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Persistent effects of playing football and associated (subconcussive) head trauma on brain structure and function: a systematic review of the literature

A A Tarnutzer,[1,2] D Straumann,[1,2] P Brugger,[1] N Feddermann-Demont[1,2]

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[1]Department of Neurology, University Hospital Zurich and University of Zurich, Zurich, Switzerland
[2]Swiss Concussion Center, Schulthess Clinic, Zurich, Switzerland

Correspondence to
Dr A A Tarnutzer, Department of Neurology, University Hospital Zurich, Frauenklinikstr. 26, Zurich 8091, Switzerland; alexander.tarnutzer@access.uzh.ch, atarnutzer@gmail.com

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ABSTRACT

Aim/objective There is ongoing controversy about persistent neurological deficits in active and former football (soccer) players. We reviewed the literature for associations between football activities (including heading/head injuries) and decline in brain structure/function.

Design Systematic literature review.

Data sources MEDLINE, Embase, PsycINFO, CINAHL, Cochrane-CRCT, SportDiscus, Cochrane-DSR=4 (accessed 2 August 2016).

Eligibility criteria for selecting studies Original studies reporting on football-related persistent effects on brain structure/function. Results from neurocognitive testing, neuroimaging and EEG were compared with controls and/or correlated with heading frequency and/or head injuries. Methodological quality was rated for risk-of-bias, including appropriateness of controls, correction for multiple statistical testing and assessment of heading frequency and head injuries.

Results 30 studies with 1691 players were included. Those 57% (8/14) of case–control studies reporting persistent neurocognitive impairment had higher odds for inappropriate control of type 1 errors (OR=17.35 (95% CI (10.61 to 28.36)) and for inappropriate selection of controls (OR=1.72 (1.22 to 2.43)) than studies observing no impairment. Studies reporting a correlation between heading frequency and neurocognitive deficits (6/17) had lower quality of heading assessment (OR=14.20 (9.01 to 22.39)) than studies reporting no such correlation. In 7 of 13 studies (54%), the number of head injuries correlated with the degree of neurocognitive impairment. Abnormalities on neuroimaging (6/8 studies) were associated with subclinical neurocognitive deficits in 3 of 4 studies.

Summary/conclusions Various methodological shortcomings limit the evidence for persistent effects of football play on brain structure/function. Sources of bias include low-quality assessment of heading frequency, inappropriate control for type 1 errors and inappropriate selection of controls. Combining neuroimaging techniques with neurocognitive testing in prospective studies seems most promising to further clarify on the impact of football on the brain.

INTRODUCTION

Concussions (ie, a subtype of mild traumatic brain injury (mTBI) without structural abnormalities on conventional CT or MRI)[1] represent 1–5% of all football-related (soccer-related) injuries.[2–5] While most players return to play within 7–10 days, head-trauma-related symptoms may last for weeks to months in 10–15% and even persist in selected cases.[6] Neurodegenerative disorders (such as Alzheimer disease) have been reported in retired professional football players and in athletes from other contact sports as rugby and American football.[7 8] A postulated association between football play and chronic traumatic encephalopathy, however, remains controversial,[9] and the effect of football-related concussions is not well understood.

Likewise, the impact of purposeful heading the ball to play and guide its direction—unique to football—on the brain has been debated.[10 11] On average, players head the ball 1–16 times during a competitive football match,[12–16] accumulating over a season to several hundred headings[17–19] and to many thousand headings during a professional football career. This has raised concerns that heading may—similar to boxers receiving punches to the head—pose players at increased risk for 'subconcussive' trauma,[20–24] potentially resulting in neuronal damage similar to that in repetitive concussions but not accompanied by overt symptoms.[20–23 25] These considerations have led to uncertainty in football players and their (medical) attendants,[1] albeit such a link is far from being established and the impact of parameters such as heading technique, player's age and playing position remains unclear. Nonetheless, with raising concerns and facing a concussion litigation, the football federation of the USA issued in November 2015 a ban for heading in children aged 10 years or less and limited heading in children aged 11–13 years.[26] Concerns that the maturing brain could be especially vulnerable to subconcussive head injury may have supported this decision.

Research interest in associations between concussion, heading and persistent changes of the human brain has grown substantially. At the end of the last century, a series of case–control studies indicated persistent neurocognitive impairments in Dutch professional[16 19] and amateur[27] football players. These studies were the basis for further investigations addressing functional, structural and metabolic brain changes in football players. While some studies confirmed neurocognitive abnormalities compared with controls,[28 29] others found no such evidence.[14 15 30 31] Likewise, associations between neurocognitive deficits and heading frequency were reported by some,[16 17 19 28 29] but not by others.[14 15 30–34]

In accordance with neuroimaging for TBI,[35] different protocols were applied to study structural (diffusion tensor imaging (DTI),[36] voxel-based MR morphometry (VBM)) and metabolic (functional MRI (fMRI), magnetic resonance spectroscopy

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(MRS)) brain changes in football players and to correlate with neurocognitive function. In two small case–control studies, memory impairment was linked to cortical thinning in former professionals[37] and to diffuse white matter abnormalities in amateur players,[17] while recently in a prospective case–control study over 5 years in professional players, no such link could be drawn.[38]

In summary, whether or not football play is linked to persistent changes in brain function/structure remains controversial. Against this background, we aimed to systematically review the literature on associations between football play and persistent changes in brain function/structure and the impact of heading frequency and concussive head injuries. Assessing study quality and identifying methodological limitations using standardised tools for reporting risk-of-bias was a special focus.[10]

MATERIALS AND METHODS

Data sources and searches

A literature search (MEDLINE, Embase, PsycINFO, CINAHL, Cochrane CRCT, SportDiscus, Cochrane DSR=4) was performed (2 August 2016) to identify articles reporting on associations between football play and especially heading and football-related head injuries and *persistent* structural/functional changes of the brain. The MEDLINE (OVID) search strategy was translated for each database, and is reported in online supplementary file 1.

'Persistent' changes were defined as changes that were still recognisable >6 months after a potential impact or linked to exposure to football play for >6 months or a full season. We adhered to the time-frame usually applied for the persistent postconcussive syndrome,[39] albeit no consensus-based definition of this term exists.

We also performed a manual search of reference lists from eligible articles. We did not seek to identify research abstracts from meeting proceedings or unpublished studies, nor non-English language studies. Retrospective or prospective studies with five or more participants were eligible. This review complies with PRISMA guidelines.[40]

Study selection

We identified 2191 citations for screening and included 30 studies for quantitative synthesis (figure 1) based on abstract and for selected studies full-text review by two experienced neurologists (NF-D, AAT). Articles were selected using predetermined criteria (see online supplementary file 1).

Data extraction and quality assessment

Reports on neurocognitive testing, neuroimaging, postural control and EEG were considered. Data extraction was performed by AAT and confirmed by NF-D. When extracting data from selected studies, we assessed the type of study, the type of diagnostic tests performed, the frequency of heading and head injuries and the level of play, distinguishing between youth, high school/college (including interscholar), university, amateur, active professional and former professional players. In studies reporting on neurocognitive testing, all tests applied were retrieved and assigned to the category that best described the domain of neurocognitive function evaluated. Categories were: abstract reasoning, attention, (verbal) creativity and divergent thinking, decision-making, executive functions, intelligence, language and language-associated functions, memory/learning, mood, motor skills and visuospatial skills.

