasks (fig 2). In addition, there was no relations between the number of headings per match and the neuropsychological test score on any of the subtasks (fig 3), nor between estimated lifetime heading exposure and test scores (fig 4). These results did not change if we excluded players with potential language problems (3%).

There was also no difference in the neuropsychological test results of players with the lowest heading frequency (0–5 times per match) and those heading most frequently (>11 times per match). The mean difference in performance on the seven subtasks between the groups ranged from −0.24% to 0.68% (p values ranging from 0.27 to 0.99). Comparison of

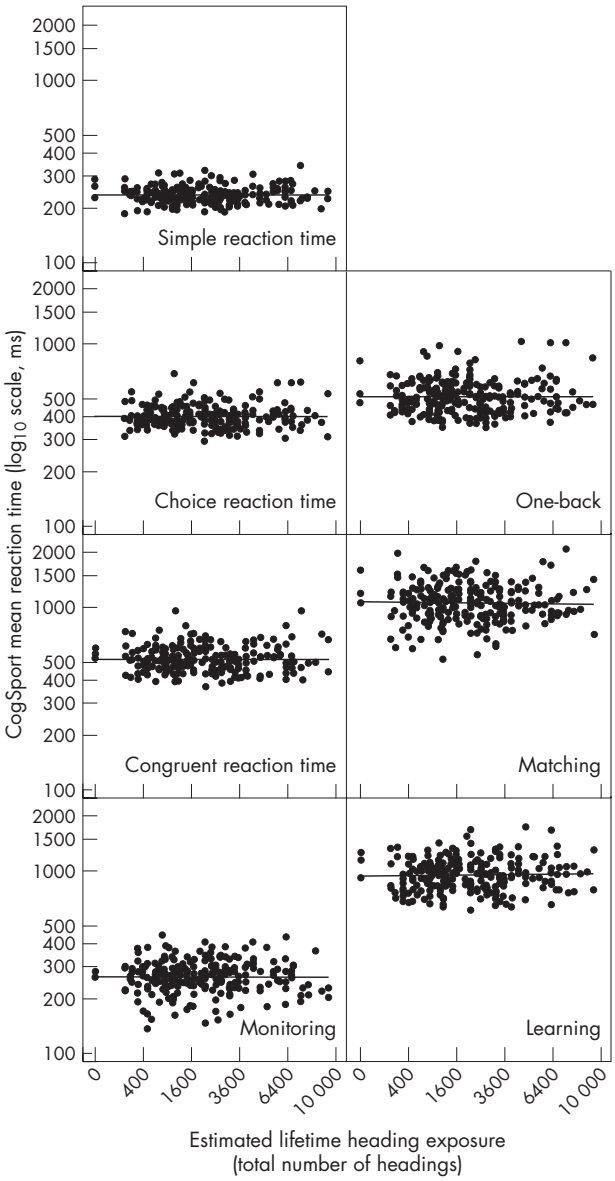

Figure 4 Relation between estimated lifetime heading exposure and mean reaction time (log_{10}, ms) for the seven CogSport subtasks (n = 243). Goalkeepers are excluded.

the never concussed group and those with three or more previous concussions also did not reveal any differences in neuropsychological performance (mean difference ranging from −0.47% to 0.02%, p values from 0.295 to 0.957).

There was no difference between goalkeepers (n = 26, excluded from the regression analyses of heading exposure *v* test performance above) and the rest of the group in neuropsychological test performance. When the two groups of players with the highest self-reported heading frequency (defensive players and attackers) were compared with the group of players playing other positions (excluding goalkeepers) there were no differences in neuropsychological performance (p values generally above 0.6).

Nineteen players (5.9%) scored lower than the lower limit of the 95% confidence interval on one or more subtask (outliers). Three of these were in the group with potential language problems. However, there was no difference between this subgroup and those within the 95% confidence interval in match or lifetime heading exposure or in the number of previous concussions. None of the 19 players reported having experienced a concussion in the previous month and they reported significantly lower symptom scores on the PCSS than the rest (mean 1.5 (0–6.8); p = 0.006 *v* the rest of the players).

The PCSS scores showed a skewed distribution with 46.7% (n = 127) reporting no symptoms. The highest registered score was 35 out of a possible 120. There was no significant difference in test performance between the players in the upper quartile on PCSS score and those who reported no symptoms. Although monitoring (mean difference (log_{10}, ms): 0.025 (−0.001 to 0.050), p = 0.050) and choice reaction time (mean difference 0.015 (−0.002 to 0.032), p = 0.088) showed a directional trend, the results indicated that the group with more symptoms tended to perform better on the test.

Only four players (1.5%) qualified as outliers for one or more subtasks when compared with the normal range as defined by the test manufacturers (that is, outside the 95% confidence interval of the normal population). Five players had too many errors on the more complex tasks and their tests were reported as abnormal in the CogSport test reports. However, these two groups did not differ from the others regarding previous concussions or heading exposure.

DISCUSSION

In contrast with Matser *et al*,[3–5] Tysvaer,[2 35] and Witol and Webbe,[7] we did not find any relation between self-reported heading exposure or history of previous concussions and neuropsychological performance in a group of elite football players. The present study was carried out on a large cohort of mature professional football players with a high response rate (90% of the players in the league). We collected the data on and adjusted for potential confounders (such as education, alcohol, age, playing experience), and used a validated computer based neuropsychological test battery. In this way, we could also compare our data with a large control sample of uninjured athletes from other sports. However, our data did not show any trend towards a relation between football playing, heading exposure, or previous concussions and neuropsychological tests, even on refraining from adjusting for multiple statistical tests (for example, Bonferroni correction). In addition, to make the statistical tests as sensitive as possible, we also compared the most extreme player groups with respect to heading exposure and concussion history. Here, too, we did not observe any difference in test results. Previous studies argue for a dose–response relation between neuropsychological deficits and lifetime heading exposure estimated from age and heading frequency per match.[5 7] We examined age and heading frequency both independently and together in a multiple regression model in this study but without finding any significant relation.

The apparent discrepancy between the current findings and previous studies is not easily explained. In general, the present study is based on similar methodology as the preceding studies in the field, including cross-sectional neuropsychological testing, and heading and concussion exposition based on self-report. In a recent comprehensive review of studies addressing the neuropsychological consequences of heading and head trauma in football, Rutherford *et al* concluded that there was no definitive evidence that football, and heading in particular, caused deterioration in neuropsychological function among football players.[1] Furthermore, they stated that all the neuropsychological studies conducted so far suffer from methodological problems and that, at best, a few of these studies may be regarded as exploratory.[1] The principal methodological limitations include small and/or inappropriate subject groups,

low or unknown response rates, inappropriate statistical methods (type 1 errors, not adjusting for multiple comparisons or potential confounders).[1 9] For instance, Matser *et al*'s study suggesting neuropsychological impairments in amateur football players is generally criticised for conducting up to 283 statistical tests without proper adjustment of the level of significance.[1] When planning the current study, we sought to rectify some of these limitations.

Conventional *v* computerised tests

All the previous studies have used conventional paper and pencil tests. It has been argued that these tests have problems with normal ranges, sensitivity and specificity, and practise and learning effects.[19 36] Recent studies of reliability of computerised neuropsychological testing have suggested that measures of response speed are more reliable than measures of response accuracy in healthy young adults.[32 33] This may be important, since the output from conventional neuropsychological tests used to study cognitive deficits from heading and concussion exposure is typically either an accuracy score or a gross measure of the total time to perform the task.[3–7 35] In contrast, we used exact measures of reaction time from computer based tests.[34]

We were not able to include conventional paper and pencil tests in the current study, but other studies suggest that computerised tests may be particularly sensitive to the cognitive consequences of sports related concussions,[22–25 37] although both methods have been shown to be sensitive for detection of post-concussive neurocognitive changes.[14 22 23 38 39] Nevertheless, a meta-analytic review of neuropsychological studies addressing persisting brain damage after minor head trauma suggested that conventional neuropsychological assessment had a positive predictive value of less than 50%.[40] In contrast in several studies computerised reaction time measures show evidence of persisting impairment after sports concussion, even in the presence of normal performance on traditional clinical neuropsychological measures.[37] However, even if there were differences in sensitivity between conventional and computerised neuropsychological tests in favour of the latter, this does not explain why the potentially less sensitive method (paper and pencil) would detect differences that are not identified using the more sensitive method (computer).

Readministration of tests

To minimise variability, we asked the athletes to perform two consecutive neuropsychological tests. For computerised tests, a practise effect is seen between the first and second administration with only smaller non-significant improvements with further serial testing.[41] Macciocchi conducted repeated testing of 110 athletes with conventional neuropsychological tests and showed that the athletes had a definite capacity to improve performance with only one readministration of the test.[42] For instance, the widely used Trail Making Test showed a mean improvement of 20% ($p = 0.008$).[42] Thus, the results from a second administration of a neuropsychological test, both conventional and computerised, provide a more reliable description of the group's neuropsychological performance. In the previous studies which showed neuropsychological deficits among footballers neither the footballers nor the control groups performed a practise test.

Control group

There is yet another distinction between the current and previous studies that may be more important. We chose not to include a non-football control group, based on the principle that participants should differ only on the variable under examination (such as heading and concussion). For example in Downs and Abwender's study,[6] the young footballers and control group had different proportions of men and women, and the older groups consisted exclusively of men. Consequently, any difference might have been due to sex rather than an aspect of football play. This issue was thoroughly discussed by Rutherford *et al*.[1]

Our approach enabled us to investigate the effects of heading and concussion more specifically compared with the studies of Tysvaer and Lochen,[35] or Matser *et al*,[3 4] where the main comparison was between the footballers and the non-football controls. Furthermore, we found no evidence of cognitive impairment even when we compared the test results to the normal range defined by the test manufacturers. Only a handful of players qualified as outliers for one or more subtasks and they did not differ from the others regarding history of previous concussions or heading exposure.

Response rate

Finally, the current study is the largest study conducted on football players to date and with a high response rate. Among the previous studies, only Webbe and Ochs reported response rates.[43] In their study, which showed an association between heading recency and neurocognitive performance, 48% of the players invited declined, most citing the reason as insufficient time to accommodate testing.[43] Even so, there is a potential for a selection bias. We invited all the players in the Norwegian top league and 90.3% agreed to participate, minimising selection bias and securing a group of players all playing at the same level. Many previous studies were performed on amateur level players or on a mixture of amateur, professional, and former professional players.[4 6 35 43]

LIMITATIONS OF THE PRESENT STUDY

Some methodological issues must be considered when interpreting the results of the current study. In particular, these are related to the accuracy of the main independent variables, concussion history and heading exposure, which were self-reported as in most previous studies.

Heading frequency

The ability of players to self-report heading frequency is debated in the literature.[1] Heading frequency may also be subject to great variability among different playing cultures and styles, between continents, countries, different teams and even matches against different opponents. Matser *et al* claimed that players usually underestimate the number of headers per match in an interview setting, even though their players reported an average of 16 headings per match ranging from 0 to 42.[3] In contrast, studies based on *direct observation* show that across the whole team, the average number of headers is between 6 and 16 per match.[44] This is the basis for the grading scale used in the present study to group the participating players according to heading frequency: never, 1–5, 6–10, 11–20 and >20 times per match. Although based on a limited number of games, our observations suggest that the players rated their heading frequency quite well, even though the absolute values were slightly high. Thus it is not likely that the results are biased by misclassification of heading exposure. As mentioned above we also compared the upper and lower *extremes* of heading frequency groups to minimise this effect—still without detecting any differences in neuropsychological performance. Even so, heading frequency may be questioned as a valid measure of brain impacts. To reduce angular or rotational acceleration, good heading technique requires good timing and coordination of the muscles of the neck to stabilise the head. A more frequent header may be more likely to have a superior heading

technique than a player who heads less frequently, and consequently less frequent headers may be more at risk during the few times they actually head. Analyses based exclusively on heading frequency will not pick up the consequences of poor heading technique or *unexpected ball to head contact*, and can potentially mask cumulative effects of minor impacts when heading. A recent study from the same league shows that such head impacts are very common.[12] However, ball to head contact represented only 5% of the incidents. In contrast, a hit from the elbow, arm, or hand appeared to cause 43% of the incidents and head to head contact caused 32%. The latter two also represented the vast majority of the head injuries recorded.