A standardised risk-of-bias assessment was performed using the Newcastle–Ottawa Scale (NOS).[41] Its use for non-randomised case–control studies and observational studies has been promoted by the Cochrane Collaboration.[42] The NOS requires rating the selection, comparability and exposure/outcome for a total of nine items. Study quality was rated as 'good', 'fair' or 'poor' (see ref. [43] and online supplementary file 2). Studies rated as 'poor' were excluded. The NOS included an assessment of the response rate when asked to participate. Studies with a low (<50%) participation rate, with participation rates differing >10% between football players and controls or studies that did not report response rates were rated as high risk for selection bias. Whenever non-football playing controls were available (n=21 studies), their suitability was rated. Only control groups that were age-matched and gender-matched and that participated in non-contact sports with a comparable physical activity profile (eg, swimming, track, tennis) were considered 'appropriate' or low risk for bias. A distinct (ie, lower/higher) physical activity profile may introduce a bias and observed differences may be attributed falsely to effects of football play. Controls falling short of these criteria were considered 'inappropriate' or high risk of bias.

Based on previously described methodological limitations, we further assessed the quality of included studies regarding assessment of heading frequency and history of head injuries and control for type 1 errors.[10] Rutherford *et al*[10] identified insufficient control for type 1 errors as a potential source for false-positive statistical differences. To follow-up on this limitation, we assessed methods for avoiding type 1 errors. Only studies that reported sufficient controlling for multiple testing (eg, by applying the Bonferroni correction) were considered 'appropriate' or low risk for type 1 errors, while studies falling short of these criteria were considered 'inappropriate' or high risk. Heading frequency and head injuries may be overstated or understated by players, posing them at risk for recall bias. Therefore, only studies that prospectively collected data on heading frequency (eg, by an independent observer) were considered low risk of bias, while studies falling short of these requirements (eg, relied on self-reported numbers, a heading exposure index[44]) were considered high risk. We did not require loss of consciousness for making the diagnosis of concussion and relied on the original study authors' assessment.

Data synthesis and analysis

Excel 2011 (Microsoft Corp, Redmont, USA) and Matlab V.7.0 (The MathWorks, Nantuck, USA) were used for data analyses. Statistical analyses were performed using two-sample t-tests (with the Bonferroni correction) and ORs including 95% CIs.

RESULTS

From the 32 studies included for qualitative synthesis (figure 1), one was excluded because of 'poor' quality on NOS[45] and one was removed because of duplicity of data.[46] Among the 30 studies included for quantitative synthesis (n=1691, 22.4% females), only 6 were prospective. Twenty-three studies (76.7%, n=1518) reported on results of neurocognitive testing, while data on neuroimaging were provided in eight studies (26.7%, n=143). Information on EEG (6.7%, n=106) was available from two; postural stability (3.3%, n=15) was provided in one study (tables 1 and 2). Four studies reported on more than one modality (see online supplementary file 3). NOS ratings were 'good' and 'fair', respectively, in 15 studies each (see online supplementary file 2). Key domains for neurocognitive testing of (sub)concussive brain injury (attention, executive functions, memory) were assessed by 18 of 23 studies, while in the remaining 5 studies, 1 (n=3) or 2 (n=2) key domains were missing.

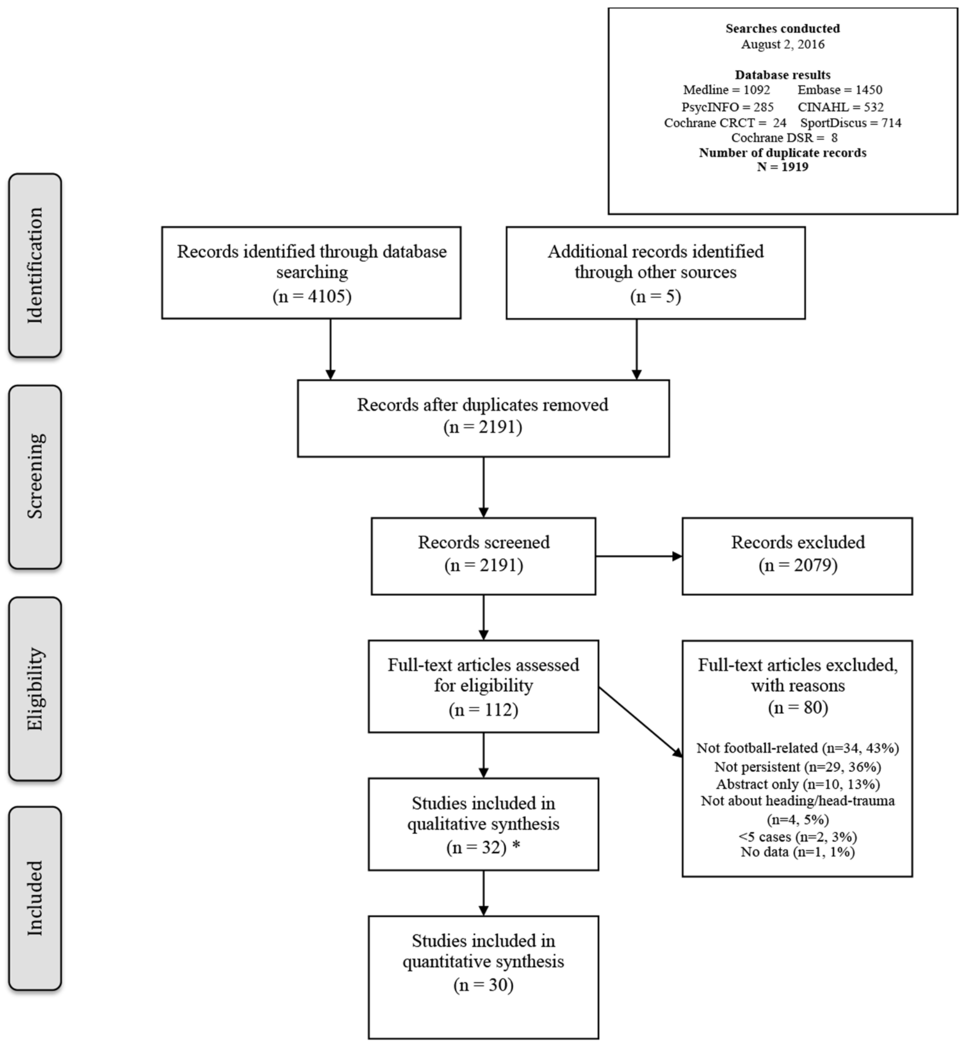

Figure 1 Flow chart depicting the selection process of identified articles. *One study was excluded because of duplicity of data;[46] another study was excluded because of a 'poor' risk-of-bias rating (Newcastle–Ottawa Scale).[45]

Case–control studies reporting on neurocognitive testing

Fourteen studies compared neurocognitive test results in football players (n=581) with those from controls (n=348). On average, 8.7±5.8 tests covering 4.4±1.9 categories were administered. Eight studies (57.1%) reported significantly lower results for the football players than for the controls in at least one test (2.8 ±2.7 tests, average±1 SD). Most frequently, deficits of attention, executive function and memory were noted (table 3 and figure 2).

Studies reporting neurocognitive deficits had a higher rate of inappropriate control of type 1 errors (OR=17.35 (95% CI (10.61 to 28.36)) and higher odds for inappropriate controls (OR=1.72 (1.22 to 2.43)) than studies not reporting any differences. The fraction of female players was about the same for both groups (OR=0.82 (0.47 to 1.47)). The fraction of younger players (youth/high school/college) compared with more elderly players was larger in studies with negative findings than in those with significant deficits (OR=1.92 (1.38 to 2.68)) (table 3).

Impact of heading on neurocognitive functions

A potential link between heading exposure and performance on neurocognitive testing was analysed in 17 studies (n=1173, 26.4% females). On average, 8.5±5.1 neurocognitive tests covering 4.4±1.8 categories were obtained (table 3). Two-thirds of the studies did not find any relation between heading frequency and neurocognitive test performance, while six studies (35%) reported a correlation in 2.0±1.1 tests. Deficits of attention, memory and intelligence were most frequent (table 4). The quality of heading frequency assessment was lower for those studies reporting a link than for those studies without such a link (OR=14.2 (9.0 to 22.4)). The rate of inappropriate control of type 1 errors was similar in studies confirming or discarding such a link (OR=0.74 (0.53 to 1.04)). The fraction of players with more extensive exposure (amateurs, university, (former) professionals) was significantly higher among those studies reporting neurocognitive deficits than for those studies that did not observe deficits (OR=2.15 (1.63 to 2.85)).

Impact of head injuries on neurocognitive functions

A potential association between previous head injuries and neurocognitive deficits was investigated in 13 studies (n=1103, 26.6% females) (table 3). On average, 11.3±4.9 neurocognitive tests covering 5.2±1.4 categories were obtained. Seven studies (54%) reported a correlation, with abnormalities noted in 2.4±1.8 tests. Deficits of visuospatial functions, decision-making, attention and executive function were most frequent (table 4). The rate of inappropriate control of type 1 errors was

Table 1 Metadata of included studies (n=30)

Citation, year	Study design	Level of play	Control group	Sample size (test/control group) (n), gender	Observation/exposure duration to competitive football play (mean±1 SD)	Focus of study	NOS rating ('good', 'fair' or 'poor')	Controls appropriate/ appropriate control of type 1 errors/response rate (%)	High-quality assessment of heading frequency
Abreau *et al*, 1990[47]	Retrospective, case–control	College	College tennis players	31/31, male	≥2 seasons (college level)	NCP football players vs controls	Fair	Yes/no/62/220 (28%)	NA
Adams *et al*, 2007[48]	Retrospective, case–control	College	Non-football playing college students	10/10, male	≥8 years	Grey matter density and volume (VBM)	Fair	No/yes/NR	NA
Downs and Abwender, 2002[28]	Retrospective, case–control	College/pro	College swimmers	32/29, female +male	≥4 years (collegiate/national level)	NCP football players vs controls, impact of heading	Fair	No/no/NR	No (heading exposure index)
Ellemberg *et al*, 2007[49]	Retrospective, cross-sectional	University	NA	22/NA, female	6–8 months since concussion, 15 years of play	Impact of concussion on NCP	Fair	NA/yes/NR	NA
Forbes *et al*, 2014[13]	Prospective, cohort	Interscholastic	NA	210/NA, female	27±21 months since (last) concussion, 9 years of play	Impact of concussion on NCP	Good	NA/unclear/NR	Yes
Guskiewicz *et al*, 2002[31]	Retrospective, case–control	Collegiate	Non-football contact sports, (n=96), no sports controls (n=53)	91/149, female +male	≥5 years	NCP football players vs controls, impact of concussion	Fair	No/yes/NR	NA
Janda *et al*, 2002[18]	Prospective, cohort	Youth	NA	57/NA, female +male	9 months (prospective)	Impact of heading on NCP	Good	NA/unclear/NR	Yes
Jordan *et al*, 1996[44]	Retrospective, case–control	Active pro	Elite track athletes	20/20, male	17.7±3.1 years	Structural abnormalities (MRI)	Good	Yes/no/20/25 (80%)	NA
Kemp *et al*, 2016[38]	Prospective, case–control	Active pro	Various non-contact sports athletes from local university	32/33, male	≥5 years of competitive football play	NCP football players vs controls, structural abnormalities (MRI)	Fair	Yes/yes/NR	NA
Koerte *et al*, 2012[50]	Retrospective, case–control	Active pro	Swimmers from competitive clubs	12/11, male	13.3±2.9 years	White matter integrity (DTI)	Good	Yes/yes/12/40 (30%)	NA
Koerte *et al*, 2015[51]	Retrospective, case–control	Former pro	Former non-contact pro athletes	11/14, male	Trained since childhood, >1 year as pro	Brain biochemistry (MRS), correlation with NCP	Good	Yes/no/NR	No (self-reported)
Koerte *et al*, 2015[37]	Retrospective, case–control	Former pro	Former non-contact pro athletes	15/15, male	Trained since childhood, 4.7 ±3.6 years as pro	Grey matter thickness (VBM), correlation with NCP	Good	Yes/no (NCT), yes (imaging)/NR	No (self-reported)
Kontos *et al*, 2011[12]	Prospective, cross-sectional	Youth	NA	63/NA, female +male	Btw. 6.7±3.0 and 8.5 ±4.6 years	Impact of heading on NCP	Good	NA/yes/NR	Yes
Lipton *et al*, 2013[17]	Retrospective, cross-sectional	Amateur	NA	37/NA, female +male	>5 years	White matter microstructure (DTI), correlation with NCP	Good	NA/yes/NR	No (self-reported)
Matser *et al*, 1998[16]	Retrospective, case–control	Active pro	Elite non-contact sports athletes	53/27, male	≥4 years amateur (median=12 years) and ≥1 year pro (median=5 years)	NCP, impact of heading/ head injuries	Good	Yes/no/NR	No (self-reported)
Matser *et al*, 1999[27]	Retrospective, case–control	Amateur	Amateur athletes (swimming/track)	33/27, male	≥5 years (avg=17 years)	NCP football players vs controls, impact of head injuries	Good	Yes/no/33/33 (100%)	NA
Matser *et al*, 2001[19]	Retrospective, cross-sectional	Active pro	NA	84/NA, male	≥1 year pro play (median=4 years)	Impact of heading and head injuries on NCP	Good	NA/no/NR	No (self-reported)

Continued

Table 1 Continued

Citation, year	Study design	Level of play	Control group	Sample size (test/control group) (n), gender	Observation/exposure duration to competitive football play (mean±1 SD)	Focus of study	NOS rating ('good', 'fair' or 'poor')	Controls appropriate/ appropriate control of type 1 errors/response rate (%)	High-quality assessment of heading frequency
Rutherford *et al*, 2005[52]	Retrospective, case–control	University	Rugby players (n=17), non-contact sports (n=24)	22/41, male	≥5 years	NCP football players vs controls, impact of heading/head injuries	Good	Yes/yes/109/156 (70%)	Yes
Rutherford *et al*, 2009[14]	Retrospective, case–control	University	Rugby players (n=30), non-contact sports (n=22)	25/52, male	≥5 years (avg=6.1±0.1 years)	NCP football players vs controls, impact of heading/head injuries	Good	Yes/yes/165/254 (65%)	Yes
Salinas *et al*, 2009[53]	Prospective, cross-sectional	Youth	NA	49/NA, female +male	3.1±1.9 years	Impact of heading on NCP	Fair	NA/unclear/NR	Yes
Stephens *et al*, 2010[15]	Retrospective, case–control	High school	rugby players (n=27), non-contact sports (n=16)	54/43, male	3.4±1.0 years	NCP football players vs controls, impact of heading/head injuries	Fair	Yes/yes/193/337 (57%)	Yes
Straume-Naesheim *et al*, 2005[32]	Retrospective, cross-sectional	Active pro	NA	271/NA, male	Btw. 2.8±2.4 and 3.3 ±2.4 years at highest league	Impact of heading/head injuries on NCP	Good	NA/ no/271/300 (90%)	No (self-reported)
Straume-Naesheim *et al*, 2009[33]	Prospective, cohort	Active pro	NA	144/NA, male	1 year (ie, 1 season)	Impact of concussion on NCP	Good	NA/yes/NR	NA
Svaldi *et al*, 2016[54]	Prospective, case–control	High school	High school athletes from various non-collision sports	14/12, female	1 season plus 3–4 months	Cerebrovascular reactivity related to head acceleration (heading)	Good	Yes/yes/NR	Yes (head acceleration event monitoring
Tysvaer and Storli, 1989[55]	Retrospective, case–control	Active pro	Men with various occupation	69/69, male	128 games in pro league (avg)*	EEG disturbances	Fair	No/unclear/NR	NA
Tysvaer *et al*, 1989[56]	Retrospective, case–control	Former pro	Men from 'different occupational groups'	37/37, male	359 games in pro league (avg)*	EEG disturbances	Fair	No/unclear/43/50 (86%)	NA
Tysvaer and Lochen, 1991[57]	Retrospective, case–control	Former pro	Patients hospitalized for various disorders	37/20, male	359 games in pro league (avg)*	NCP football players vs controls, impact of heading	Fair	No/no/NR	NR
Vann Jones *et al*, 2014[34]	Retrospective, case–control	Former pro	UK-based MCI prevalence study[58]	92/NA, male	14.5±3.2 years of pro play	NCP football players vs controls	Fair	NA/no/138/300 (46%)	No (heading exposure index)
Witol and Webbe, 2002[29]	Retrospective, case–control	Interscholastic, amateur/pro	Non-soccer playing controls	60/12, male	Btw. 9.1±5.0 and 13.9±6.5 years	NCP football players vs controls, impact of heading	Fair	No/no/NR	No (self-reported)
Zhang *et al*, 2013[59]	Retrospective, case–control	High school	Non-football players (high school level)	12/12, female	5–12 years (median: 8 years)	NCP football players vs controls, impact of heading	Fair	Unclear/unclear /NR	No (self-reported)