Lifetime heading exposure

Our measure of lifetime heading exposure might have been biased, since it does not consider the level of play for all the years incorporated in the variable. As all our participants were selected from the top league it is reasonable to assume that they had played top level football since the age of 16. As players specialise early, it is also highly likely that they have played the same playing position throughout their careers, with a similar relative frequency of involvement in heading situations. The heading frequency and risk of injury may have increased when progressing from junior to senior ranks even for these elite players, which would lead to an error in the absolute numbers estimated. However, a gradual increased exposure to heading situations would not have influenced a player's relative rank with respect to heading frequency within the group.

Concussion history

Our measure of concussion history is also based on self-recall, and therefore subject to considerable recall bias, most likely resulting in an underestimation. In a study on a group of US college football players and grid iron football players, Delaney *et al* showed that four of five concussions were not recognised by the player, even if the player remembered having symptoms on the field when examined retrospectively.[13] These results can only partly be explained by recall bias, and probably also reflect the many different grading systems and definitions of head trauma and concussions. Until recently, the approach to concussion management in Norway has been uniform and conservative, using to the old definition requiring loss of consciousness and/or amnesia. This definition was therefore also used in the player questionnaire. Based on the system of injury registration established in 2000 for Tippeligaen, the doctors for 12 of the included teams registered eight concussions during the 2003 season (0.09 per 1000 players hours of exposure, including matches and training) (TE Andersen, personal communication). This figure is lower than the 24 concussions reported by the players during the same time period (14 teams)—19 during a football match or training (1 January 2003 to 31 December 2003). This comparison indicates that player recall was not a major problem, at least for concussions resulting in amnesia and/or loss of consciousness during the previous season. However, a recent study from Tippeligaen using video analysis to document the injury mechanisms of head injuries showed that only about 10% of all incidents involving impacts to the head were reported by the team doctors as concussions.[12] Given the definition used for previous concussions in the present study, we were not able to take such minor head trauma into consideration in the regression model. Guskiewicz *et al*[8] defined concussion as

> injury resulting from a blow to the head that may have resulted in one more of the following conditions: headache, nausea, vomiting, dizziness or balance problems, fatigue, trouble sleeping, drowsiness, blurred vision, difficulty remembering or difficulty concentrating.

Yet they found a similar prevalence of concussions as in our study (49.5% reporting a history of one or more concussions compared with 49.1% in our study), and the concussion history was not associated with depressed neurocognitive performance. Even though that study was performed on college soccer players (average age 19 years),[8] the results were similar to the current study. Guskiewicz *et al* also revealed a higher prevalence of concussions among the footballers, but did not demonstrate any difference in neurocognitive performance compared to the non-football athletes or students.[8]

On the other hand the vast majority of head impacts and concussions in football happen in heading duels, where a hit from the opponent's arm or head to head collisions represent the most frequent mechanisms of injury.[12] Frequent headers are more frequently involved in heading duels. Consequently, they may be exposed to head trauma more often than less frequent headers. This hypothesis is supported by the significant association shown between estimated lifetime heading exposure and the number of previous concussions. This makes it difficult to separate the effects of heading exposure from previous concussions in studies based on self-reported retrospective data. It could be argued that heading frequency is just as good a measure for previous concussions and minor head impacts during football as the self-reported numbers of concussions.

CONCLUSION

This study does not support the hypothesis that concussive and/or subconcussive trauma caused by heading has a cumulative effect causing neuropsychological impairments among football players.

What is already known on this topic

- Based on neuropsychological paper and pencil test studies have suggested a higher frequency of cognitive impairments among football players compared with controls
- The evidence that such impairment occurs as a result of general football play, concussions on the football field, or normal football heading is limited

What this study adds

- Computer based neuropsychological testing of Norwegian professional footballers did not show any neuropsychological impairment compared with normative control data among the vast majority of the players (98.5%) and revealed no evidence of cognitive impairment associated with heading exposure or number of previous concussions
- Heading frequency and concussions are weakly associated, identifying heading duels as risk situations for head injuries

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Paper III

Minor Head Trauma in Soccer and Serum Levels of S100B

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Abstract

Objective: To compare the serum levels of S100B after a head trauma to the effect of heading, high-intensity exercise and playing a league match. Heading and head traumas in soccer have been suspected to cause brain impairment. The protein S100B is a marker of acute neuronal tissue damage.

Method: Baseline S100B was measured in 535 Norwegian professional soccer players. 228 head impacts were registered from 352 league matches. Three teams (N=48) performed a high-intensive exercise session without heading and a low-intensity session with heading exercises. Blood samples were drawn within one hour (B1) and the following morning (B12) after a match/training for the four groups: Head Impact (N=65), Match Control (Match participants without head impact, N=49), High-Intensive Exercise (N=35), Heading (N=36).

Results: Serum S100B increased from baseline to B1 for all groups. The increase for the match groups (Head Impact and Match Control) was significantly higher than for both the training groups. However, no significant differences between the Head Impact and Match Control groups or between the two training groups were found. A total of 39 (33.9%) players showed elevated B1 values ($\geq$ 0.12 ng/mL) after a match, but these were equally distributed between the Match Control Group and the Head Impact Group.

Conclusion: Both soccer training and soccer matches cause a transient increase in S100B. There is a possible additive effect of activity with high intensity and heading, but minor head impacts do not seem to cause an additional increase.

Running Title: MHT in Soccer and S100B

Keywords: Soccer [MeSH]; closed head trauma [MeSH]; Brain injury [MeSH]; S100 Proteins [MeSH]

Introduction

Soccer is one of the few sports where an unprotected head is used actively for heading and advancing the ball (30). When heading was introduced in soccer, this feature was first looked upon as ludicrous and "not soccer", but later it has developed to become an important part of defensive and offensive play (49). However, during the last two decades there has been an increasing concern that heading could lead to chronic brain injury as seen in boxing. This was first postulated by Tysvaer in 1992 (65) based on a series of cross-sectional studies using neurological exams, neuropsychological tests, computer tomography (CT) scans and electroencephalography (EEG) exams on active and older retired Norwegian soccer players. Since then, some cross-sectional studies have indicated that soccer can cause measurable cognitive impairment (19, 33-35), while others have not detected such a relationship (23, 60). Heading duels also expose the players to an increased risk of sustaining a head trauma (2, 60), and it has been hypothesized that the reported cognitive deficits are more likely to be the result of accidental head impacts that occur during the course of the matches rather than heading (29).

Among injuries related to soccer, 6-13% are head injuries (3, 22). The reported incidence of head injuries for men during matches is 1.7 - 3.5 per 1000 player hours (2, 22). This incorporates all types of head injuries including facial fractures, contusions, lacerations, and eye injuries, while the estimated incidence of concussion is 0.3-0.5 per 1000 match hours (2, 13, 22, 45). However, the rate of brain injuries is difficult to assess (15), and the reported incidences are likely to represent minimum estimates. Andersen et al. (2) identified 192 head impacts on video recordings from elite soccer matches (18.8 per 1000 hours), but only five of these were reported as concussions. A study by Delaney et al. (15) revealed that only one out of five concussions are recognised by the players after a head impact in a match, indicating that many players continue to play with undiagnosed concussions.

Several different markers for brain injury have been investigated during recent years. Based on these, Ingebrigtsen & Romner (26) have concluded that the S100B protein is currently the most promising marker for evaluation of traumatic brain injury in patients with minor head injury. Protein S100B is a Ca^{2+}-binding protein mainly attached to the membranes in glial cells in the central and peripheral nervous system (astrocytes or Schwan cells), although it is also expressed in melanocytes, adipocytes and chondrocytes outside the nervous system (18, 62, 68). The serum levels of S100B increases rapidly after a traumatic brain injury and some studies have reported a 10-15 fold increase above baseline levels, followed by a significant decrease the next 4-6 hours due to its short half-life (10, 27, 28, 38, 48, 63). An increased level of S100B after minor head traumas has been reported to be associated with pathological findings on CT scans (9, 36), prolonged in-hospital stays (38), prolonged absence from work (59), post concussive complaints (14, 50) and disability one year after the incident (53). In addition, S100B is associated with the Glasgow Coma Scale score at admission and the outcome after more severe head injury (46, 64). Nevertheless, the specificity of S100B to brain injury has been questioned (4, 17, 32, 40, 43, 57, 66). Highly increased values have been reported after multi-trauma and burns without head injury (5), as well as smaller increases after swimming (16), running and boxing (16, 42). Yet, the increase seen in S100B concentration after exercise was lower than values reported after minor head traumas (9, 12, 14, 27, 36, 41, 48, 53).

S100B is increased after playing a soccer match and appears to be related to the number of headers (54, 56). However, no large-scale prospective study has assessed S100B levels after minor head impacts in soccer. Thus, this study was designed to assess whether minor head impact in soccer could cause injury to the nervous tissue, measured as an increase in the serum S100B concentration. In addition, we wanted to assess the specific effect of high-

intensity exercise and heading on the serum concentration of S100B to control for these factors.

Methods

Study Design

This is a prospective study in a cohort of professional soccer players, where the serum level of S100B was compared between four different conditions: 1) after a head impact occurring during a regular league match (Head Impact Group), 2) after a regular league match with no recorded head trauma (Match Control Group), 3) after a high-intensity training session without heading (High-Intensity Exercise Group), and 4) after a low-intensity training session with heading exercises only (Heading Group). The blood sampling protocol included in each case a baseline sample (before the season or before the training session), a follow-up blood sample taken right after the match/training session and an additional sample the following morning.

Participants and Test Procedures

All players in the Norwegian elite soccer league, Tippeligaen, were asked to participate in the study prior to the 2004 and 2005 seasons. Tippeligaen comprises 14 teams, each with 23-28 players on an A-squad contract, yielding a total of 320-390 players each season. Written informed consent was obtained from all participants, and the study design was approved by the Regional Committee for Medical Research Ethics, Helse Sør, and the Data Inspectorate.

A total of 289 players consented to participate in the study in 2004 and 332 players in 2005. Thus, the study covered 621 player seasons (161 of these players were included in both seasons). Baseline morning blood sampling prior to both seasons was performed for all teams but one during their preseason training camp at the training centre of the Football Association of Norway (NFF) at La Manga, Spain, in February or March. The final team was tested at their local training facilities in Norway during the same time period. In addition, baseline blood sampling was performed in a subgroup of players (N=49) on three different days during

their two-week training camp to assess the variation in baseline serum S100B concentration. All baseline samples were taken before training between 7:30 and 10:00 am.

Match Study

During both seasons, all regular league matches were observed live by medical personnel present at the venue and they were asked to record all head impacts during the match. The personnel were either the team's own medical staff covering the match or other local medical personnel recruited by the study administrators. The criteria for including head impacts (Head Impact Group) in the sample were: All situations where; 1) a player appeared to receive an impact to the head (including the face and the neck), 2) the match was interrupted by the referee, and, 3) the player laid down on the pitch for more than 15 s (3).

In any case of a head impact (irrespective of whether or not the player was removed from play), the medical personnel were instructed to draw a blood sample from the player straight after the match, preferably within 1 hour after the trauma (B1), as well as a sample the following morning (within 12 hours after the match, B12). Video recordings of all matches were provided by the Norwegian Broadcasting Corporation (NRK) and reviewed the following morning by one of the authors (TMSN) or a research assistant. When a head impact was identified, the respective team's medical personnel were contacted by phone to check on the follow-up status and, if necessary, to arrange for B12 blood sampling. A control group of players from six of the teams included in the study was recruited to give blood samples within one (B1) and 12 hours (B12) after a regular match where they had not experienced any head trauma (Match Control Group). These six control matches were reviewed on video to verify that no head impacts had occurred to these players and a count was made of the number of headers and other head accelerating events per player (i.e. falls or collisions that did not qualify as head impacts).