*These studies did not provide years of play, but games played. Assuming a total of 30–60 games per season, in all cases, more than one season of professional play can be assumed.
avg, average; btw, between; DTI, diffusion tensor imaging; MRS, magnetic resonance spectroscopy; NA, not available; NCP, neurocognitive performance; NOS, Newcastle–Ottawa Scale, NR, not reported; pro, professional; VBM, voxel-based morphometry.

Table 2 Summary information about included studies (n=30)

	Studies (n, (%))	Female football players (n (%))	Male football players (n (%))	All football players (n (%))
Control of type 1 errors				
Appropriate	12 (40.0)	104 (27.4)	414 (31.6)	518 (30.6)
Inappropriate/unclear	18 (60.0)	275 (72.6)	898 (68.4)	1173 (69.4)
Total	30 (100.0)	379 (100.0)	1312 (100.0)	1691 (100.0)
Selection of controls				
Appropriate	12 (40.0)	12 (11.1)	224 (54.2)	236 (45.3)
Inappropriate/unclear	8 (26.7)	96 (88.9)	189 (45.8)	285 (54.7)
NA	10 (33.3)	NA	NA	NA
Total	30 (100.0)	108 (100.0)	413 (100.0)	521 (100.0)
Response rate*				
High (>50%)	7 (23.3)	0 (0.0)	462 (35.2)	462 (27.3)
Low (≤50%)	3 (10.0)	0 (0.0)	135 (10.3)	135 (8.0)
Not reported	20 (66.7)	379 (100.0)	715 (54.5)	1094 (64.7)
Total	30 (100.0)	379 (100.0)	1312 (100.0)	1691 (100.0)
Gender				
Football players	NA	379 (22.4)	1312 (77.6)	1691 (100.0)
Control participants	NA	108 (20.7)	413 (79.3)	521 (100.0)
Category†				
NCT	23	365	1153	1751
Case–control studies	14[14–16 27–29 31 34 37 38 47 52 57 59]	56	525	512
Impact of heading	17[12–19 28 29 32 34 37 52 53 57 59]	310	863	1459
Impact of head injuries	13[13–19 27 31–33 49 52]	188	810	980
Neuroimaging	8[17 37 38 44 48 50 51 54]	22	121	138
EEG	2[55 56]	0	106	106
Postural control	1[37]	0	15	15
Level of play‡				
Youth	3 (10.0)	69 (18.2)	100 (7.6)	169 (10.0)
High school/college	9 (30.0)	280 (73.9)	234 (17.8)	514 (30.4)
University	3 (10.0)	22 (5.8)	47 (3.6)	69 (4.1)
Amateur	2 (6.7)	8 (2.1)	62 (4.7)	70 (4.1)
Professional	8 (26.7)	0 (0.0)	677 (51.6)	677 (40.0)
Former professional	5 (16.7)	0 (0.0)	192 (14.6)	192 (11.4)
Total	30 (100.0)	379 (100.0)	1312 (100.0)	1691 (100.0)

*Fraction of participants that agreed to participate after being invited to participate in the study. This includes football players and control participants.
†Some studies provided testing for more than one modality (eg, neurocognitive testing and neuroimaging or neuroimaging and balance testing), resulting in a total study number larger than 31. Within neurocognitive testing, also some studies provided case–control data as well as a correlation analysis for, for example, heading frequency and neurocognitive deficits in the football players.
‡Level of play as reported in the original studies. Age range for youth football players was 10–13[18] and 13–18.[12] The category 'High school/college' includes the 'interscholastic' as well.
NA, not available; NCT, neurocognitive testing.

lower in studies with positive findings compared with studies with negative findings (OR=0.20 (0.15 to 0.26)).

Data on previous head injuries were available in 10 studies with average numbers of concussions ranging between 1.0 and 2.1, with the most recent event between 6 and 8 months and several years ago. The assessment of previous head injuries was based on players' reports in all but two studies.[13 49] Only football-related concussions were considered in five of seven studies with positive findings and in three of six studies with negative findings, while the remaining five studies included other, non-football-related concussions as well or did not further specify.

Neuroimaging studies

We identified eight studies (n=143, 15.4% females) using imaging modalities focusing on brain structure (conventional MRI, VBM, DTI) or brain metabolism (fMRI, MRS). DTI (2 studies, n=49), conventional MRI (2 studies, n=44) and VBM (2 studies, n=25) were most frequently applied (table 5). All studies used a case–control design with selection of controls rated as 'appropriate' in six (75%). Most players were professionals (active=56; former=26) or amateurs (n=37). Only two studies were prospective.[38 54] In one prospective study, no conventional MRI changes could be depicted in professional players (observation period=5 years).[38] Prospectively observing female high-school players over one season using fMRI, significant reductions in frontotemporal cerebrovascular reactivity persisting up to 4–5 months after the season had ended were reported,[54] resembling the pattern described in mTBI.[60 61] Retrospectively, in former professionals, VBM demonstrated cortical thinning in the right inferolateral parietal, temporal and occipital cortex[37] and MRS showed higher choline and myo-inositol levels in the posterior cingulate gyrus.[51] In professional players, DTI indicated widespread white matter abnormalities (albeit no changes in fractional anisotropy),[50] but conventional MRI did not demonstrate changes related to the years of football participation.[44] In college-football players, VBM showed decreased grey matter density and volume within the anterior–temporal cortex.[48]

Four studies linked neuroimaging with neurocognitive data.[17 37 38 51] Cortical thinning was associated with worse