In order to check how many of the head impact that resulted in actual time-loss injuries (21), the impacts were also cross-referenced with the injuries reported by the team's medical staff through the injury surveillance system (TISS) administrated by Oslo Sports Trauma Research Centre. This register receives data from all the teams in Tippeligaen, and includes all injuries from all team activities that have resulted in absence from training or match (time-loss injuries), as well as the time and date of the injury, type of match, diagnosis, and the number of days before the player returned to training or match (3). The study protocol also included neuropsychological testing of the players the day after the head impact/control match. These results are described in detail in a separate report (61).

Training Study

Moreover, three of the included teams were asked to participate in two separate training sessions prior to the 2006 season (N=48); one high-intensity soccer training session where heading of the ball was not allowed (High-Intensity Exercise Group) and one low-intensity training session with heading exercises (Heading Group). These sessions were planned in cooperation with the team coach and led by the regular coaching staff. The high-intensity soccer play and heading exercise were organized to be as close to the match situation as possible in terms of the level of intensity, or the number and force of the headers. Normal values for the number of headers per player per match was established by counting all headers in matches that were followed live by one of the study administrators during the 2005 season (N=241 players, 2-4 matches counted per player). The mean number of headers per player was 5.7 (95% CI: 0 to 14.8) per match with large variations between the different playing positions, ranging from 2.8 (95% CI: 0 to 6.9) for the midfielders to 9.6 (95% CI: 3.9 to 20.7) for the central defenders. Goalkeepers practically never headed the ball (0.04 [95% CI: 0 to 0.5]). Thus, no standard number of headers was set for the heading exercise session. However, each player was asked to fill in a questionnaire after both sessions (High-Intensity Exercise

and Heading) assessing their level of fatigue and how often they headed the ball during the current day's training compared to a regular match (much less, less, a little less, same, a little more, more or much more). This score was dichotomized to "less" and "same or more" in the analyses. From video recordings of the heading sessions, one or two different players were selected for each of the drills performed and the number and force (i.e. light, moderate or hard) of the headers were counted. The number of headers for each drill was then summarized to create an estimate of the mean number of headers per player per training session. New baseline morning samples were drawn before the first training session, and subsequently within one hour (B1) and the following morning (B12) after each of the two sessions. The training sessions were arranged on separate days and lasted for 90 minutes excluding warm up, and no other training was done in-between the two follow-up blood samples.

S100B Assay

Venous blood samples were collected from an antecubital vein and drawn into a standard gel 7 mL tube (BD Vacutainer® Blood Collection Tube, New Jersey, USA) and allowed to clot for 30 min before centrifugation (3000g) for 10 min. The resulting serum was divided into two 1.5 mL Eppendorf tubes and frozen within two hours. Serum S100B concentrations were measured using an electro-chemiluminescence assay (ROCHE Elecsys®, ROCHE Diagnostics, F. Hoffmann-La Roche Ltd, Basel, Switzerland). The lower detection limit of the assay is 0.005 ng/mL (ROCHE Elecsys® product information). All analyses were performed at the Department of Clinical Chemistry and Clinical Biochemistry, University of Munich, Germany according to the procedure described by Mussack et al. (40) and Bieberthaler et al. (9). Based on previous studies on S100B after minor head trauma, (9, 11, 12, 26, 38), a cut-off value of 0.12 ng/mL was used to classify the B1 samples as elevated or within the normal range.

Statistics

All blood sample data were log transformed to meet the criteria for normal distribution. The reproducibility for the measurement of the baseline concentration of S100B was assessed using ANOVA for repeated measurements. The square root of the residual mean square was divided by the joint mean of all three measurement points to create a coefficient of variation (CV).

The main effect variables for the study were the serum concentration of S100B at B1 and B12, the Delta B1 values (change from baseline to post impact/match/training), and the proportion of players within each group with an elevated B1 sample value. The null hypothesis that there was no difference between groups in S100B serum concentration was tested using repeated measurements ANOVA with Bonferroni post-hoc p-value adjustments and pair-wise t-test comparisons. Further differences between subgroups were examined using independent sample t-tests, while paired samples t-tests were used for testing differences within each group. Categorical variables were tested for between-group differences using Chi-square or Fischer's exact tests and bivariate correlations were calculated with the Spearman's rho correlation coefficient. All S100B concentrations presented in the text are back-transformed values from the log10 values used in the analyses. Descriptive data are presented as the mean with 95% confidence intervals (CI) of the distribution, while comparative data are presented as mean and the corresponding 95% CI of the mean. Based on the standard deviation from the baseline samples, the lowest true difference between the groups that could be identified was 0.017 ng/mL with at least 25 players in each group, with a power of 80% (β=0.8). All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 13.0, SPSS inc., Chicago, USA).

Results

Baseline Characteristics and Compliance

Baseline blood samples were drawn from 255 (88.2%) of the players who consented to participate prior to the 2004 season and 280 players (84.3%) prior to the 2005 season. Hence, 535 baseline samples were collected in total and the mean serum concentration of S100B was 0.045 (95% CI: 0.018 to 0.11) ng/mL. A total of 15 (2.8%) of the baseline samples were equal or above the cut-off at 0.12 ng/mL. Three repeated baseline measurements were performed on a total of 49 players and the mean baseline concentrations of S100B for the three different test days ranged from 0.049 (95% CI 0.026 to 0.093) ng/mL to 0.056 (0.028 to 0.11) ng/mL with a CV of 18.4%.

A total of 228 head impacts that met the inclusion criteria were identified on video from 352 matches. Sixty-nine (30.3%) of these were followed up with a blood sample within one hour after the impact (B1, N=65), or an additional blood sample the following day (B12, N=40), or both (N=37). The baseline characteristics and compliance with the sampling protocol for all four groups are presented in *Table 1*.

Insert *Table 1* near here

As presented in *Table 2* only 13 (5.7%) of the 228 impacts were reported in as time-loss injuries to TISS, including 7 (3.1%) concussions (0.6 per 1000 playing hours). In the followed-up group, a total of 27 (39.1%) players reported having symptoms directly after the impact, but only 9 (33.3%) of these were taken out of play.

Insert *Table 2* near here.

Two players experienced a head impact during the heading exercise session and were consequently excluded from further analyses. The serum concentration of S100B at baseline was not significantly different for any of the four groups (ANOVA, p=0.408).

Changes in the Serum Concentration of S100B

All groups had a significant increase in serum concentration of S100B between baseline and B1, and a similar significant decrease from B1 to B12 (*Figure 1*). Both match groups displayed higher B12 values compared to baseline, but only the B12 value for the Head Impact Group was significantly different from baseline (Baseline: 0.041 [95% CI 0.034 to 0.051] ng/mL, B12: 0.051 [95% CI: 0.43 to 0.59] ng/mL , p=0.040). For both training groups the B12 value had returned to their baseline level. However, it has to be emphasised that the time from the end of the activity until B12 sampling the following morning was on average 5.8 (95% CI: 5.0 to 6.6) hours longer for the training groups compared to the match groups ($p<0.001$), since the matches usually were played in the evenings while the training sessions took place around noon.

Insert *Figure 1* near here

Significant differences were neither seen between the two training groups nor between the two match groups for any of the sampling time points. The joint match groups (Match Control and Head Impact groups taken together) revealed a significantly higher mean serum S100B concentration at B1 compared to the joint training groups (*Figure 1*). A similar pattern was evident for the Delta B1 values, where the joint match groups had a significantly higher increase from baseline compared to the joint training groups (Delta B1: Training Groups: 0.026 [95% CI: 0.020 to 0.031] ng/mL, Match Groups: 0.062 [95% CI: 0.052 to 0.073], $p<0.001$). However, within the match and training groups, there were no significant differences in the Delta B1 values.

For the soccer players in the joint match group, a total of 39 (34.2%) B1 samples scored equal to or slightly above the cut-off (≥ 0.12 ng/mL), but they were equally distributed between the Head Impact and the Match Control groups (Chi-square: $p = 0.48$). Based on the symptoms reported either by the team medical personnel or by the players themselves, a total of 26

(37.7%) of the followed up impacts in the Head Impact Group were classified as concussions according to the criteria set by the 1st International Conference on Concussion in Sports in Vienna in 2001 (i.e. any impairment to neurological function after a head trauma) (7). Ten (38.5%) of these scored equal to or above the cut-off for B1 versus 14 (35.9%) of the 39 impacts that did not classify as concussions (Chi-square, p = 0.83). Only five B1 samples in the training group were equal or above the cut-off for B1. Although four out of these where within the High-Intensity group, the numbers were too small to test for any significant differences in the distribution.

The Effect of Heading and High-Intensive Exercise on Serum S100B

As shown in *Table 3,* the players in the Heading Group who reported the same number or more headers in the training session compared to a regular league match, had significantly higher Delta B1 values than the other players. However, this finding resulted from a significantly lower baseline serum level of S100B for the subgroup who reported the same or more frequent heading intensity. There was no significant difference in the serum concentration of S100B at B1 between the two subgroups. Within the High-Intensity Exercise Group no differences were discovered with respect to the effect of the exercise intensity level compared to a regular match (*Table 3*).

Insert *Table 3* near here

For the players in the Match Control Group there was a trend towards a positive correlation between the number of headers in the respective match and serum S100B at B1 (Spearman's rho = 0.28, p = 0.056), but not for Delta B1 (Spearman's rho = -0.20, p = 0.89). However, the players who headed ten times or more during the respective match (upper quartile: 0.045 [95% CI: 0.033 to 0.061] ng/mL) exhibited a trend towards a higher serum S100B concentration at baseline compared to the players who headed three times or less (lower

quartile: **0.029** [95% CI: 0.019 to 0.044] ng/mL, p=0.11). When the number of all other head accelerating events and the number of headers were added, a significant correlation with serum S100B at B1 was found (Spearman's rho = 0.36, p = 0.012), but still there was no correlation with Delta B1 (Spearman's rho = 0.025, p = 0.87).

Discussion

This study followed elite soccer players for two seasons to determine whether minor head traumas in soccer cause detectable brain tissue injury. The serum concentration of S100B after head trauma was compared to the effect of heading, high-intensity exercise and playing a regular league match without any head trauma. Our main finding was that all conditions led to a moderate, but significant increase in serum S100B concentration, which returned to baseline levels within the next day. Although the increase was higher for the two match conditions compared to the two training conditions, there were no significant differences between the two match groups at any time point.

S100B and Minor Head Trauma

The post-match serum S100B levels after a head trauma were not different from levels measured after playing 90 minutes of professional soccer without experiencing any head impacts. The increase in both match groups was comparable to serum S100B levels measured in Swedish professional male and female soccer players after playing a regular match (54, 56). In addition, there was no difference between the Match Control Group and the Head Impact Group in the proportion of players with elevated serum S-100B levels. Even for the impacts that were classifieds as concussions based on their symptoms, the proportion of players with elevated levels was not different from the remaining Head Impact Group or the Match Control Group.

Data from the league injury surveillance system, which is administrated by Oslo Sports Trauma and Research Center, showed that thirteen of the head impacts recorded caused an injury (i.e. concussion or facial fracture) that kept the player away from regular matches and training for 1 up to more than 21 days. However, B1 samples were available for nine of these impacts and none of these samples were above the theoretical maximum serum level of

S100B which can be achieved by stress or exercise induced failure of the blood brain barrier only (32). In addition, the Head Impact Group's mean B1 level was below the values reported for patients admitted to hospital with minor head trauma (Glasgow Coma Scale 13-15) (9, 12, 27, 36, 41, 48, 53), and under the half of the mean serum S100B levels reported for minor head trauma patients with CT and/or MRI abnormalities (9, 12, 41).

However, there are some limitations which must be borne in mind when interpreting the results. Firstly, a possible source of bias is that only 69 (30%) out of the 228 head impacts were followed up. After numerous efforts towards the teams and their medical personnel, we identified that the main reason for the low compliance was that the players were reluctant to be tested after the match mainly because they regarded the impacts as trivial. Analyses of all the impacts identified from the match videos revealed that 24.6% of the players who were followed up with blood samples after a head impact, did not return to play compared to 8.8% of the cases where the impacts were not followed up. Thus, a player who was taken out of play was nearly three times more likely to be followed up compared to the ones who returned to play. Consequently, the followed-up group was likely to include a higher proportion of more severe impacts, and accordingly 39.1% of these were retrospectively classified as concussions. Nevertheless, the majority returned to play after the head impact, indicating that both the players and the team medical personnel regarded the majority of the impacts as benign.

Secondly, the samples of both the Head Impact and the Match Control groups were drawn within an hour after the end of the match, although the head impacts occurred on average 56 minutes prior to the end of the match. The biological half-life of S100B in serum has been reported to be as short as 25.3 (95% CI: 15.3 to 35.3) minutes (28), and consequently an increase in S100B caused by the head impact would decrease substantially during the time from the impact until the end of the match.

Nevertheless, even when considering these limitations, the head impacts did not have an additive effect on the S100B concentration when compared to playing a soccer match only, indicating that the head impact did not cause substantial nervous tissue injury.

S100B and Soccer Play

The present study showed an increase in serum S100B after playing a regular match irrespective of whether or not the players had experienced any head impacts. In addition, about 35% of these cases the values were above the suggested cut-off (0.12 ng/mL) used for severity screening of minor head trauma patients in hospitals (12). A somewhat smaller increase was found after a high-intensity exercise without heading. Comparable increases in serum S100B have been reported after various physical activities where head traumas and other sudden head-accelerating events like heading, are rare, such as long-distance running (42), swimming (16) and basketball (55). The effect of physical activity on the serum level of S100B and the source of S100B release into the serum under these circumstances are unresolved (4, 5, 17, 54, 56). Extracerebral sources of S100B are well known, such as in chondrocytes, melanocytes and fat cells (68), but the concentrations in these cells are very small compared to astroglial and Schwann cells (24, 27). Although, an increase of S100B has been reported in patients with multi-trauma (5) or isolated single bone fractures (66) without an obvious direct head injury, this does not exclude an indirect disturbance of nervous cells via inflammatory factors like cytokines released in high amounts in these trauma situations (20, 31, 37). Similar short term cell activating effects may occur during intensive physical work-out and could explain the increases reported after exercise, indicating that the source for S100B in serum may indeed be the nervous tissue (44, 54, 58).

Severe damage to the brain is typically accompanied by a breakdown of the blood-brain barrier function (32), but recent studies have established that the blood-brain barrier also can be disrupted under physical activity, such as prolonged moderate exercise in warm conditions

(67) and 30 minutes of forced swimming (animal study, (52)). Based on mathematical modelling of the S100B kinetics across the blood-brain barrier, Marchi et al. (32) proposed that up to a level 0.34 ng/mL, serum S100B is primarily a marker of increased blood-brain barrier permeability, whereas higher values are associated with neuronal damage and poor patient outcome. In comparison, the highest value in our study was 0.33 ng/mL, and this sample was drawn 20 minutes after a league match from a midfield player in the Match Control Group. He did not head the ball during that particular match and his baseline and B12 samples were normal.

Exertion, stress and increased circulating levels of epinephrine have also been shown to increase the blood-brain barrier permeability (1, 25, 51) thus enabling a rise in the serum S100B levels. Playing a competitive match is associated with high levels of stress, adrenaline and physical intensity which it is difficult to mimic in a regular training session. This was reflected in the post-training questionnaire, where 53% of the players reported a lower level of fatigue after the training session compared to a league match. Hence, the higher B1 values for the match groups compared to training groups in our study could be due to different level of exertion only.

Properties of the S100B measurement procedure could also have affected the results. The measured S100B in this study refers to the summed concentrations of the S100B monomers in S100A1B and S100BB. A recent study has found a higher increase in S100A1B in patients with minor head traumas compared to patients with minor orthopaedic injuries, while the increase in S100B was equal for the two different groups (41). Nevertheless, although the specificity for brain injury after a minor head trauma seems to be higher for S100A1B, the sensitivity to detect brain tissue damage is comparable for S100B.

S100B and Heading

In our heading exercise session, the idea was to minimize the effect of physical activity and subsequently tease out the effect of heading only. However, after correcting for the difference in the S100B baseline values within the Heading Group, we could not detect any relationship between S100B and perceived heading intensity. Furthermore, we found no correlation between the observed number of headers and head accelerating events and the Delta B1 values as previously reported in the studies on the Swedish soccer players (54, 56). Yet, a closer examination of the baseline levels for the upper quartile compared to the lower quartile with respect to the number of headers in the match, revealed a trend towards higher baseline levels for those who headed most frequently and consequently this could cause a subsequent bias of the delta values for our Match Control Group. A plausible explanation could be that the baseline samples were collected during a training camp where the players had two or three training sessions per day, and although the baseline blood sampling was performed in the morning before training, there could be some effects left from the training sessions the day before for the most frequent headers.

The goalkeepers also represent a problem in these correlations. Goalkeepers practically never head the ball, and their level of exertion during a match is lower compared to the outfield players (6, 47). Consequently the goalkeepers will be grouped among the low frequency headers, and there is a chance that the correlation between number of headers and the increase in S100B would be confounded by differences in physical activity during the match. The studies by Stalnacke et al. (54, 56) provide no information regarding the goalkeepers and their results are therefore difficult to compare directly with ours.

In contrast to our results from the heading session, Mussack et al. (39) found that an exercise session with repetitive controlled headers led to a higher transient increase in serum S100B than an exercise session only. However, this study was performed on young amateur players

and a significant increase was only seen for the youngest group of players (from 12 to 15 years). According to Kirkendall and Garrett (29), coaches do not incorporate heading in the training sessions until the players are 12 years or older. Consequently controlled repetitive heading for 55 minutes was most likely a heavier exposure for the youngest players in the study of Mussack et al. (39) compared to the more experienced 16-17 year old players. This is in line with biomechanical studies of heading where brain accelerations during normal heading by adult players have been estimated to average less than 0.1% of the accepted levels required to produce brain injury in a single impact, while "accidental" heading and heading with poor technique could cause brain accelerations within the concussive range (8).

Conclusion

The serum level of S100B increases transiently after soccer training and soccer matches. There is a possible additive effect of heading and high-intensity exercise, but minor head impacts do not seem to cause an additional increase in S100B beyond the levels seen after a regular game. Thus, there is no evidence suggesting that there is significant brain tissue injury after these minor head impacts in soccer. However, for clinical use S100B is not an ideal marker for brain injury in athletes due to the confounding effect exercise alone.

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Tables

TABLE 1. Baseline characteristics and compliance with the sampling protocol for the players who experienced a head trauma in a football match (Head Impact), the players who participated in a football match without experiencing a head trauma (Match Control), the High-Intensive Exercise group which did not practise any heading and the Heading exercise group.

Variables	Head Impact (N=69)	Match Control (N=56)	High-Intensive Exercise (N=48)	Heading (N=46)
Age	28.1 (22.5 to 35.0)	26.2 (19.0 to 33.0)	26.1 (18.5 to 33.6)	26.1 (18.4 to 33.7)
Height in cm	185 (175 to 194)	183 (172 to 191)	182 (171 to 195)	183 (171 to 195)
Weight in kg	81.6 (70.8 to 93.0)	79.2 (70.0 to 90.0)	78.1 (63.5 to 94.1)	78.2 (63.0 to 94.4)
Nationality				
Norwegian or Scandinavian	55 (79.7%)	43 (87.8%)	39 (81.3%)	37 (80.4%)
Playing positions				
Goalkeeper	4 (5.8%)	3 (6.1%)	6 (12.5%)	6 (13.0%)
Central Defender	22 (31.9%9	13 (26.5%)	11 (22.9%)	11 (23.9%)
Full Wingback	11 (15.9%)	9 (18.4%)	5 (10.4%)	5 (10.9%)
Central Midfielder	11 (15.9%)	12 (24.5%)	13 (27.1%)	12 (26.1%)
Midfielder	4 (5.8%)	4 (8.2%)	6 (12.5%)	5 (10.9%)
Striker	16 (23.2%)	8 (16.3%)	7 (14.6%)	7 (15.2%)
Number of Headers				
Respective match/training	-	6.8 (0.0 to 16.0)	-	18.9 (7.0 to 33.0)
Compliance with the test protocol				
Baseline sample (BL)	60 (87%)	49 (88%)	48 (100%)	46 (100%)
One-hour sample (B1)	65 (94%)	49 (88%)	35 (73%)	36 (78%)
Twelve-hour sample (B12)	40 (58.0%)	46 (82.1%)	33 (69%)	28 (61%)
Post-training questionnaire	-	-	36 (75%)	35 (76%)
Minutes from impact/end of match/training to B1	77.7* (32.3 to 153.3) (N=29†)	33.2 (20.0 to 80.0) (N=48)	26.3 (12.6 to 45.8) (N=35)	23.0 (9.7 to 40.8) (N=36)
Hours from impact/end of match/training to B12	14.9 (10.5 to 24.8) (N=20†)	13.3 (11.4 to 14.7) (N=46)	20.6 (17.7 to 22.1) (N=33)	18.6 (16.7 to 22.5) (N=28

**Significantly different, p<0.02. †The exact sample time was not available for all the samples in the Head Impact Group.*

TABLE 2. Reported injuries and retrospectively classified concussions based on the Vienna concussion definition for the identified head impacts (N=228)

	Head Impacts. Post match follow up status groups	
	Not followed up	Head Impact S100B
N	159	69
Reported time loss injuries to TISS	3 (1.9%*)	10 (14.5%)
Concussion	2 (1.3%)	5 (7.2%)
Facial fracture	1 (0.6%)	2 (2.3%%)
Other	0	3 (4.3%)
Loss of consciousness (LOC)	1 (0.6%)	4 (5.8%)
Post traumatic amnesia (PTA)	-	2 (2.9%)
Classified as concussions (Vienna definition)†	-	27 (39.1%)
Taken out of play due to concussion	-	9 (13.0%)

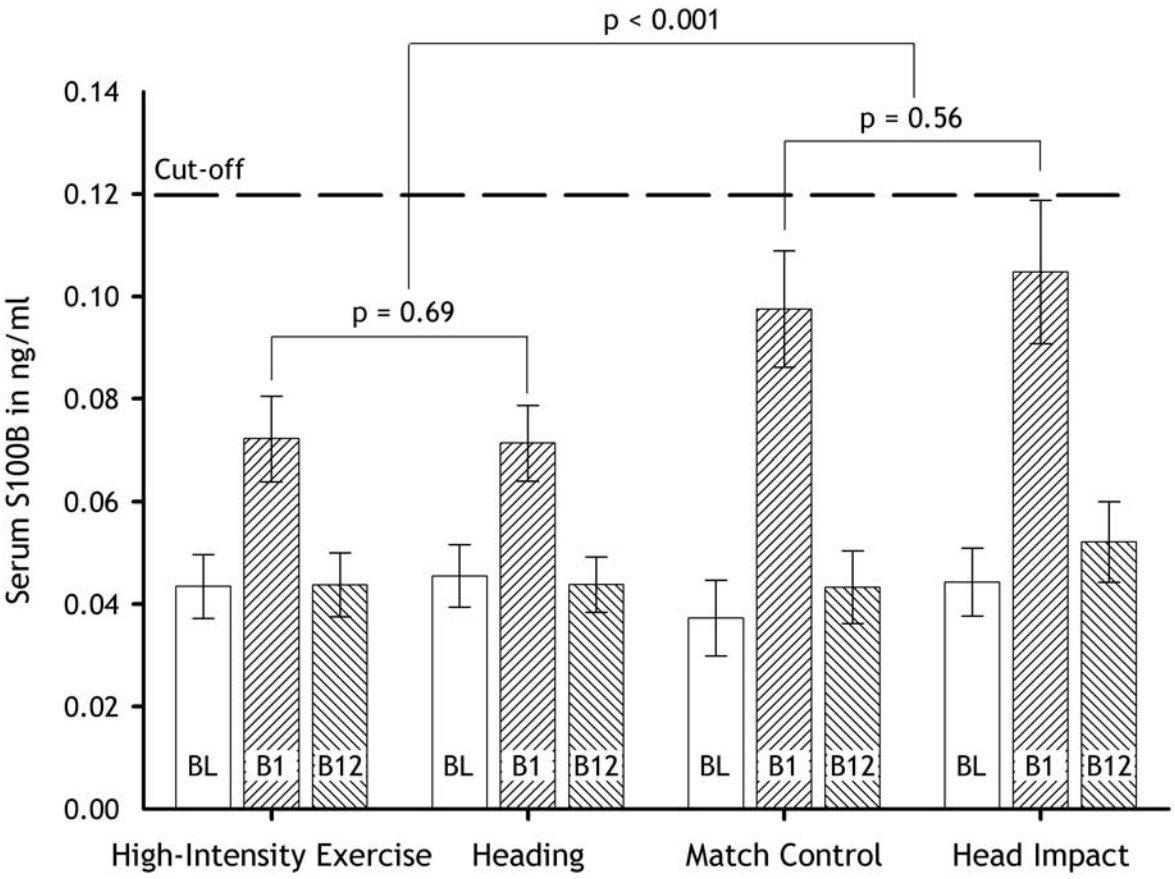
**Percentages are reported within each group, the followed up cases and the group not followed up.*
†Retrospective classification based on symptoms reported by the medical personnel or the players themselves.