Table 3 Studies reporting on neurocognitive testing (NCT) in football players*

	Case–control studies				Studies addressing the impact of heading frequency				Studies addressing the impact of head injuries			
	Studies with significant differences in NCT†	Studies without sign. differences in NCT	All studies	Stats	Studies with significant impact on NCT†	Studies without sign. impact on NCT	All studies	Stats	Studies with significant impact on NCT†	Studies without sign. impact on NCT	All studies	Stats
Studies (n (%))	8 (57.1)	6 (42.9)	14 (100)		6 (35.3)	11 (64.7)	17 (100.0)		7 (53.8)	6 (46.2)	13 (100.0)	
Control of type 1 errors (number of studies/number of participants (%))												
Appropriate	1/22 (8.3)	4/194 (61.2)	5/216 (37.2)	OR=17.35 (10.61 to 28.36)‡	2/59 (20.5)	3/142 (16.0)	5/201 (17.1)	OR=0.74 (0.53 to 1.04)‡	4/242 (58.7)	3/153 (22.1)	7/395 (35.8)	OR=0.20 (0.15 to 0.26)‡
Inappropriate/unclear	7/242 [91.7)	2/123 [38.8)	9/365 [62.8)		4/229 (79.5)	8/743 (84.0)	12/972 (82.9)		3/170 (41.3)	3/538 (77.9)	6/708 (64.2)	
Selection of controls (number of studies/number of control participants (%))§												
Appropriate	5/155 (58.2)	5/225 (71.0)	10/380 (65.4)	OR=1.72 (1.22 to 2.43)‡	NA	NA	NA	NA	NA	NA	NA	NA
Inappropriate/unclear	3/109 (41.3)	1/92 (29.0)	4/201 (34.6)		NA	NA	NA		NA	NA	NA	
Response rate (number of studies)¶												
High (>50%)	3	2	5		1	4	5		3	2	5	
Low (≤50%)	0	2	2		0	1	1		0	0	0	
Not reported	5	2	7		5	6	11		4	4	8	
Football players according to gender (number of participants (%))												
Females	23 (8.7)	33 (10.4)	56 (9.6)	OR=0.82 (0.47 to 1.44)‡	19 (6.6)	291 (32.9)	310 (26.4)	OR=0.14 (0.09 to 0.23)‡	22 (5.3)	271 (39.2)	293 (26.6)	OR=0.09 (0.06 to 0.14)‡
Males	241 (91.3)	284 (89.6)	525 (90.4)		269 (93.4)	594 (67.1)	863 (73.6)		390 (94.7)	420 (60.8)	810 (73.4)	
Total	264 (100.0)	317 (100.0)	581 (100.0)		288 (100.0)	885 (100.0)	1173 (100.0)		412 (100.0)	691 (100.0)	1103 (100.0)	
Gender controls (number of participants (%))												
Females	27 (16.3)	69 (37.9)	96 (27.6)		NA	NA	NA		NA	NA	NA	
Males	139 (83.7)	113 (62.1)	252 (72.4)		NA	NA	NA		NA	NA	NA	
Total	166 (100.0)	182 (100.0)	348 (100.0)		NA	NA	NA		NA	NA	NA	
Sample size (mean±SD)**												
Football players	33±17	53±32	42±26	p=0.157	48±22	80±83	61±63	p=0.371	59±43	115±101	85±78	p=0.208
Controls	21±7	36±34	27±22	p=0.221	NA	NA	NA		NA	NA	NA	
NCTs (mean±SD)**	9.1±6.4	8.2±5.4	8.7±5.8	p=0.773	11.0±5.5	7.2±4.6	8.5±5.1	p=0.147	14.1±4.1	8.0±3.6	11.3±4.9	p=0.162
NCT categories (mean ±SD)**	4.6±2.0	4.0±2.0	4.4±1.9	p=0.573	5.2±1.6	4.0±1.8	4.4±1.8	p=0.213	5.9±1.2	4.5±1.4	5.2±.1.4	p=0.086
Heading assessment (number of participants)												
Self-reported	NA	NA	NA		234 (81.3)	298 (33.7)	532 (45.4)	OR=14.20 (9.01 to 22.39) ††	NA	NA	NA	
Heading exposure index	NA	NA	NA		32 (11.1)	92 (10.4)	124 (10.6)		NA	NA	NA	

Continued

Table 3 Continued

	Case–control studies				Studies addressing the impact of heading frequency				Studies addressing the impact of head injuries			
	Studies with significant differences in NCT†	**Studies without sign. differences in NCT**	**All studies**	**Stats**	**Studies with significant impact on NCT†**	**Studies without sign. impact on NCT**	**All studies**	**Stats**	**Studies with significant impact on NCT†**	**Studies without sign. impact on NCT**	**All studies**	**Stats**
Prospectively	NA	NA	NA		0 (0.0)	433 (48.9)	433 (36.9)		NA	NA	NA	
Combination	NA	NA	NA		22 (7.6)	25 (2.8)	47 (4.0)		NA	NA	NA	
NR	NA	NA	NA		0 (0.0)	37 (4.2)	37 (3.2)		NA	NA	NA	
Level of play (number of studies/number of participants (%))												
Youth	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	OR=1.92 (1.38 to 2.68)‡‡	0/0 (0.0)	3/169 (19.1)	3/169 (14.4)	OR=2.15 (1.63 to 2.85)‡‡	0/0 (0.0)	1/57 (8.2)	1/57 (5.2)	OR=7.13 (5.16 to 9.84)‡‡
High school/college	3/104 (39.4)	3/176 (55.5)	6/280 (48.2)		2/92 (31.9)	3/276 (31.2)	5/368 (31.4)		1/54 (13.1)	2/301 (43.6)	3/355 (32.2)	
University	1/22 (8.3)	1/25 (7.9)	2/47 (8.1)		1/22 (7.6)	1/25 (2.8)	2/47 (4.0)		2/44 (10.7)	1/25 (3.6)	3/69 (6.3)	
Amateur	1/33 (12.5)	0/0 (0.0)	1/33 (5.7)		1/37 (12.8)	0/0 (0.0)	1/37 (3.2)		1/33 (8.0)	1/37 (5.4)	2/70 (6.3)	
Professional	1/53 (20.1)	1/24 (7.6)	2/77 (13.5)		2/137 (47.6)	1/271 (30.6)	3/408 (34.8)		3/281 (68.2)	1/271 (39.2)	4/552 (50.0)	
Former professional	2/52 (19.7)	1/92 (29.0)	3/144 (24.8)		0/0 (0.0)	3/144 (16.3)	3/144 (12.3)		0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	
All	8/264 (100.0)	6/317 (100.0)	14/581 (100.0)		6/288 (100.0)	11/885 (100.0)	17/1173 (100.0)		7/412 (100.0)	5/691 (100.0)	13/ 103 (100.0)	

*Studies may have provided data both for neurocognition in football in general and specifically related to heading frequency and/or the number of head injuries.
†In these studies, statistically significant (p<0.05) differences (between cases and controls or related to heading frequency or the number of head injuries) in at least one neuropsychological test were reported.
‡OR (OR; including 95% CIs in parentheses) comparing fractions of a given condition (eg, appropriateness of type 1 errors or gender) between studies with or without significant differences in NCT.
§Controls were considered appropriate if the following criteria were met: (1) age-matched and gender-matched, (2) physical activities of comparable intensity but without body contact, that is, swimming, running or cycling, (3) no additional (recreational) exposure to football or other contact sports.
¶This includes football players and control participants.
**Two-sample t-tests using the Bonferroni correction for multiple testing.
††OR for high-quality heading assessment (prospective recorded or combined prospective and retrospective approach) versus low-quality heading assessment (self-reported heading rates or calculation of heading-exposure-risk based on player's position).
‡‡OR between studies with or without significant differences in NCT comparing younger (youth, high school, college, interscholastic) and more elderly (university, amateur, professional, former professional) football players.
NCT, neurocognitive testing; NR, not reported; OR, OR including 95% CIs.

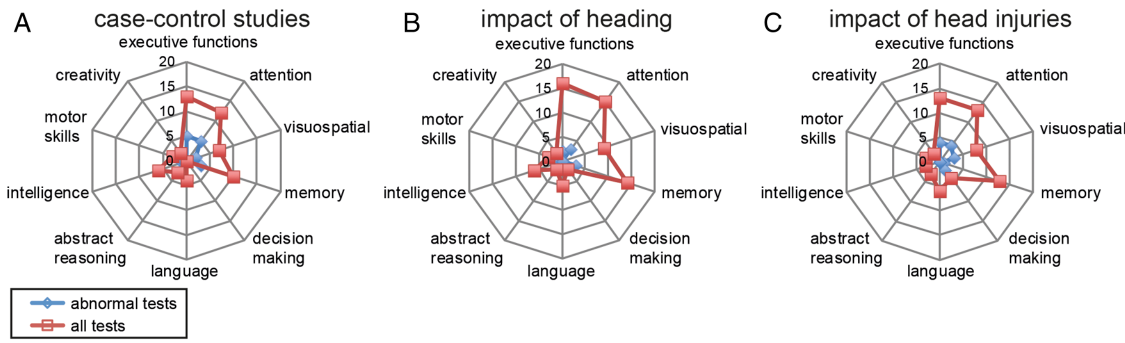

Figure 2 Spider plots illustrating in how many studies the different neurocognitive categories were evaluated (in red) and how often an abnormal test result was retrieved in this category (in blue). The number of studies is provided along the intersection of the web. Separate plots are provided for all case–control studies (A), for all studies investigating the impact of heading on neurocognitive tests (B) and for all studies reporting on the impact of head injuries on cognition (C). Irrespective of the study categorisation, attention, executive functions, memory and visuospatial functions were the cognitive domains most frequently tested and also most frequently impaired.