TABLE 3. Serum concentration of S100B in ng/ml at all three test points for the High-Intensity Exercise Group and the Heading Group. Both groups are dichotomized according to self reported level of fatigue or number of headers compared to a regular match.

	High-Intensity Exercise Group			Heading Group		
	Level of fatigue vs. match			No. of headings vs. match		
S100B sample	Less (N=19, 53%)	Same or more (N=17, 47%)	p	Less (N=10, 29%)	Same or more (N=25, 71%)	p
Baseline	0.043 (0.035 to 0.053)	0.045 (0.036 to 0.056)	0.82	0.061 (0.043 to 0.087)	0.039 (0.034 to 0.045)	0.009
One hour sample (B1)	0.070 (0.060 to 0.081)	0.075 (0.061 to 0.092)	0.57	0.078 (0.057 to 0.11)	0.066 0.060 to 0.072)	0.16
Twelve hour sample (B12)	0.041 (0.035 to 0.048)	0.047 (0.036 to 0.062)	0.40	0.052 (0.036 to 0.075)	0.041 (0.036 to 0.048)	0.20
Delta B1	0.025 (0.011 to 0.038)	0.032 (0.019 to 0.045)	0.73	0.016 (-0.005 to 0.036)	0.025 (0.020 to 0.031)	0.022

Figure Legends

FIGURE 1. Mean S100B values in ng/mL for the Head Impact, Match Control, Heading and High-Intensity Exercise groups at baseline (BL), one hour (B1) and twelve hours post impact/match/training (B12). The error bars represent the 95% confidence interval of the mean.



Paper IV

Do Minor Head Impacts in Football Cause Concussive Injury? – A Prospective Case Control Study

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Abstract

Background: It has been suggested that heading and sub-concussive head impacts could cause cognitive impairments among football (soccer) players. However, no prospective study has investigated the acute effects of sub-concussive head impacts on neuropsychological performance.

Main objective: To determine whether minor head traumas in an elite football match causes measurable impairment in brain function.

Method: Professional football players in the Norwegian elite league, Tippeligaen, conducted a neuropsychological test (CogSport) prior to the 2004 or 2005 seasons (N=462, of whom 144 were tested both years). A player who experienced a head impact during a league match completed a follow-up test the following day (Head Impact Group). Video tapes of all the impacts were collected and reviewed. A group of players without head impact was also tested after a league match to serve as controls (Match Control Group, N=47).

Results: A total of 228 impacts were identified in the video review during the two seasons and 44 (19.3%) of these were followed up with a CogSport test. The video analyses indicated that the more severe impacts where more likely to be followed-up, although only 6 concussions were reported. The Head Impact Group had a greater change in reaction time from baseline to follow-up compared to the Match Control Group with regard to the three simplest tasks. However, there were no differences for the higher cognitive domains. Seven control (15%) versus 15 (34%) in the Head Impact Group had declined performance on two or more tests ($\chi^2 = 4.57$, $p = .033$). The largest deficits were seen among the players reporting acute symptoms after the impact, but deficits were also demonstrated among asymptomatic players. Players who experienced one or more head impacts during the 2004 season showed a reduction in neuropsychological performance when tested prior to the 2005 season. Their

non-injured colleagues showed no change or a slight improvement. However, none of these footballers were impaired when compared to normative control data.

Conclusion: A reduced neuropsychological performance was found after minor head impacts in football, even in allegedly asymptomatic players. However, the followed-up impacts represented the more severe spectrum of the mild head traumas in football. Still, only six of these impacts were reported as concussions. The test performance was reduced from one year to the next in footballers who had experienced head impacts during the season, but all tests were within the normal range. Consequently, the clinical significance of this finding is uncertain.

Introduction

Football (soccer) is a vigorous sporting activity, with one event with injury potential every sixth second of a competitive game, resulting in approximately one injury every 45 minutes (Rahnama *et al.*, 2002). Between 6% and 15% of these injuries are recorded as injuries to the head (Andersen *et al.*, 2004b; Fuller *et al.*, 2005), mainly as a result of aerial challenges for the ball with an unprotected head (Andersen *et al.*, 2004a; Fuller *et al.*, 2005).

Results from cross-sectional studies performed in the nineties have led to the concern that repetitive sub-concussive blows to the head in terms of headers and head traumas, could cause cognitive impairment among footballers (Tysvaer, 1992; Tysvaer and Lochen, 1991; Tysvaer and Storli, 1989; Matser *et al.*, 1998; Matser *et al.*, 2001; Downs and Abwender, 2002). However, all of these former studies suffer from limitations generated by their retrospective design and other methodological problems. Thus, a recent critical review concluded that there is not conclusive evidence that cognitive impairment occurs as a result of general football play or normal football heading (Rutherford *et al.*, 2003). This is in line with biomechanical studies of heading, where linear and angular brain acceleration during normal heading by adult players has been estimated to be well below those thought to be associated with traumatic brain injury (Babbs, 2001; Naunheim *et al.*, 2003). Consequently, the main concern is related to the potential consequences of repetitive head traumas during football play (Kirkendall and Garrett, 2001).

Chronic traumatic brain injury (CTBI) due to multiple head traumas has been known to occur in professional boxing since Martland introduced the term “Punch Drunk syndrome” in 1928 (Martland, 1928). There seems to be an agreement that this condition has a prevalence of 17-23% among professional boxers, and that the aetiology is a cumulative effect of concussive and sub-concussive head impacts (Roberts, 1969; Jordan *et al.*, 1997; Blennow *et al.*, 2005). However, the condition has not convincingly been proven to affect amateur boxers (Blennow

et al., 2005; Porter, 2003; Butler, 1994; Haglund and Eriksson, 1993), and it is a matter of discussion whether other athletes, like footballers, are at risk (Blennow *et al.*, 2005; Broglio *et al.*, 2006; Butler, 1994; Collie *et al.*, 2006b; Guskiewicz, 2002; Iverson *et al.*, 2006b; Matser *et al.*, 2001; Rutherford *et al.*, 2003; Straume-Naesheim *et al.*, 2005b; Tysvaer, 1992).

In professional boxing the concussion incidence has been reported to be 39.8 per 1000 fight participations (66.3 per 1000 match hours) (Zazryn *et al.*, 2003). This is in contrast to the reported incidence in football of 0.3 - 0.5 concussions per 1000 playing hours (Andersen *et al.*, 2004a; Fuller *et al.*, 2005). Nevertheless, a study from the Norwegian football elite league, revealed an incidence of events with a head injury potential of 22.0 per 1000 playing hours (Andersen *et al.*, 2004a), and it has been shown that four out of five concussions are not recognised by the players (Delaney *et al.*, 2002). Another factor to be considered is that while the mean number of career bouts for modern professional boxers has been estimated to 13 (approximately 7.8 hours) (Clausen *et al.*, 2005), the majority of professional footballers play more than 450 matches during their career (over 675 hours) (Turner *et al.*, 2000). Hence, the total exposure to head trauma in football is considerable, especially if the potential for non-recognised concussions is considered.

Computerised neuropsychological tests have been proven to detect cognitive deficits in concussed athletes who are seemingly asymptomatic at the time of testing (Lovell *et al.*, 2004; Warden *et al.*, 2001; Bleiberg *et al.*, 1998). The sensitivity for detecting concussions has been reported to increase from 64% to 93% by adding computerized neuropsychological test information to the assessment of symptoms (Van Kampen *et al.*, 2006).

The main objective of this prospective study was to determine whether minor head impacts cause measurable brain function impairment among elite football players. A secondary objective was to investigate whether there was any change in neuropsychological test

performance from one year to the next in individuals who experienced one or more minor head impacts during the course of a regular season.

Methods

Study Design and Participants

This is a prospective case-control study where a cohort of professional football players was assessed with a computerised neuropsychological test prior to the 2004 and 2005 seasons. Players suffering a head impact during a regular league match were asked to participate in a follow-up test the next morning (Head Impact Group). These cases were compared to a control group consisting of players who were tested the morning after a regular league match where no head impacts were recorded (Match Control Group). A one-year follow-up was also conducted where the cases, defined as players who had experienced one or more head impacts, were compared to the players in the cohort without any recorded head impacts.

All 14 teams in the Norwegian elite football league, Tippeligaen, were invited to participate comprising their A-squad contract players prior to the 2004 and 2005 seasons. Written informed consent was obtained at baseline for all participants. The study design was approved by the Regional Committee for Medical Research Ethics, Helse Sør, and the Data Inspectorate.

Baseline Testing

Pre-season baseline testing was performed for all teams but one at the official league training camp at La Manga, Spain in February and March. The final team was tested at their local training facilities in Norway during the same period. Of the 326 players who went on to play one or more matches in Tippeligaen in 2004 (VG, 2007), baseline testing was available for 235 (72.1%). The corresponding number for the 2005 season was 227 (68.0%) of 334 players with registered matches in Tippeligaen 2005, yielding a total of 462 completed baseline tests. A total of 205 players participated in the league both years and 144 (70.3%) of these were baseline tested prior to both seasons.

Each player completed two consecutive computer-based neuropsychological tests where the first was regarded as a practise run and discarded from further analyses (Falleti *et al.*, 2003; Straume-Naesheim *et al.*, 2005a). In addition, the participants were asked to complete a form to document their history of head injuries, neurological disease, age at which they started organised football training, learning disabilities, activity disorders, alcohol intake and use of other drugs.

Head Impact Cases - Sampling and Evaluation

During both regular league seasons, which lasted from April through October, the participants were followed during all regular league matches and all 'head impacts' were recorded by local medical personnel present at the stadium (team medical personnel or other medical personnel recruited by the administrators of the study). The criteria for including a head impact in the sample were: 1) All situations where a player appeared to receive an impact to the head (including the face and the neck), 2) the match was interrupted by the referee, and 3) the player laid down on the pitch for more than 15 s (Andersen *et al.*, 2004a).

In case of a head impact (irrespective of whether or not the player was taken out of play), the local medical personnel were instructed to perform a clinical evaluation of the player immediately after the match. This included completing a form assessing acute symptoms (Post Concussion Symptom Scale, Lovell and Collins (1998)), Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974), and the presence and duration of loss of consciousness and amnesia. In addition, the player completed a neuropsychological test the following day supervised by the team's medical staff. The study protocol also included blood sampling of the player one and 12 hours after the head impact for assessing potential serum markers of brain cell injury. The results from the blood sample analyses are described in a separate report (Straume-Naesheim *et al.*, 2007).

In addition, all matches were reviewed the following morning on video tape provided by the Norwegian Broadcasting Corporation (NRK). This was performed by the first author (TMSN) or a research assistant. If one or more head impact were identified, the respective team's medical personnel were contacted by phone to check on the follow-up status and, if necessary, arrange for neuropsychological testing and blood sampling. Video images of all head impacts were copied to a computer and saved for a more detailed video analysis later.

In order to check how many of the head impact that resulted in actual time-loss injuries (Fuller *et al.*, 2006), the impacts were also cross-referenced with the injuries reported by the team's medical staff through the injury surveillance system administrated (TISS) by Oslo Sports Trauma Research Centre. This register, which was established in 2000, receives data from all the teams in Tippeligaen, and records all injuries from all team activities that have resulted in absence from training or match (time-loss injuries), and includes information on the time and date of the injury, type of match, diagnosis, and the number of days before the player returned to training or match (Andersen *et al.*, 2004b).

Match Control Group

Players from the same cohort were recruited as controls (Match Control Group). After playing a regular league match where they did not experience any head impact, they completed the same follow-up regime as the Head Impact Group with post-match symptom assessment and neuropsychological testing the following day.

One Year Follow-up

A total of 161 players participated in both seasons, 2004 and 2005, and were thus available for one year follow-up. The group of players who had experienced one or more head impacts during the 2004 season, irrespectively of the follow-up status of these impacts, were defined

as the Season One Head Impact Group and compared to the remaining players who had not experienced any head impacts during the 2004 season (Season One Control Group).

Video Analysis

All head impacts were analysed independently on video by two of the authors (TMSN and AM). The results were then compared and disagreements were re-reviewed in a consensus group meeting (TMSN, AM and TEA), where a final decision was made. Both AM and TEA were blinded to the injury outcome of the impacts.

Each case was first classified as definite, doubtful or "could not be assessed" with respect to whether the actual impact to the head was visible or not. This classification along with the global impression of severity (severe or not severe) and whether the player returned to play in the same game or not, was considered as general assessments of the potential severity of each incident. In addition, a more specific impact severity assessment was created using the following four factors: relative speed (which included a gross estimate of the direction of the players involved; same direction or towards each other), head movement contribution, location of impact to the head and striking body part (mass/hardness). These are qualitative factors that reflect biomechanically pertinent factors that contribute to kinetic energy and forces.

The head impacts that were successfully followed up with neuropsychological testing were identified and compared with head impacts where follow-up testing was not done to assess whether there was any selection bias with respect to the severity of the incidents.

Assessment of Neuropsychological Performance

Neuropsychological performance was assessed using a commercially available computer-based neuropsychological test battery (CogSport, CogState Ltd, Charlton South, Victoria, Australia). The CogSport test has proven to be sensitive in detecting cognitive changes

induced by concussion (Makdissi *et al.*, 2001), fatigue (Falleti *et al.*, 2003), alcohol (Falleti *et al.*, 2003), early neurodegenerative disease (Darby *et al.*, 2002), and coronary surgery (Silbert *et al.*, 2004). The reliability of the test and its correlation to conventional paper-and-pencil test have been documented (Collie *et al.*, 2003).

The test battery consists of seven different tasks assessing the following different cognitive functions: Psychomotor function, Decision-making, Simple attention, Divided attention, Working memory, Complex attention, and Learning & Memory. The different tasks are described in detail elsewhere (Straume-Naesheim *et al.*, 2005a; Collie *et al.*, 2005), but they all use on-screen playing cards as stimuli. Mean reaction time in ms, standard deviation and accuracy data are provided for all tasks. The Complex attention task was omitted from the analyses due to its low reliability (Collie *et al.*, 2003). Preliminary studies of reproducibility of the test based on the two consecutive baseline tests performed prior to the 2004 season (N=289), identified the reaction time measure as the most reliable measure for all subtasks tested (Straume-Naesheim *et al.*, 2005a). Hence, only the reaction time measurements were considered in this study. The CogSport battery also includes a symptom check list assessing the presence of: dizziness, headache, nausea, vomiting, blurred vision, feeling confused, drowsiness, difficulty falling asleep, difficulty remembering, difficulty concentrating, irritability, balance problems, sensitivity to light and sensitivity to noise at the time of testing and at the time of the incident.

Effect Variables and Statistical Methods

The main effect variable was global change in neuropsychological test performance from baseline to follow-up for the head impact groups (Head Impact and Season One Head Impact) compared to the controls (Match Control and Season One Control, respectively). If a significant difference was found, a post-hoc test was performed to identify potential

differences on each of the six sub-tasks. A within-person comparison was also performed to identify individual players with significant deteriorations from baseline to follow-up.

The test-retest differences in reaction times (delta values) for all six subtests (Psychomotor function, Decision-making, Simple attention, Divided attention, Working memory, and Learning & Memory) were divided by their corresponding mean baseline reaction time to create a percent change score that could be compared between the different tests. The global changes in neuropsychological performance between the groups were assessed using a (multivariate linear) model where the percent change for all six subtasks were entered at the same time (Multivariate Analysis of Variance, MANOVA). Post-hoc pair-wise t-test comparisons with Bonferroni corrected p-values were performed to reveal significant differences between the examined groups for any of the six subtasks.

As recommended by Erlanger et al. (2003), the change in performance for each individual was assessed using the standardised regression-based reliable change index (RCIsrb) (Sawrie *et al.*, 1999). The test-retest performance for the control groups were used to develop regression equations that predict retest scores from the observed baseline scores. The following factors were derived from the baseline questionnaire and entered into the model and investigated for possible predictive value: Total number of headings, number of previous concussions, number of active seasons, alcohol consumption (short version of WHO's AUDIT (Saunders *et al.*, 1993)), playing position, age at incident, days from baseline to follow-up, highest level of education, exposure to solvents, and number of times having received general anaesthesia. The number of previous concussions was the only factor that contributed significantly in the prediction of the follow-up scores, but only for Decision-making and Working memory. All the reaction time scores were log10 transformed before they were entered into the regression model to meet the criteria for normal distribution, and

the data presented were then back-transformed from the log10 values. The prediction equations are displayed in Table 1.

Insert Table 1 near here

Similar equations were created for the comparison between baseline 2004 and baseline 2005, but the only contributing factor entered here was the number of active seasons in the predictive equation for the Simple attention task.

The observed values were then subtracted from the predicted values, and the differences were divided by the standard error of the estimate from the regression model, creating a standardised Z-value or a reliable change index (RCIsrb). In agreement with previous literature, a RCIsrb value below 1.64 (95^{th} percentile, one-sided) on two or more tests was considered as impaired neuropsychological performance (Lewis *et al.*, 2006; Rasmussen *et al.*, 2001).

All statistics were performed using the Statistical Package for the Social Sciences (SPSS, SPSS Inc. Chicago, USA). Distributions were compared using chi square or Fischer's exact tests, and relative risk (RR) was used for comparing risk. Independent samples t-test was used for comparison between normally distributed data, while the Mann-Whitney U test was the non parametric test of choice. Paired pre-post comparisons within each group are presented for descriptive purposes only. The mean reaction time data were log10 transformed in the analyses to obtain a normal distribution. However, back-transformed data in ms are presented in the tables. Unless otherwise stated, the level of significance for all tests were set to p=.05, two-sided.

Results

Head Impact Identification and Video Evaluation

A total of 228 head impacts that met the inclusion criteria were identified on video from the 352 matches observed (i.e. 19.6 incidents per 1000 playing hours). Of these, 44 (19.3%) incidents were followed up with neuropsychological testing the following day (Head Impact Group). A player removed from play due to the head impact was more likely to be followed up than a player who returned to play (RR=5.1; 95% confidence interval: 2.7 to 9.5). Of the incidents that were followed up, 29.5% (N=13) were characterised as "severe" on the global impression of impact severity, compared to 13.6% (25) of the missed incidents (RR=2.2; 95% confidence interval: 1.2 to 3.9) (Table 2). The incidents which were followed up did not differ from the remaining incidents with respect to the estimated speed involved in the incident, the head movement contribution, the location of the impact or the mass of the striking body part (Table 2).

Insert Table 2 near here

The 228 impacts resulted in 13 (5.7%) "time-loss" injuries (Fuller *et al.*, 2006) that were reported through the injury surveillance system, including 7 (3.1%) concussions (0.6 per 1000 playing hours). Six of these were included among the 44 cases in the Head Impact Group (Fisher's exact test: $p<0.001$) including 5 with loss of consciousness and 2 with post-traumatic amnesia. In two of the cases where a "time-loss" concussion was reported, the player had returned to play in the same game after the head impact.

Baseline characteristics

A total of 47 controls completed the neuropsychological follow-up test (Match Control Group). The baseline characteristics of the Head Impact Group and the Match Control Group

are presented in Table 3. The mean interval from the baseline investigation to the follow-up testing was significantly longer for the Match Control Group compared to the Head Impact Group, and the proportion of players playing in a position with an increased risk of head trauma was higher (defenders and attackers) (Straume-Naesheim *et al.*, 2005b; Andersen *et al.*, 2004a). Otherwise, the groups did not differ significantly at baseline, neither for demographic features such as age and number of previous concussions, nor for neuropsychological test performance.

Insert Table 3 near here

Neuropsychological Testing

Global testing of the reaction time change from baseline to follow-up for all six neuropsychological test variables revealed a significant difference between the Head Impact Group and the Match Control Group (Wilks' lambda 0.82, p=.008).

Post-hoc tests revealed that the Head Impact Group had a significantly larger decline in performance on the follow-up test for the three simplest tasks; Psychomotor function, Decision-making and Simple attention (Fig. 1). After correction for multiple testing, only Psychomotor function and Decision-making remained significant.

Insert figure 1 near here

With respect to the within-person change from baseline to post-match follow-up, there were more players in the Head Impact Group with reduced performance on two or more tasks compared to the Match Control Group (Table 4). In addition, a total of five players in the Head Impact Group scored below the 99th percentile (RCIsrb >2.58) for two or more tasks.

Insert Table 4 near here

Symptomatic and Asymptomatic Players

A total of 22 (50%) of the players in the Head Impact Group reported one or more symptoms at the time of the incident. Headache was the most common symptom and was reported by 17 (38.6%) of the players in the Head Impact group, followed by dizziness (N=12, 27.3%) and concentration problems (N=8, 36.4%).

Both the symptomatic and the asymptomatic players were significantly different from the Match Control Group on the global test (Wilks' lambda: Symptomatic =.76, p=.008, Asymptomatic =.78, p=.016). Even though performance for the three simplest tasks was reduced among the asymptomatic and symptomatic players compared to the Match Control Group, significant differences were only demonstrated for the two simplest tasks, and for the symptomatic group only (Figure 1). The proportion of symptomatic players with impaired neuropsychological performance (8 of 22, 36.4%) was significantly different from the Match Control Group (7 of 47, 14.9%, p=.04). In the asymptomatic group performance was impaired for 7 (31.8%) of the 22 tests on two or more subtasks (chi square: p=.10). Four of the players that were asymptomatic directly after the impact, reported to have symptoms at the time of the testing the next day, and two of these were among those with an impaired test performance.

In 17 of the 44 impacts that were followed up, the footballer did not return to play. Eleven cases were due to concussions, as diagnosed retrospectively based on the symptoms reported by the medical staff or player. Six of these (54.5%) showed a decline in performance on more than one test (Fisher's exact test, p=.010 vs. the Match Control Group), but only three of these were reported to TISS as time-loss injuries (two concussions and one jaw contusion). Five players did not return to play after the incident because of other injuries (i.e. two jaw sprain and three facial fractures). No time-loss injuries were reported for the impacts that were not followed up.