Table 4 Distribution of neurocognitive testing categories (in alphabetical order) and percentage of abnormal tests*

	Case–control studies (n=14)		Studies reporting on heading frequency (n=17)		Studies reporting on the number of head injuries (n=13)	
	Studies with sign. effect/all studies reporting (%)	Studies with sign. effect/all studies reporting abnormal NCT in at least one category (n=8) (%)	Studies with sign. effect/all studies reporting (%)	Studies with sign. effect/all studies reporting abnormal NCT in at least one category (n=6) (%)	All studies with sign. effect/all studies reporting (%)	Studies with sign. effect/all studies reporting abnormal NCT in at least one category (n=7) (%)
Abstract reasoning	0/3 (0)	0/2 (0)	0/2 (0)	0/2 (0)	0/3 (0)	0/3 (0)
Attention	5/12 (42)	**5/7 (71)**	3/15 (20)	**3/6 (50)**	4/13 (31)	**4/7 (57)**
Creativity	0/2 (0)	0/0 (0)	0/2 (0)	0/0 (0)	0/2 (0)	0/1 (0)
Decision-making	0/0 (0)	0/0 (0)	0/3 (0)	0/1 (0)	**2/4 (50)**	**2/2 (100)**
Executive functions	5/13 (38)	**5/8 (63)**	2/16 (13)	2/6 (33)	4/13 (31)	**4/7 (57)**
Intelligence	1/6 (17)	1/3 (33)	1/6 (17)	**1/2 (50)**	0/3 (0)	0/2 (0)
Language	0/4 (0)	0/3 (0)	0/6 (0)	0/2 (0)	0/6 (0)	0/4 (0)
Memory	3/10 (39)	**3/5 (60)**	3/14 (21)	**3/5 (60)**	1/13 (8)	1/7 (14)
Motor skills	1/3 (33)	1/3 (33)	1/3 (33)	1/3 (33)	0/3 (0)	0/3 (0)
Visuospatial functions	2/7 (29)	2/5 (40)	0/9 (0)	0/4 (0)	3/8 (38)	**3/5 (60)**

*Studies may have provided data both for neurocognition in football in general and specifically related to heading frequency and/or number of head injuries. Categories with ≥50% of studies with abnormal NCT results are in bold.
NCT, neurocognitive testing; sign, significant.

performance on 1 of 6 tests (Rey-Osterrieth complex-figure long-delay recall),[37] Glutathion levels were linked to inferior results in 1 of 4 tests (trail making test B)[51] and lower levels of fractional anisotropy in parieto-occipital areas were associated with 1 of 6 tests (poorer memory).[17] In the only prospective study, neither changes in neurocognitive performance nor in conventional MRI could be depicted over an observation period of 5 years.[38]

A link between heading exposure and structural/metabolic neuroimaging changes was investigated in five studies.[17 37 44 51 54] Lifetime estimates of heading numbers were inversely correlated with cortical thickness in the right parietal/occipital lobes[37] and with myoinositol and glutathione levels.[51] Fractional anisotropy levels in temporoparietal white matter were inversely correlated with the annual number of headings.[17] A high cumulative head acceleration exposure was linked to more profound reductions in cerebrovascular reactivity, outlasting the end of the season by 4–5 months before returning to baseline by month 8.[54] No correlation between career heading exposure and abnormalities on conventional MRI were reported in another study.[44] The potential impact of remote head injuries on brain structure was examined in two studies, both demonstrating no association.[17 44]

EEG studies

Two studies used EEG in active (n=69)[55] and former (n=37)[56] professional male players. In both studies, standard EEG recordings were examined by a clinical neurophysiologist and EEGs were classified as 'normal', 'slightly abnormal' or 'abnormal' based on background activity and α-activity. EEG ratings in the players were compared with those in age-matched men of 'various occupations'. With information on matched physical activities lacking in the controls, their quality was rated 'inappropriate'. The rate of EEGs considered normal was lower in active and former players compared with controls. Among the active players, all abnormal EEGs were observed in players who considered themselves as non-headers.[55] Among former players, there were no EEG differences between headers and non-headers.[56]

Postural stability

One study (n=15) reported on balance, using the balance error scoring system.[37] This study described no significant differences between players and controls.

Table 5 Persistent effects of football on the brain: neuroimaging studies (n=8)

	Effect confirmed (n (%))	No effect (n (%))	All (n (%))
Studies (n)	6 (75.0)	2 (25.0)	8 (100.0)
Selection of controls (number of studies/number of participants (%))*			
Appropriate	4/52 (83.9)	2/37 (100.0)	6/89 (89.9)
Inappropriate/unclear	1/10 (16.1)	0/0 (0.0)	1/10 (10.1)
NA	1/NA	0/NA	1/NA
Total	6/62 (100.0)	2/37 (100.0)	8/99 (100.0)
Gender football players (number of participants (%))			
Females	22 (22.2)	0 (0.0)	22 (15.4)
Males	77 (77.8)	44 (100.0)	121 (84.6)
Total	99 (100.0)	44 (100.0)	143 (100.0)
Gender controls (number of participants (%))			
Females	12 (19.4)	0 (0.0)	12 (12.1)
Males	50 (80.6)	37 (100.0)	87 (87.9)
Total	62 (100.0)	37 (100.0)	99 (100.0)
Sample size (mean±1SD)			
Football players	16.5±10.2	22.0±2.8	17.9±14.1
Controls	12.4±2.1	18.5±2.1	14.1±3.5
Type of imaging (number of studies/number of football players (%))			
Conventional MRI	0/0 (0.0)	2/44 (100.0)[38 44]	2/44 (30.8)
Diffusion tensor imaging (DTI)	2/49 (49.5)[17 50]	0/0 (0.0)	2/49 (34.3)
Voxel-based MR morphometry (VBM)	2/25 (25.3)[37 48]	0/0 (0.0)	2/25 (17.5)
MR spectroscopy (MRS)	1/11 (11.1)[51]	0/0 (0.0)	1/11 (7.7)
Functional MRI (fMRI)	1/14 (14.1)[54]	0/0 (0.0)	1/14 (9.8)
Total	6/99 (100.0)	2/44 (100.0)	8/143 (100.0)
Level of play (number of studies/number of football players (%))			
Youth	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
High school/college	2/24 (24.2)	0/0 (0.0)	2/24 (16.8)
University	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Amateur	1/37 (37.4)	0/0 (0.0)	1/37 (25.9)
Professional	1/12 (12.1)	2/44 (100.0)	3/56 (39.2)
Former professional	2/26 (26.3)	0/0 (0.0)	2/26 (18.2)
Total	6/99 (100.0)	2/44 (100.0)	8/143 (100.0)
Correlating neuroimaging with NCT (number of studies)			
Structural and NCT changes correlate	3[17 37 51]	1[38]	4
No correlation	0	0	0
NA	3[48 50 54]	1[44]	4
Correlating neuroimaging with heading frequency (number of studies)			
Changes on neuroimaging and heading frequency correlate	4[17 37 45 51]	0	4
No correlation	0	1[44]	1
NA	2[48 50]	1[38]	3
Correlating neuroimaging with the number of head injuries (number of studies)			
Changes on neuroimaging and number of head injuries correlate	0	0	0
No correlation	1[17]	1[44]	2
NA	5[37 45 48 50 51]	0	5

*Controls were considered appropriate if the following criteria were met: (1) age-matched and gender-matched, (2) physical activities of comparable intensity but without body contact, that is, swimming, running or cycling, (3) no additional (recreational) exposure to football or other contact sports.
NCT, neurocognitive testing; NA, not available.

DISCUSSION

With the recently issued ban for heading in child-football players in the USA,[26] the ongoing debate about potential persistent effects of football and football-related (subconcussive) trauma on brain function received increased attention and caused uncertainty among football players, medical staff and media. Given the worldwide popularity of football,[62] football-related health issues may have far-reaching implications that have to be balanced and compared with benefits due to regular activity. This emphasises the need to intensify hypothesis-driven research and the study of associations between football play and persistent structural/functional changes of the brain.

Under-representation of female players

For most aspects evaluated, female players were in a minority, consistent with reportedly lower numbers of active female football players.[62] While no conclusions could be drawn on football-related changes in neuroimaging and EEG, women were under-represented in studies that reported neurocognitive impairment compared with those not observing such deficits. This observation was unexpected since the rate of football-related head injuries was reportedly higher in women.[63–66] Of note, none of the studies reported on (former) professional female players. Also, for studies reporting on neurocognitive testing, female players were over-represented in lower levels of play (youth, high school/college) compared with higher levels (university, amateur, (former) professional) (OR=28.57 (19.25 to 42.41)). These observations suggest that cumulative exposure to football play or cumulative intensity has been lower in female players, not reaching levels that may be necessary to result in brain abnormalities. Future studies should pay special attention on functional/structural brain changes in female players with more extensive football exposure.

Neurocognitive testing in (former) football players

Applied in 77% of studies, neurocognitive testing remains the most common approach to investigate potential associations between football play and changes in brain function. Most studies dealt with effects of heading (74%) and head injuries (57%). Over 60 different neurocognitive tests were used, most of them only in few studies. With all three key domains (attention, executive function and memory) assessed by 78% of studies, risk for false-negative results due to inappropriate selection of neurocognitive test domains seems low. Even for the most frequently used tests in those domains considered most important in patients with (sub)concussive brain injury (see online supplementary file 4), the fraction of abnormal test results was low (0.29±0.18). This suggests that reported neurocognitive impairments were rather subtle and their detection may have depended on study-specific parameters as age, gender, level of play and selection of controls. Also, among all tests administered in a given study, those with abnormal outcome were infrequent (fraction=0.21±0.27). In 19 of 23 studies, more than one neurocognitive test was applied to evaluate a single category (eg, TMT-B and Stroop for executive functions). Noteworthy, in 42% of these studies, discrepant test results in a given category were noted. This affected 37% (17/46) of all categories in studies that received multiple testing. These results suggest that changes are subtle and may get identified only by some tests. Moreover, these inconsistencies underline the importance of standardised neurocognitive testing in football.

Persistent neurocognitive changes in (former) players compared with controls

Fifty-seven per cent of case–control studies reported persistent associations between football and neurocognitive impairment focusing on attention, executive function and memory. These categories are primarily mediated by the frontal and temporal lobes and are typically involved in mTBI.[67] Based on the quality assessment performed, several confounders must be considered to put the significance of these observations in context. Probably of the most far-reaching implication is the finding that the rate of appropriate control for type 1 errors was smaller among studies with abnormal test results (OR=17.35 (10.61 to 28.36)). These studies thus bear an increased risk for false-positive test results. Choosing the right controls is essential. Including control participants without matching the profile of physical activity might point to global effects of physical activity rather than to football-related changes.[14] While in our review, controls were judged as 'appropriate' in 67% of case–control studies, the odds for inappropriate controls were higher for studies reporting neurocognitive deficits (OR=1.72 (1.22 to 2.43)). This indicates that inappropriate selection of control participants may represent a serious source of bias. As a consequence, caution is warranted when interpreting impairment in neurocognitive testing based on the existing literature. Noteworthy, with the fraction of younger players being larger in studies with negative findings than in those with significant deficits, this might suggest that the exposure duration was simply not long or intense enough to cause a significant effect, further limiting conclusions.

No clear evidence for heading-related persistent impairment of neurocognitive function

Six of 17 studies that correlated heading frequency with neurocognitive deficits reported a link (mostly for attention, executive functions and memory), but these studies also contained more methodological limitations than those reporting no link. Most importantly, the assessment quality of heading frequency was lower in studies with positive findings (OR=14.2 (9.0 to 22.4)). Self-reported heading frequencies tend to be higher than those obtained by more reliable approaches,[68] indicating potential risk of reporting bias. This emphasises the need for prospective observer-based assessments of heading frequency in future studies. Furthermore, studies so far remained incomplete in providing an accurate estimate of heading exposure, since heading during practice sessions was not considered and other variables such as heading technique and ball properties and ball velocity were not available. Studies focusing on former players with heading exposure decades ago[45 56 57] may also be biased by differences in the properties of the ball—heavy leather balls, in common use until the mid-1970s and even heavier on wet undergrounds, should not be compared with the more lightweight balls used thereafter.

The ratio of more senior to more junior players was higher in studies reporting significant impact of heading than in those with negative findings (OR=2.15 (1.63 to 2.85)). For more senior players, the lifetime heading number is higher and the duration of exposure is longer. Current studies therefore cannot exclude that in more senior players, neurocognitive deficits may eventually arise due to a decreased cerebral reserve capacity in view of accumulated (sub)clinical head trauma.[14 69] Of note, in retired professional UK-football players, no signs for accelerated cognitive decline were found.[34] Furthermore, female players were under-represented in studies that noted a link between heading frequency and neurocognitive impairments. A lower heading frequency in female players[18] and the skewed distribution of female players towards lower levels of play may explain this seemingly 'protective effect' of female gender on heading related neurocognitive impairments.

Based on our review, no firm conclusions on an association between heading frequency and accelerated neurocognitive decline can be drawn. Methodological limitations identified more often in studies with positive findings emphasise caution in linking heading to persistent neurocognitive deficits. This extends conclusions of a previous review on acute and persistent effects of concussions and heading in football.[70] Whether or not significant differences in neurocognition arise with increasing heading exposure awaits further clarification, especially in former professional players with extensive exposure and better control for head injury.

Repetitive concussions may be linked to persistent cognitive impairment

A negative impact of (repetitive) head injuries to brain function has been reported for other contact sports as American football,[71 72] rugby[52] or boxing.[73–75] For football (soccer) play, Barnes *et al*[76] estimated a 50% risk that a professional male player will suffer a concussion within a 10-year period, while the corresponding figure for female players was 22%. Neuropathological changes associated with mTBI are axonal injuries with a focus on the orbitofrontal and temporal polar zones.[67] Cognitive functions affected most are delayed memory, executive functions, language and attention.[77 78] Based on our review, 54% of studies addressing the influence of head injuries on neurocognitive test performance found a link in one or more categories. Seventy-one per cent of studies with positive findings restricted their analysis to football-related concussions, which indicates a low risk that football-unrelated concussions biased the results. Furthermore, the rate of studies with inappropriate control of type 1 errors was even lower among studies with positive findings compared with those with negative findings.

Distinguishing between effects secondary to heading and head trauma,[11 32] however, may be difficult or even impossible for several reasons: first, up to 50% of concussions are not reported by players or team physicians.[63 79 80] Second, 89% of studies controlled only for recent (3–6 months) head trauma or did not take head trauma into account at all. Most studies relied on self-reporting of head injuries, introducing risk of recall bias. Even more importantly, lack of control for head injuries bears the risk that effects of heading and head trauma are mixed as players with higher heading frequencies tend to experience head injuries more frequently.[14 19 32] Third, definitions for football-related head injuries have been applied differently,[52] potentially resulting in inconsistencies between studies. Assuming that effects of heading and head injury may have been intermingled, one would expect overestimating the link between heading frequency and neurocognitive deficits. In fact, the opposite was true; refuting the assumption that head-injury-related effects have significantly biased results in the assessment of heading-related persistent effects. In summary, the link between head injuries and persistent neurocognitive impairment was moderate only and its impact may have been overestimated due to several methodological shortcomings.