Among the remaining 27, who returned to play (RTP Group), a total of eleven reported playing with one or more symptoms. The RTP Group was significantly slower than the Match Control Group on the follow-up test (Wilks' lambda: .76, p=.004). The post-hoc analyses of each subtest revealed that only the Psychomotor function was significantly different from the Match Control Group (% change: RTP 13.8 [SE 3.2], Match Control Group 2.9 [SE 1.3], p=.004), but both the Decision-making and Simple Attention tasks showed a tendency towards a larger percent change for the RTP group compared to the Match Control Group (% change: Decision-making: RTP 5.9 [SE 3.4], Match Control Group ÷0.9 [SE 1.4], p=.010 and Simple Attention: RTP 6.7 [SE 2.8], Match Control Group 0.4 [SE 1.4], p=.056). There were no trends or significant differences for the three more complex subtasks. The proportion of players with reduced neuropsychological performance did not differ significantly between the RTP group (8 [28.6%]) and the Match Control Group (7 [14.9%], p=.15).

Neuropsychological Performance at One-year Follow-up

A total of 144 (89.4%) of the players participating both years completed a baseline test each year. From this group we identified 107 players who did not experience any head impacts in the 2004 season (Season One Control Group) and 37 players who had experienced at least one impact (Season One Head Impact Group), but in most cases only one incident (N=31, 83.7%). However, one player who experienced as many as 6 impacts was still within the normal range for all tests at the one-year follow-up. The mean time from the last incident to the one-year follow-up was 200 days (range 107-303). The Season One Head Impact Group was slightly older than the Season One Control Group, had a higher proportion of players playing in a position with an increased risk of experiencing a head trauma and headed more frequently compared to the Season One Control Group (Table 3).

At the one-year follow-up (baseline 2005), the Season One Head Impact Group showed a larger increase in reaction times compared to the Season One Control Group

(Wilks' lambda = 0.91, p = 0.043). Figure 2 shows the change for the six subtests for the two groups. The post-hoc tests revealed that the Decision-making task was the only task that was significantly different between the two groups, while there was a trend in the same direction for the Psychomotor function task. Within the Season One Head Impact Group there were 7 reported concussions that led to time loss from training or matches, but only one of these had a deteriorated performance on two or more tasks. This player was also below the 99th percentile of the predicted scores and had sustained two concussions during the 2004 season, each keeping him out of training and matches for more than 21 days.

Insert figure 2 near here

Discussion

This prospective study identified 228 head impacts from 352 matches (rate 19.6 per 1000 playing hours) during the two competitive seasons of 2004 and 2005. The vast majority of these impacts were minor and the player was taken out of play in only 13% of the cases. We were able to follow up 44 cases (19,3%) with neuropsychological testing the following day, and these showed significantly poorer performance compared to controls. However, the differences were limited to the two simplest subtasks in the test battery, and deficits were mainly found among the players reporting to be symptomatic directly after the head impact.

Interpretation of the Neuropsychological Performance

This study is the first to assess prospectively neuropsychological changes after head impacts during regular football matches, irrespective of whether the impacts were diagnosed as concussions or not. The participants in the Head Impact Group and the Match Control Group did not differ with respect to the mean number of headers per player per match, and thus, the main difference between the two groups were the head impacts. This is in contrast to the previous studies, where a retrospective design makes it difficult to separate the effects of

heading versus sub-concussive head trauma (Tysvaer and Lochen, 1991; Tysvaer and Storli, 1989; Rutherford *et al.*, 2003; Matser *et al.*, 1998; Matser *et al.*, 2001; Downs and Abwender, 2002; Rutherford *et al.*, 2003).

The decline in neuropsychological performance for the Head Impact Group is comparable to the results from other relevant studies. Moriarity et al. (2004) investigated amateur boxers within two hours after one, two or three tournament bouts using the same neuropsychological test battery as in the current study. They found a significant change in performance compared to the control group for the boxers whose contests were stopped by the referee or who sustained epistaxis. However, none of these boxers were diagnosed as concussed by the medical personnel present at the tournament. Compared to the boxers, the footballers in our study were faster on both the baseline test and the follow-up test, but the relative change in performance from baseline was comparable. In both studies, the deficits were limited to Psychomotor function and Decision-making only. Still, the authors concluded that these boxers should be considered to have acute cognitive impairments until proven otherwise (Moriarity *et al.*, 2004).

In contrast, a group of students assessed after 24 hours of sustained wakefulness showed significant deficits for five of the six Cogsport tasks (Falleti *et al.*, 2003). Compared to our study, their reaction times at baseline were slower than the footballers and the magnitude of the relative change from baseline to follow-up was twice that of the Head Impact Group. These students were also tested under the influence of alcohol, which resulted in less deterioration compared to sustained wakefulness, with a pattern more similar to the Head Impact Group (Falleti *et al.*, 2003).

None of the groups mentioned showed any deterioration in the higher cognitive domains. And although there is no consensus in the literature as to which specific tasks will detect cognitive deficits after concussions, previous studies on concussion in sport and more serious traumatic

brain injuries show similar results (Bleiberg *et al.*, 2004; Frencham *et al.*, 2005; Warden *et al.*, 2001; Van Zomeren and Deelman, 1978; Van Zomeren and Deelman, 1976; Stuss DT *et al.*, 1989; Collie *et al.*, 2006a). However, there seem to be an agreement that minor traumatic brain injury is not associated with gross deficits in higher cognitive domains, such as intelligence and memory (Frencham *et al.*, 2005).

When interpreting the results from the present study, it must be borne in mind that only 19.3% of the head impacts were followed up with neuropsychological testing. In general, the video analyses revealed that the impacts that gave the impression of being severe, and where the player did not return to play, were more likely to be followed up. On the other hand, for the specific impact severity assessment no significant differences were evident. The definition of a head impact used in this study was liberal, and the main reason for the low compliance was that players were reluctant to be tested after impacts they regarded as trivial. In addition, only six concussions were reported among the Head Impact Group, indicating that the majority of these impacts were considered to be benign, as well. As previously mentioned, the study protocol also included assessment of S100B as a serum marker for brain cell injury, and in keeping with the the current result, the blood sample analyses did not reveal any evidence of that there was any significant brain cell injury after these minor head impacts (Straume-Naesheim et al., 2007). Nevertheless, some deficits in cognitive function were observed in the Head Impact Group when compared to footballers that had played a match without experiencing any head impacts.

Symptomatic Versus Asymptomatic Players

For the Head Impact Group in this study, neuropsychological deficits were found in both the symptomatic and the asymptomatic players when compared to controls. This is in contrast to the results for the non-concussed amateur boxers where deficits were found only in the cases where the match were stopped (Moriarity *et al.*, 2004). Except for this study on amateur

boxers, no other prospective studies have assessed athletes after minor head impacts that were not initially diagnosed as concussions. According to the concussion definition proposed by the Concussion in Sports Group from the Vienna Conference in 2001; a concussion is defined as any impairment of neurological function caused by a direct blow or an impulsive force to the head (Aubry *et al.*, 2002). By this definition, the boxers in the study of Moriarity et al. (2004) were most likely concussed initially as well.

On the other hand, several studies have assessed initially concussed athletes where the symptoms have resolved after a few minutes or by the time of testing (Collins *et al.*, 2003; Lovell *et al.*, 2004; Collie *et al.*, 2006a; Gosselin *et al.*, 2006; Warden *et al.*, 2001; Pellman *et al.*, 2004). Consistent with the findings in our study, there seems to be an agreement that the largest deficits in neuropsychological performance are found for the players who are symptomatic at the time of testing (Collie *et al.*, 2006a; Lovell *et al.*, 2004; Pellman *et al.*, 2004). Nevertheless, other studies have revealed electrophysiological changes (Gosselin *et al.*, 2006) as well as neuropsychological deficits (Warden *et al.*, 2001) among concussed athletes where the symptoms have allegedly resolved. Our study is the first to demonstrate neuropsychological deficits after minor head impacts where the player did not report any acute concussive symptoms.

Clinical Implications

These findings supports the suggestion that concussive symptoms are often not recognised by the players (Delaney *et al.*, 2002) and that, if recognised, symptoms are often not reported to others (McCrea *et al.*, 2004). Nevertheless, our findings support the recommendations from the Vienna consensus statement where it was emphasised that a player showing ANY symptoms or signs of concussion, shall not be allowed to return to play in the current game or practise (Aubry *et al.*, 2002). In the National Football League (NFL), players have traditionally been allowed to return to the same game after a concussion if asymptomatic after

15 minutes (Grade 1 concussion, Kelly and Rosenberg (1998)). However, an examination of a group of high school athletes (Mainly American football) 36 hours after such "grade 1" concussions demonstrated a decline in memory and an increase in self-reported symptoms compared to baseline performance (Lovell *et al.*, 2004). This is in line with the results for the RTP Group in this current study. Even though the footballers in the RTP Group were allegedly asymptomatic and considered fit to play the rest of the match, many reported at the time of testing that they had indeed experienced symptoms of concussion directly after the impact or experienced a delayed onset of such symptoms. In addition, they showed a reduced neuropsychological performance compared to controls.

Long-Term Effects

Although several studies have suggested a possible cumulative effect of concussions on cognitive functioning (Gronwall and Wrightson, 1975; Carlsson *et al.*, 1987; Gaetz *et al.*, 2000; Matser *et al.*, 2001), more recent studies utilising computer-based neuropsychological tests have not been able to identify concussion history as a predictor of neuropsychological performance (Collie *et al.*, 2006b; Broglio *et al.*, 2006; Straume-Naesheim *et al.*, 2005b; Iverson *et al.*, 2006b; Macciocchi *et al.*, 2001). A comprehensive meta-analysis from 2005 of the previous studies on sports-related concussions concluded that the demonstrated neuropsychological impairments caused by these injuries resolve within the first few days and no evidence of impairments was found when the testing was completed later than 7 days after the incident (Belanger and Vanderploeg, 2005). In contrast, the players who experienced a head impact during the 2004 season exhibited a significant, albeit small, reduction in neuropsychological performance compared to their uninjured colleagues when tested 6 months (108 to 297 days) after the incident. This group includes all head impacts, including those that were not followed up acutely, and thus a selection bias is unlikely. The main effect for this group was found for the Decision-making task. Neuropsychological tasks measuring

choice reaction time comparable to the Decision-making task in the CogSport battery have been shown to detect deficits 3-10 months after closed head trauma in patients with allegedly good outcomes (Hugenholtz *et al.*, 1988; Stuss *et al.*, 1985; Stuss DT *et al.*, 1989). These previous studies consisted of cases initially hospitalised for their injury and thus represented a more severe spectrum of minor traumatic brain injuries.

A comparison of the Season One Head Impact Group and the Season One Control Group revealed, not surprisingly, that the Season One Head Impact Group both headed more frequently and had a larger proportion of players playing in a position with an increased risk of injury. Since there was no registration of impacts after the end of the regular season in late October until the follow-up testing in February/March, we can *not* exclude that these players had experienced unreported minor head impacts in a match or during training close to the follow-up test, which could have influenced their performance. On the other hand, this skewness in risk for head traumas between the two groups would have been present prior to the baseline testing in 2004 as well, when no significant differences between the two groups were found. This is in agreement with a previous study based on the 2004 baseline assessment of the same cohort, where no effects of heading frequency and concussion history on neuropsychological performance were found (Straume-Naesheim *et al.*, 2005b). A plausible explanation for the discrepancy between the baseline and follow-up assessments could be that the measured differences at follow-up were based on pre-post test comparisons for each individual, while the comparisons at baseline 2004 were only group based. Within-group comparisons have been suggested as more sensitive than control group comparisons for detecting head injury related neuropsychological effects (Sundstrom *et al.*, 2004). This is supported by Iverson et al. (2006a) who found no performance decrement or symptoms in group analyses of 30 concussed athletes after 10 days, although individual analyses revealed that 37% had a declined performance on two or more tests (2 out of 5 test composites in total).

On the other hand, for the Season One Head Impact group all 37 follow-up tests were within the normal range defined by the test manufacturer and only 4 (10.8%) showed a declined performance on two or more subtests. Consequently, the clinical significance of the statistical deficits demonstrated for the Season One Head Impact Group compared to the Season One Controls is not known.