Structural and metabolic changes on neuroimaging

Neuroimaging in football players was driven by the hypothesis that repetitive subconcussive head trauma result in structural/metabolic changes similar to those known from mTBI.[81 82] Along with the anterior–posterior gradient in brain vulnerability,[83] anterior regions may also be linked to executive and neurocognitive deficits in mTBI.[84]

With a limited number of study participants (n=143) and studies (n=8), different neuroimaging modalities and levels of play, all but two studies reported significant brain changes in football players. These changes were localised preferentially to frontal and anterior–temporal regions.[45 48 50 51 54] Structural abnormalities located in parieto-occipital areas,[17 37] that is, in areas opposite to the presumed point of heading impact, may be explained in analogy to the principle of contre-coup injury.[17]

In 3 studies with 63 players, changes depicted on neuroimaging could be linked to subclinical neurocognitive deficits, suggesting that these changes may be functionally relevant.[17 37 51] While these studies used advanced neuroimaging, no changes could be observed on conventional MRI in the only prospective study (5-year observation period). Whereas there is extensive experience in the interpretation of standard MR sequences, changes in advanced imaging as DTI, VBM and MR spectroscopy are much more difficult to put into clinical context due to their relatively recent use.

A correlation between heading exposure and persistent changes on neuroimaging was observed in four out of five studies,[17 37 44 51 54] albeit reversible within 8 months after season end in the only prospective study.[54] While these findings suggest a possible link between heading frequency and neurodegeneration, the heading exposure assessment was low quality in four out of five studies, posing them at increased risk for recall bias. Correction for multiple statistical testing was reported by Svaldi *et al*[54] and in one study by Koerte *et al*,[37] but not in another,[51] indicating possible increased risk of false-positive correlations. In the study by Lipton *et al*,[17] a link was observed only for players with more than 885–1500 headings per year, suggesting that heading below this threshold may be safe. Overall, taking the methodological limitations and the small sample sizes into consideration, support for a link between heading frequency and persistent structural brain changes seems weak. Our review did not find any evidence for an association between (repetitive) concussions and structural brain changes on neuroimaging, albeit small sample sizes limit conclusions.[17 44]

Low quality of EEG-based studies

Both studies included reported higher incidences of EEG abnormalities in male professional players than in controls.[55 56] With only 106 players analysed, conclusions on persistent effects of football on EEG can be considered preliminary only. Caution is warranted as significant limitations were identified: control groups were rated 'inappropriate' and the authors did not control for remote head injury. The clinical implications of the higher incidence of EEG abnormalities remain unclear, especially since no information on the location of EEG abnormalities was provided. Both studies did not provide any evidence for a link between heading and EEG changes as in the group of active football players, all abnormal EEGs were observed in players who considered themselves as non-headers.[55] In the group of former players, no EEG differences were detected comparing headers and non-headers.[56] Nonetheless, the authors concluded that the reason for the EEG abnormalities was most likely repeated minor head trauma. Considering the limitations listed above, evidence in support of this conclusion is unconvincing.

Limitations

Studies varied in the criteria for reporting previous concussions and we were lacking details to validate the ratings. Self-reporting was standard in most studies, posing them at high risk for recall bias. Therefore, the impact of previous concussions on brain structure/function may have been overestimated or underestimated in our review. The impact of heading depends on many parameters. However, only scarce information about player's position, circumstances of heading (purposeful, passively hit) and heading skills could be retrieved. This limits the assessment of a possible association between heading and structural/functional brain changes. Lack of systematically controlling for timing and time lags between exposure and testing potentially weakens reported associations. Likewise, failure to assess and/or correct for potential confounders as concussions unrelated to football, different physical activity profiles, medical conditions (hypertension, overweight, diabetes) and lifestyle (eg, alcohol consumption, smoking) may have biased associations between (former) football play and structural/functional brain changes.

A pooled analysis of individual study data (ie, a meta-analysis) was not possible due to the heterogeneity in study design, data collection and data analysis. This may have resulted in the incorrect detection or blinding of high-quality studies due to a higher number of low-quality studies.

We did not identify any studies that compared the diagnostic accuracy of different neurocognitive testing procedures that assessed the same neurocognitive domains. Moreover, single studies obtaining more than one neurocognitive test for a specific domain often demonstrated discrepancies. This limits any recommendation on specific neurocognitive tests and emphasises the need for prospective, controlled studies comparing the diagnostic accuracy of neurocognitive tests.

CONCLUSIONS

There is weak to non-existent evidence from the medical literature for football-related persistent functional and structural brain deficits and a putative role of (repetitive) head trauma in the development of neurocognitive impairment. Comparison of included studies was limited by various methodological shortcomings. Case–control studies reporting neurocognitive deficits in football players significantly more often included inappropriate controls and control of type 1 errors than studies reporting no deficits. Furthermore, no clear link between heading frequency and neurocognitive deficits could be established and low-quality assessment of heading frequency was identified as the major confounder. Of special interest were studies that combined different modalities: while in four out of five neuroimaging studies, structural and metabolic deficits could be correlated with heading exposure, the clinical and preventive implications of these findings remain inconclusive, as most studies used a low-quality assessment of heading frequency. In three out of four small case–control studies, a link between neuroimaging abnormalities and subclinical neurocognitive deficits could be established, suggesting that these morphological and metabolic changes might be functionally relevant.

Further studies combining functional and structural modalities in larger numbers of football players with long-lasting football exposure appear most promising to shed more light on a potential link between football play and brain structure/function. Such studies should include neurocognitive testing of attention, executive functions and memory as well of objective tests of cervical, vestibular and ocular motor function. They should also be prospective to appropriately control for confounders as history of head injuries, heading frequency and medical conditions. Further validation and head-to-head comparison is required to provide the basis of more standardised testing batteries to improve the quality of studies and to allow for better comparability between studies. A longitudinal and cross-sectional study design will help to determine whether identified subclinical structural and functional abnormalities eventually progress to clinically relevant, symptomatic deficits or rather resolve again, especially after finishing exposure to football play.

What is already known?

- Repetitive head injuries and heading the ball were suggested to be linked to persistent neurocognitive impairments and structural brain abnormalities in advanced neuroimaging in professional and amateur football players.
- However, there is ongoing controversy to what extent these findings are real or rather result from methodological limitations.
- A systematic assessment of existing studies using prospectively defined criteria is therefore needed to improve our understanding of persistent effects of football on the brain and to better estimate the role of methodological limitations in previous studies.

What are the findings?

- While the majority of studies, addressing the effect of football play and football-related injuries on neurocognitive functions, reported significant impairment in at least one domain, methodological shortcomings were found to be more frequent in studies with reportedly significant findings.
- Evidence for a correlation between heading frequency and neurocognitive deficits was weak and likely biased by inaccurate heading frequency estimates.
- Although the rate of football-related head injuries was reportedly higher in women than men, women were under-represented in studies that reported neurocognitive impairment compared with those studies that did not identify deficits, which may be related to the fact that none of these studies included (retired) female professional football players.
- Combining neuroimaging and neurocognitive testing in prospective longitudinal and cross-sectional studies in male and female players to link structural and functional deficits seems most promising to further clarify associations between football play and brain abnormalities.

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Persistent effects of playing football and associated (subconcussive) head trauma on brain structure and function: a systematic review of the literature

A A Tarnutzer, D Straumann, P Brugger and N Feddermann-Demont

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