Conclusion

A reduced neuropsychological performance was found after minor head impacts in football, even in allegedly asymptomatic players. However, the followed-up impacts represented the more severe spectrum of the head impacts in football. Still, only six of these impacts were reported as concussions. In addition, pre-season test performance was somewhat reduced from one year to the next in footballers who had experienced one or more head impacts during the season, although not when compared to normative data. Consequently, the clinical significance of this finding is uncertain.

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Tables

Table 1 Regression-based equations for predicting the follow-up score based on baseline performance. All scores are log 10 transformed reaction times in milliseconds.

Test	Equation
Psychomotor function	Follow-up score = baseline score * 0.695 + 0.728
Decision-making	Follow-up score = baseline score * 0.683 + 0.818
Simple attention	Follow-up score = baseline score * 0.653 + prevconc * 0.006 + 0.930 .
Divided attention	Follow-up score = baseline score * 0.486 + 1.263
Working memory	Follow-up score = baseline score * 0.765 + prevconc * 0.008 + 0.635
Learning & memory	Follow-up score = baseline score * 0.759 + 0.736

Table 2 Distribution of risk factors for the head impact which were followed up and the impacts that were not followed up. Distributions were compared using chi square test.

		Head impact follow-up status		
		Followed up (N=44, 19.3%)	Not followed up (N=184, 80.7%)	p
General assessments				
Classification of the impact	Definite	35 (79.5%)	144 (78.3%)	0.27
	Doubtful	2 (4.5%)	21 (11.4%)	
	Could not be assessed	7 (16.0%)	19 (10.3%)	
Global impression of severity	Severe	13 (29.3%)	25 (13.6%)	0.04
	Not severe	30 (68.2%)	154 (83.7%)	
	Could not be assessed	1 (2.3%)	5 (2.7%)	
Returned to play	No	17 (38.6%)	12(6.5%)	<0.001
	Yes	27 (61.4%)	172 (93.5%)	
Specific impact severity assessment				
Horizontal speed and direction	No relative speed	10 (23.3%)	61 (34.1%)	0.15
	Low speed (towards)	21 (48.8%)	87 (47.8%)	
	High speed (same direction)	9 (20.9%)	30 (16.5%)	
	High speed (towards)	3 (7.0%)	3 (1.6%)	
Head movement contribution	No head movement	26 (59.1%)	127 (69.1%)	0.64
	One player	6 (13.6%)	21 (11.4%)	
	Both	8 (18.2%)	24 (13.0%)	
	Could not be assessed	4 (9.1%)	12 (6.5%)	
Location	Frontal	3 (6.8%)	13 (7.1%)	0.45
	Temporal/parietal	11 (25.0%)	31 (16.8%)	
	Other	30 (68.2%)	140 (76.1%)	
Striking body part	Head	15 (34.1%)	41 (22.3%)	0.36
	Shoulder	3 (6.8%)	12 (6.5%)	
	Elbow	5 (11.4%)	34 (18.5%)	
	Other	21 (47.7%)	97 (52.7%)	

Table 3 Comparison of the Head Impact Groups and the Control groups at baseline for the prospective match study and the one year follow study (baseline 2004 versus baseline 2005).

	Match case-control study			Baseline 2004 versus Baseline 2005		
	Head Impact (N=44)	Match Control (N=47)	p	Season One Head Impact (N=37)	Season One Control (N=107)	p
Age at incident	26.8 (25.7 to 27.9)	26.2 (25.0 to 27.5)	0.50	27.4 (25.9 to 28.9)	25.7 (24.9 to 26.6)	0.048
Audit† multiplied score (median, IQR)	4.0 (0.0 to 5.0)	4.0 (0.0 to 8.5)	0.50	3.0 (0.0 to 6.0)	4.0 (0.0 to 8.0)	0.82
Number of active seasons	7.1 (5.9 to 8.2)	5.7 (4.6 to 6.8)	0.08	6.5 (5.6 to 7.3)	5.7 (5.0 to 6.4)	0.14
Number of previous concussions (median, IQR)	1 (0 to 1)	0.0 (0 to 2)	0.92	1 (0 to 2)	1 (0 to 2)	0.98
Days from baseline to follow-up	130 (110 to 149)	161 (150 to 172)	0.009	346 (340 to 352)	349 (346 to 352)	0.44
Number of headers per player per match	7.8 (6.1 to 9.5)	6.2 (4.9 to 7.4)	0.13	7.4 (6.0 to 8.8)	5.1 (4.2 to 5.9)	0.004
Playing at a position with an increased risk of head trauma††	32 (76.2%)	24 (55.8%)	0.048	26 (70.3%)	44 (41.1%)	0.002

The numbers in the brackets represents the 95% confidence interval of the mean or the inter quartile range (IQR). †*Multiplied score of question 1-3 from the Alcohol Use Disorders Identification Test (AUDIT)by WHO (Saunders et al., 1993).* ††*Missing data on 6 players.*

Table 4 Reaction time data at baseline and follow-up for the Head Impact and Control groups for the tests performed the day after the match and the one year follow-up for the players who experienced a head impact during the 2004 season (Season One Head Impact) compared to controls (Season One Control). The number of players with a declined performance on each subtest is also presented.

Task	Baseline (ms, 95%CI)	Follow-up (ms, 95%CI)	Sign.†	Number of players with declined performance††
Prospective Match Study, both seasons				
Head Impact (N=44)				
Psychomotor function	228 (221 to 235)	251 (239 to 264)	< 0.001	10 (22.7%)
Decision-making	377 (367 to 388)	401 (381 to 422)	0.004	12 (26.7%)
Simple attention	496 (476 to 517)	530 (501 to 561)	0.005	14 (31.1%)
Divided attention	256 (239 to 275)	268 (250 to 287)	0.21	4 (8.9%)
Working memory	490 (460 to 522)	520 (486 to 556)	0.010	7 (15.9%)
Learning & Memory	903 (852 to 958)	923 (873 to 975)	0.37	0 (0.0%)
Declined performance on ≥ 2 tests				15 (34.1%)*
Match Control (N=47)				
Psychomotor function	231 (224 to 237)	236 (228 to 243)	0.082	5 (10.5%)
Decision-making	392 (377 to 407)	387 (373 to 401)	0.37	3 (6.4%)
Simple attention	505 (485 to 526)	506 (488 to 524)	0.95	2 (4.3%)
Divided attention	257 (246 to 270)	274 (260 to 288)	0.026	3 (6.4%)
Working memory	492 (467 to 518)	511 (484 to 540)	0.041	4 (8.5%)
Learning & memory	919 (867 to 974)	964 (906 to 1024)	0.032	4 (8.5%)
Declined performance on ≥ 2 tests				7 (14.9%)
One Year Follow-Up of Baseline 2004				
Season One Head Impact (N=37)				
Psychomotor function	242 (232 to 252)	247 (237 to 257)	0.23	5 (13.5%)
Decision-making	394 (378 to 411)	401 (384 to 420)	0.34	3 (8.1%)
Simple attention	523 (497 to 550)	500 (479 to 523)	0.051	4 (10.8%)
Divided attention	264 (246 to 283)	277 (259 to 296)	0.16	1 (2.7%)
Working memory	514 (479 to 553)	499 (468 to 531)	0.19	2 (5.4%)
Learning & memory	934 (885 to 987)	894 (833 to 958)	0.11	3 (8.1%)
Declined performance on ≥ 2 tests				4 (10.8%)
Season One Control (N=107)				
Psychomotor function	235 (231 to 240)	233 (228 to 239)	0.39	6 (5.6%)
Decision-making	405 (394 to 416)	389 (378 to 399)	0.001	6 (5.6%)
Simple attention	523 (507 to 540)	499 (495 to 513)	< 0.001	8 (7.5%)
Divided attention	258 (248 to 269)	253 (243 to 263)	0.31	2 (1.9%)
Working memory	520 (502 to 541)	481 (465 to 497)	< 0.001	7 (6.5%)
Learning & memory	966 (930 to 1005)	923 (889 to 959)	0.002	3 (2.8%)
Declined performance on ≥ 2 tests				6 (5.7%)

All the reaction time data are back-transformed from log10 values. †Paired samples t-test (baseline versus follow-up). ††Declined performance was defined as a reliable change index (RCIsrb) below 1.65 (90^{th}-percintile, see methods section).*Significantly higher proportion compared to the respective control groups (chi square test, p=0.033).

Figure legends

Figure 1 Change (%) in reaction time from baseline to follow-up for the Head Impact Group and the Match Control Group. Data are also shown for symptomatic and asymptomatic players in the Head Impact Group. *p<.05 vs. the Match Control Group; **p<.01.

Figure 1:

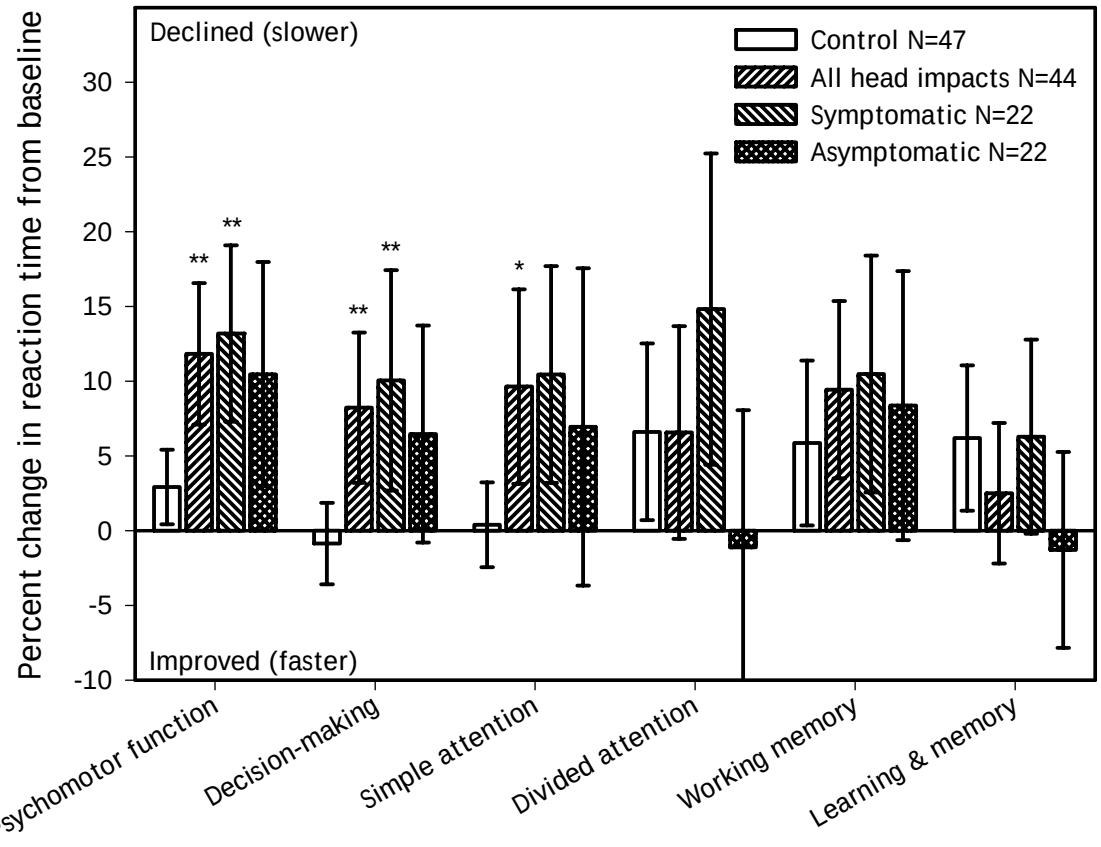

Figure 2 Change (%) in reaction time from baseline 2004 to baseline 2005 for players with (Season One Head Impact) and without (Season One Control) a registered head impact during the 2004 season (N=144).

Figure 2: