

BMJ Open Cerebral and cognitive modifications in retired professional soccer players: TC-FOOT protocol, a transverse analytical study

Sabrina Kepka ^{1,2}, François Lersy,³ Julien Godet,^{2,4} Frederic Blanc,^{2,5} Mathias Bilger,⁶ Anne Botzung,⁵ Catherine Kleitz,⁶ Jeanne Merignac,⁵ Emmanuel Ohrant,⁷ Franck Garnier,^{8,9} François Pietra,¹⁰ Vincent Noblet,² Caroline Deck,² Remy Willinger,² Stéphane Kremer^{2,3}

To cite: Kepka S, Lersy F, Godet J, *et al.* Cerebral and cognitive modifications in retired professional soccer players: TC-FOOT protocol, a transverse analytical study. *BMJ Open* 2022;**12**:e060459. doi:10.1136/bmjopen-2021-060459

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-060459>).

Received 21 December 2021
Accepted 20 October 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Sabrina Kepka;
sabrinakepka@yahoo.fr

ABSTRACT

Introduction Soccer is the most popular sport in the world. This contact sport carries the risk of exposure to repeated head impacts in the form of subconcussions, defined as minimal brain injuries following head impact, with no symptom of concussion. While it has been suggested that exposure to repetitive subconcussive events can result in long-term neurophysiological modifications, and the later development of chronic traumatic encephalopathy, the consequences of these repeated impacts remain controversial and largely unexplored in the context of soccer players.

Methods and analysis This is a prospective, single-centre, exposure/non-exposure, transverse study assessing the MRI and neuropsychological abnormalities in professional retired soccer players exposed to subconcussive impacts, compared with high-level athletes not exposed to head impacts. The primary outcome corresponds to the results of MRI by advanced MRI techniques (diffusion tensor, cerebral perfusion, functional MRI, cerebral volumetry and cortical thickness, spectroscopy, susceptibility imaging). Secondary outcomes are the results of the neuropsychological tests: number of errors and time to complete tests. We hypothesise that repeated subconcussive impacts could lead to morphological lesions and impact on soccer players' cognitive skills in the long term.

Ethics and dissemination Ethics approval has been obtained and the study was approved by the Comité de Protection des Personnes (CPP) No 2021-A01169-32. Study findings will be disseminated by publication in a high-impact international journal. Results will be presented at national and international imaging meetings.

Trial registration number NCT04903015.

INTRODUCTION

Soccer, one of the most popular sports in the world, exposes the player to cerebral concussions, or mild traumatic brain injuries, which represent 5.8%–22% of all soccer-related injuries.¹ An expert working group from the French Ministry of Sports has defined

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ To the best of our knowledge, this is the first prospective study to evaluate both the cerebral and cognitive modifications following repetitive subconcussive impacts in male professional soccer players at the end of their careers, or in retirement, a population which is understudied in the literature.
- ⇒ The major strength of this study is its combinatorial approach: the abnormalities will be evaluated by a combination of advanced MRI techniques (brain volumetry and cortical thickness, diffusion tensor, magnetic susceptibility, spectroscopy, functional MRI and cerebral perfusion), using specific modalities of analysis, by a team specialised in the biomechanics of head injury.
- ⇒ The neuropsychological workup will be based on validated tests in the field of head injuries, with a proven sensitivity for assessing those functions known to be frequently impaired by repetitive subconcussive impacts for example, processing speed, working memory, sustained attention and executive functions, and episodic memory.
- ⇒ Although the single-centre study design may be seen as a limitation, players in different soccer teams from different towns will be recruited, in order to represent a large panel of soccer players with intensive practice, while ensuring a similar imaging protocol for all participants.
- ⇒ This study is limited in its generalisability to both sexes, as only male soccer players are considered.

concussion as a brain injury caused by a direct or indirect transmission of kinetic energy to the head, resulting in an immediate and transient dysfunction of the brain.² It is characterised by at least one of the following features: loss of consciousness, loss of memory, altered mental status, and neurological signs and symptoms, which cannot be explained by another cause.² The consensus statement from the Concussion in Sport Group defined

sport-related concussion as a traumatic brain injury induced by biomechanical forces caused by a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head, resulting in the rapid onset of short-lived impairment of neurological function that resolves spontaneously, a range of clinical signs that may or may not involve loss of consciousness and cannot be explained by drug, alcohol or medication use, other injuries or other comorbidities.³

Subconcussion is a cranial impact that does not result in known or diagnosed concussion on clinical grounds.⁴ It can occur with rapid acceleration-deceleration of the body, notably when the brain is free to move within the cranium creating a 'slosh' phenomenon.⁵ While concussions are associated with neurological impairment,⁶ the consequences of subconcussion remain unclear, notably for professional soccer players.⁷ Soccer headings is a skill specific to soccer, with an average of 6–12 headings occurring per game per player, exposing soccer player to repetitive subconcussions.⁸ Repetitive exposure to subconcussion could increase its effect with accruing sufficient anatomical and/or physiological damage, explaining that these injuries are potentially expressed later in life.⁴ Indeed, it has been suggested that subconcussive impacts could increase the risk of traumatic chronic encephalopathy, a neurodegenerative disease affecting subjects who have undergone head impacts over a number of years.⁹ Clinically, subjects have memory impairment, cognitive impairment, anxiety and depressive symptoms, and psychiatric problems.¹⁰ The diagnosis is confirmed on anatomopathological examination of brain tissue, by the presence of phosphorylated tau protein deposits distributed throughout the brain, with a tendency to occur in clusters at the sulcal depths of the cortex.^{9 11–13} However, it is currently impossible to confirm the diagnosis in vivo. The link between traumatic chronic encephalopathy and repetitive subconcussive impact remains controversial as other studies have not corroborated that subconcussive impacts can be responsible for MRI abnormalities and cognitive impairments.

Conventional imaging techniques such as CT or MRI only show morphological cerebral abnormalities (intracerebral or pericerebral haemorrhages, diffuse axonal lesions) in cases of severe head injury. These morphological techniques do not usually identify an abnormality in cases of mild concussion, even when repetitive. On the other hand, advanced MRI techniques (brain volumetry and cortical thickness, diffusion tensor, magnetic susceptibility, spectroscopy, functional MRI (fMRI) and cerebral perfusion) have made it possible to detect subtle brain abnormalities in athletes or former athletes exposed to repetitive subconcussive impacts, including in the absence of proven concussion.^{14–17} Several of the aforementioned techniques have demonstrated a loss of both white and grey matter in athletes who are subjected to repeated subconcussive impacts.^{15 18 19} According to magnetic susceptibility studies, the loss of substance can be associated with haemorrhagic lesions and

inflammation.²⁰ Moreover, a study using fMRI techniques revealed a prolonged alteration in resting state functional connectivity in American football players over the course of a football season.¹⁴ This suggests that repetitive impacts could have a cumulative effect on modifications to functional connectivity in the brain networks of athletes. In former American football players, fMRI has also demonstrated a cerebral reorganisation during memory tasks, including hyperactivation in compensatory zones. It is suspected that these abnormalities are related to later development of chronic traumatic encephalopathy.^{12 17 21}

In American football players, the number of years of practice and the degree of exposure to physical impacts linked to the player's position has been shown to increase the risk of developing traumatic chronic encephalopathy.²² In soccer players, a recent systematic review revealed a higher risk of mortality from motor neuron disease than in the general population.²³ However, previous research revealed that head impacts in soccer had no effect on blood-based biomarkers for structural brain damage, such as serum neurofilament light or tau.²⁴ A limited number of studies have carried out cognitive assessments of soccer players, and have reported contradictory results.^{7 25 26} While the study of Matser *et al* suggested that soccer may adversely affect some aspects of cognitive functioning,²⁶ no association was found between exposure and cognitive performance in a recent cross-sectional study specifically evaluating the effects of soccer heading,⁷ in agreement with the results of Straume-Naesheim *et al*.²⁵ However, this study did not have a follow-up period, and soccer players were relatively young (average age of 24.6±4.5 years), meaning that any cumulative effects of heading across a player's career. Indeed, a systematic review has highlighted the lack of studies evaluating the long-term effect of heading on cognitive performance.²⁷ A further study assessing the effect of soccer heading on diffusion tensor images and cognitive function found no significant difference in terms of microstructural features and cognitive performance between non-athlete participants unexposed to heading and amateur soccer players with high exposure.²⁸ However, the players enrolled in this study were, again, of relatively young age (25.5±7.2), which could limit its long-term relevance. Moreover, to date, none of these studies have employed all neuroimaging modalities in a complementary fashion. A recent systematic review by Snowden *et al* determined that there is not enough evidence to conclude on the effects of subconcussion in soccer players, and that further studies are required to better evaluate the impact of repetitive subconcussive injuries.²⁹

Objectives

The objective of this study is therefore to evaluate, using advanced MRI techniques, the potential microstructural abnormalities and the cognitive impairment in professional soccer players at the end of their careers who have experienced repetitive subconcussive impacts. The primary objective is to identify cerebral abnormalities

observed by MRI in professional soccer players exposed to repeated subconcussive impacts, and to compare these results to those of high-level athletes who are not exposed to head impacts. The secondary objectives are to compare the cognitive performances in a group of professional soccer player exposed to repeated subconcussive impacts with non-exposed high-level athletes and to evaluate the relationship between the microstructural anomalies demonstrated by MRI and cognitive impairment.

METHODS AND ANALYSIS

Study design and setting

This is a monocentric, transversal, exposure/non-exposure study assessing the relationship between exposure to repetitive subconcussive impacts during professional soccer play and the presence of cerebral and cognitive abnormalities. This study will take place at Strasbourg University Hospital, Strasbourg, France, a public university hospital, over a study period of 24 months, with a study start date of 7 January 2022 and will end on 8 January 2024.

Patient and public involvement

Patients were not involved in the conception of this study.

Eligibility criteria

Two groups of participants will be established: a group of professional soccer players exposed to repetitive subconcussive impacts and a control group of non-exposed high-level athletes.

Inclusion criteria common to both groups are as follows: (1) male and (2) aged 32–55 years old.

Inclusion criteria specific to the exposed group are as follows: (1) professional soccer players at the end of their career; (2) playing in clubs in the French ligue 1 and ligue 2; (3) exposed to repetitive subconcussive impact and (4) no history of severe head injury or cerebral lesion.

Inclusion criteria specific to the control group are as follows: (1) high-level athletes who have never regularly played a sport exposing them to repetitive subconcussive impact and who have no history of head injury (eg, rugby, basketball, handball, American football, hockey, combat sports). Professional tennis players or former players will be preferentially recruited.

Non-inclusion criteria common to both groups are as follows: (1) refusal to participate in the study; (2) refusal to be informed of abnormalities on MRI; (3) incapacity to give informed consent or under a legal protection order and (4) history of sport related concussion defined as a traumatic brain injury induced by biomechanical forces caused by a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head, resulting in the rapid onset of short-lived impairment of neurological function that resolves spontaneously, with a range of clinical signs and symptoms that may or may not involve loss of consciousness and cannot be explained by drug, alcohol or medication use, other

injuries or other comorbidities; (5) history of severe brain/head injury; (6) history of neurological or psychiatric disorder according to the patient's declaration; (7) known cerebral abnormality diagnosed by an imaging exam (CT or MRI); (8) history of regular or occasional drug use: active smoker or non-smoker for less than 1 year, excessive consumption of alcohol (>20 g alcohol per day, evaluated with the following formula: $[8 \times \text{percentage of alcohol} \times \text{volume (cL)}] / 100$), whether current or in the past; (9) use of medication targeting the central nervous system in the 2 weeks preceding inclusion in the study; (10) prior history of severe hypertension, diabetes, chronic heart disease, progressive or disabling disease and (11) contraindication to MRI (claustrophobia, implanted material not compatible with MRI, refusal to be informed of any abnormalities discovered by MRI).

If a psychiatric disorder is suspected at the time of assessment, the participant will be automatically excluded.

Recruitment

The group of professional soccer players at the end of their careers will be recruited from clubs playing in French ligue 1 and ligue 2, with the assistance of club physicians, under the supervision of the medical director of the French Federation of Soccer (FFF). The control group of high-level athletes not exposed to head injuries will be recruited via the Medical Sport Center of Strasbourg located in Strasbourg, France, which is a referent centre for the care of high-level athletes, and by the regional delegations of the French federations of various sports (tennis, athletics, swimming). Information leaflets will be displayed within the centre and on club premises. Recruitment will take place during the entire 24-month period of the study.

Participant timeline and follow-up

An initial information visit will take place by phone call, to verify that the subject meets the eligibility criteria. Approximately 1 week after this information visit, a second visit will take place at the Radiology department of Strasbourg University Hospital. During this visit, an investigating physician will collect written informed consent. Following this, the neuropsychological evaluations and MRI tests will be carried out.

A follow-up visit will be organised by an investigating physician, in order to communicate the results of the examinations to participants. The results can fall into three categories: normal workup, fluid-attenuated inversion recovery (FLAIR) sequence MRI abnormality and/or demonstration of cognitive impairment. This visit will be carried out by telephone call in the case of normal results, and by an in-person visit at Strasbourg University Hospital in the case of abnormal results.

Outcomes

The primary outcome of this study is the results of brain MRI in professional soccer players exposed to repeated subconcussive impact potentially related to chronic

traumatic encephalopathy, compared with high-level athletes who are not exposed to head injuries, using advanced MRI techniques, namely: diffusion tensor imaging, cerebral perfusion, fMRI, cerebral volumetry and cortical thickness, MR spectroscopy and susceptibility imaging. The main evaluation criterion corresponds to the quantitative MRI modifications (professional soccer player compared with control group).

Secondary outcomes of this study are the results of the neuropsychological tests:

- ▶ Performance in a targeted battery of neuropsychological tasks as evaluated by the number of errors and time to complete tests.
- ▶ Questioning on recurrent symptoms such as headaches (number of years the subject has experienced headaches, since when, frequency), fatigability, sleep disturbance, dizziness, blurry vision, photophobia/phonophobia.

Data collection, storage and verification

Sociodemographic and clinical data

Sociodemographic and clinical characteristics of patients will be recorded by an investigating physician: age, education level, medical history including cardiovascular risk factors, neurological history, history of COVID-19, type of sport practised and the modalities of practice. For the group of soccer players, the position played will also be recorded.

Neuropsychological assessment

For the neuropsychological assessment, we have decided to employ a series of validated tests, that have shown sensitivity in the field of head injuries, in order to assess the functions frequently impaired by subconcussive impacts, that is, processing speed, working memory, sustained attention and executive functions, and episodic memory. This assessment will last approximately 2 hours, and will be carried out by specialised neuropsychologists, ensuring the quality of the data.

The following tests were chosen:

1. Montreal Cognitive Assessment scale: an overall efficiency assessment test (=10 min).³⁰
2. RL RI 16 items (a French adaptation of the Free and Cued Selective Reminding Test) to assess the functioning of verbal episodic memory (encoding=10 min).³¹
3. Copy of Rey's complex figure assessing visual-constructive abilities and planning (=5 min).³²
4. Auditory-verbal and visuospatial spans to assess short-term working memory (Wechsler scale Memory form III) (=5 min).³³
5. Trail Making test A and B, assessing treatment speed and mental flexibility (= 5 min).³⁴
6. The Brixton test, a spatial anticipation task that also evaluates executive functioning (= 15 min).³⁴
7. RL RI 16 items to assess the functioning of verbal episodic memory (delayed recall at 20 min).³¹
8. Memory reproduction of Rey's complex figure in order to assess episodic visual memory (delayed recall at 20 min).³²
9. Phonological and semantic fluency tests for executive functions (letter P and animals; 2 min per test, 4 min total).³⁴
10. Computerised attention tests will also be used to measure reaction times and executive aspects. Subtests: Phasic Alert, Split Attention and Incompatibility V.2.3.1. This is a computerised battery of tests, using no paper questionnaires (= 15 min).³⁵
11. Social cognition test 'Reading the Mind in the Eyes', to assess ability to read the emotions of others which, in turn, is related to performance in team problem-solving tasks (= 10 min).³⁶

In addition to the aforementioned tests, two further questionnaires will be carried out:

1. A self-administered questionnaire, Behaviour Rating Inventory of Executive Function-Adult Version, evaluating executive functions (<10 min).³⁷
2. Questioning on recurrent symptoms such as headaches (number of years the subject has experienced headaches, since when, frequency), fatigability, sleep disturbance, dizziness, blurry vision, photophobia/phonophobia.

MRI

Acquisition

MRIs will be carried out on 3 Tesla MRI scanners.

The following sequences will be acquired:

1. 3D T1 gradient echo (GRE): anatomy, registration, cerebral, white and grey matter volume, cortical thickness.
2. Multi-echo 3D T2 GRE: quantitative susceptibility mapping (QSM), iron overload quantification.
3. 3D FLAIR.
4. Continuous arterial spin labelling (ASL) 3D: cerebral perfusion.
5. Resting-state fMRI: functional connectivity.
6. 64-direction DTI (b=1000 and 2500): alterations in white matter and its microstructure, anatomic connectivity.
7. Monovoxel spectroscopy of the mesencephalus with short echo time (TE).

Any contraindications will be verified before performing MRI. The patient should preferably be wearing a hospital gown without snaps for safety reasons. The patient's head should be placed so as to acquire DTI and 3D ASL sequences without having to tilt the views in the axis of the petrous bones (angles at 0° and good right/left symmetry of the acquisitions).

The images will be acquired with the examination room door closed. Checks will be carried out prior to image acquisition, to ensure that there is sufficient disc space in the database, and the image quality will be checked during the acquisition. If artefacts are present, the sequences will be repeated after correction.

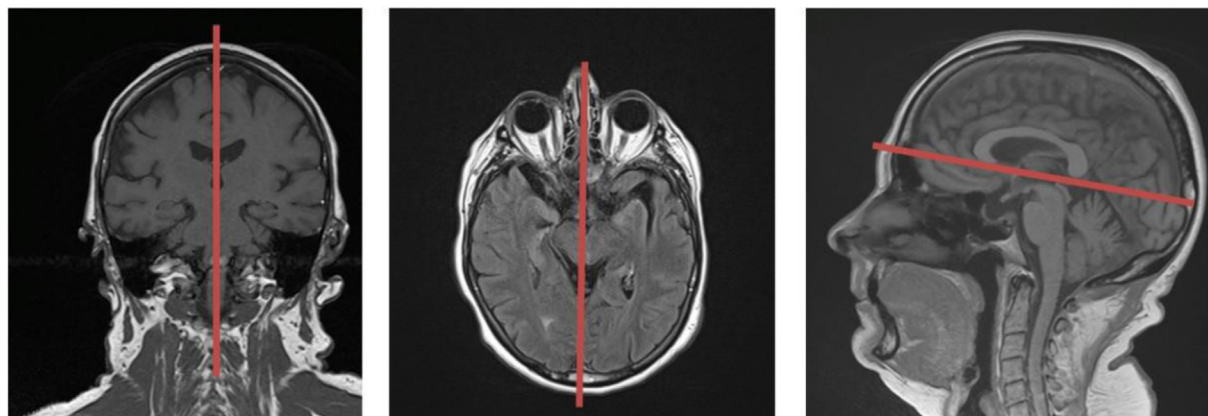


Figure 1 Human brain in the three spatial planes: coronal, horizontal and sagittal sections. From left to right: coronal T1-weighted, axial FLAIR and sagittal T1-weighted images. FLAIR, fluid-attenuated inversion recovery.

The sequences should be oriented respecting the three spatial planes (figure 1).

- ▶ The T1 sagittal sequence should cover the entire encephalon.
- ▶ The 3D T1, 3D FLAIR and the multiecho T2 GRE sequences should cover the entire encephalon.
- ▶ The DTI, fMRI and 3D ASL sequences should be oriented strictly axial (angles at 0°). All of the encephalon should be covered.

The monovoxel spectroscopy should be placed on the brain stem (figure 2). The voxel should be placed on the posterior two-thirds of the brain stem and cover the entire height.

Image processing and analysis

Each of the imaging modalities will be analysed independently, at different levels of analysis: (1) overall analysis conducted on all white matter and all grey matter, (2) regional analysis on a limited number of regions of interest (cerebral anatomic structures, cortical regions) and (3) focal analysis (or voxel based) on the entire brain.

Cerebral atrophy will be studied by analysing the 3D T1 GRE morphological sequences, globally, using the SIENAX method implanted in the FSL library (University of Oxford).³⁸ Regional analysis (volume of anatomic structures and mean cortical thickness of certain cortical

regions) will be carried out using FREESURFER software,³⁹ and focal analysis will be carried out using the Voxel-Based Morphometry approach,⁴⁰ using the implantation available in the Statistical Parametric Mapping software (Wellcome Centre for Human Neuroimaging).

The completeness of the white matter will be investigated by analysing the tensor diffusion MRI sequences, globally and regionally, using segmentations obtained from morphological MRI (see preceding paragraph), and focally using the tract-based spatial statistics method implanted in the FSL library.

Vascular damage will be assessed via the study of global and regional cerebral perfusion in ASL, as well as by regional analysis of microhemorrhages and of iron deposits revealed by the QSM sequences. These analyses will also be carried out using the segmentations obtained from morphological MRI. It should be noted that focal analysis of these modalities cannot be performed given the high level of anisotropy in terms of the spatial resolution of these sequences.

Finally, the impact on cerebral functional connectivity will be investigated via the analysis of resting-state fMRI. Connectivity matrices will be calculated for each individual based on cortical fragmentation obtained from morphological MRI, then compared between the two groups. The connectivity defects within a limited number of key regions (to be defined depending on the results obtained on the analysis of the above-mentioned methods) will also be studied. All of these analyses will be performed with the CONN toolbox.⁴¹

Statistical analysis

Analysis of this unmatched exposure/non-exposure study will include a descriptive analysis of the different variables collected. Neuropsychological results will be compared with normative data by education level and age adapted to the country.

For each continuous variable, we will calculate the statistical distribution parameters (means, medians, quartiles, percentiles of interest, range) as well as the dispersion parameters (SD, variance, IQR, CI of the main values).

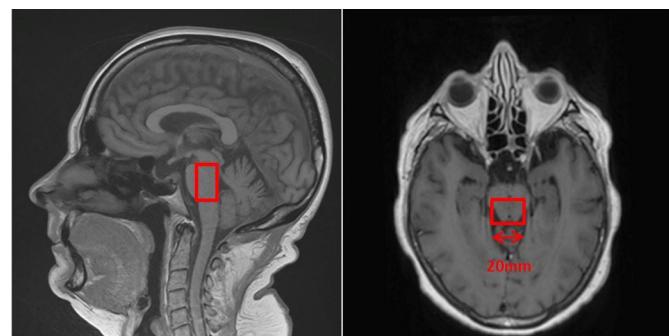


Figure 2 Short echo time monovoxel 1-hour MR spectroscopy of the brainstem. With a width of 20mm, the voxel is placed on the two posterior thirds of the pons and must cover its entire height.

Qualitative variables will be described using the number of members and proportion of each category.

We will then explore whether a relationship exists between the different evaluation criteria and the participants' sociodemographic or clinical variables (age, education level, medical history including cardiovascular risk factors, neurological history, history of COVID-19, type of sport practised and the modalities of practice), so as to identify the presence of any confounding factors that may influence the measurement of the relationship between exposure and the MRI abnormalities.

Generalised linear models will be used to assess differences between the two groups, exposed and unexposed, in terms of the cerebral modifications identified by MRI, as well as to assess the correlations between these imaging results and the neuropsychological test results. Confounding variables identified in univariate analysis (participant age, etc) will be considered as potential adjustment variables. Given the number of subjects in this study, only a limited number of adjustment variables (one or two) will be used, in order to ensure a sufficient power. The estimations of adjusted ORs and their confidence intervals will be calculated using regression models.

The effects of exposure to heading will be estimated on the resulting a posteriori distributions (obtained by Markov chain Monte-Carlo methods). Differences between the two groups will be considered statistically significant if the probability that the difference is positive exceeds 0.95, or if the probability that the OR >1 exceeds 0.95. All analyses will be carried out using R software.

Sample size and power calculations

The sample size was calculated based on the primary outcome, using the proportion of subjects presenting at least one MRI alteration. The size of the sample was calculated within an unmatched case-control study model (one case for one control subject)—setting the type-I error at 5%, power at 80% and assuming that 50% of the exposed cases will present at least one MRI alteration. The calculations were performed with EpiData software. A total of 40 subjects per group (Kesley formula) or 39 subjects (Fleiss formula) will allow us to demonstrate ORs of 4 or higher (or 0.25 or lower) between the two groups.

Missing, unused or invalid data

After data entry and verification, the missing or invalid data will be analysed in order to determine whether there is a non-random distribution or not. After verification that there is no relationship between these data and the judgement criteria, the corresponding subjects will be excluded from the analysis.

Study management

Strasbourg University Hospital is the Sponsor of this study. The study will be overseen by the Department of Clinical Research and Innovation of Strasbourg University Hospital, in collaboration with the team of investigating physicians. A data monitoring committee is not

required for this study, as data collection takes place over the course of a single visit.

DISCUSSION

Cerebral and cognitive impairments due to repetitive subconcussive impacts in soccer remains unknown, as studies provided contradictory results. Indeed, no differences were verified in brain structure on MRI between soccer players and controls in the study of Jordan *et al.*⁴² But, men in the soccer group were young, with a mean age of 24.8 years. Concerning biomarkers of brain injury, if some studies revealed that S-100B serum levels increase after heading,⁴³ other studies found no difference with control group.⁴⁴ Finally, studies evaluating effect on brain function revealed contradictory findings. Some studies revealed that an increasing number of headings and concussions were associated negatively with cognitive functioning^{45 46} whereas other studies found no relationship between either cumulative head injury or cumulative heading and cognitive functioning but were conducted among young soccer players.^{25 47}

To the best of our knowledge, this study will be the first prospective study to evaluate both cerebral and cognitive modifications in professional retired soccer players who have been exposed to subconcussive impacts.

The current study had some limitations. The primary limitation is its monocentric nature. However, players in different soccer teams from different towns will be recruited, in order to represent a large panel of soccer players with intensive practice. Furthermore, it allows pursuing a similar imaging protocol for all participants, to ensure comparability of sequences between the groups, thus increasing the internal validity of the study. Another limitation is the focus on male soccer players, preventing the generalisability of the study to both sexes. Although it has been found that male players are more frequently exposed to heading than female players,²⁴ studies suggest that subconcussion and its consequences are also relevant to female players.⁴⁸ Indeed, female soccer players seem to be at an elevated risk of concussion due to increased ball-to head impact.⁴⁹

However, despite these limitations, this study presents several strengths. To date, no previous study focusing on cerebral modifications in athletes exposed to repetitive subconcussive head impacts has employed a combination of these different neuroimaging modalities with the aim of detecting subtle brain abnormalities.^{14–17} This combinatorial approach is the major strength of this study, in addition to the complementary neuropsychological workup, which will allow the evaluation of cognitive modifications in this population. By focusing on participants at the end of their professional careers, we hope to gain a more global vision of the cumulative effects of heading over the entire course of a footballer's career. Previous studies have featured populations with relatively young average ages, where the cumulative effects of heading impacts may not yet be detectable.

A further strength of this project is its highly collaborative nature. This project will be carried out in collaboration with research teams of the ICube laboratory (IMAGeS and MMB), who have specialised in the biomechanics of head injury for the past 20 years.^{50–52} This team has acquired a good knowledge of single head injuries and has recently opened its research to the topic of repeated concussions. This protocol has been devised in collaboration with the French Football Federation, and this partnership will also ensure the feasibility of the study in terms of recruitment of professional soccer players.

We expect that this study will provide interesting data about cerebral structures and cognitive function of professional male soccer players exposed to subconcussive impacts. This could ultimately contribute to the establishment of suitable, scientifically founded follow-up and preventive measures in this population, which do not yet exist, and the extension of these measures to all those who practice this sport, especially children.

Ethics and dissemination

Ethical approvals, data and safety monitoring

Ethics approval has been obtained: the study was approved by the Comité de Protection des Personnes (CPP) No 2021-A01169-32. A declaration of conformity to the Commission Nationale de l'Informatique et des Libertés (CNIL) was obtained (agreement number 2208067v0). This trial is registered with Clinical Trials Registry, NCT04903015. Any important modifications to the protocol will be submitted for approval to the CPP. If approved, updated versions of all trial documents will be provided to all persons involved in the study. Written informed consent will be obtained for each participant prior to enrolment, and each signature will be personally dated by the participant. The consent form will be securely retained by the investigator of the study. All participants will be informed that their personal study-related data will be used by the principal investigator in accordance with the local data protection law. Although no adverse events are expected in this trial (no contrast agent will be employed, and no medicinal product administered), any adverse events will be reported via the French Ministry of Health's Adverse Health Event Reporting Portal. Only the investigating team will have access to the trial dataset.

Dissemination

The findings of this study will be disseminated by publication in an international journal and in presentations at international conferences of neuroradiology. We plan to work in collaboration with the Medical Writer of Strasbourg University Hospital concerning the drafting and edition of this article. Participants will be notified of the results of their examinations by a follow-up visit with an investigating physician. Participants, the FFF and regional delegations will be sent the final publication reporting study results.

Author affiliations

- ¹Emergency Department, University Hospital Centre Strasbourg, Strasbourg, France
- ²ICube, UMR 7357, University of Strasbourg-CNRS, Strasbourg, France
- ³Imaging Department, University Hospital Centre Strasbourg, Strasbourg, France
- ⁴Public Health Unit, University Hospital of Strasbourg, Strasbourg, France
- ⁵Geriatrics and Neurology Departments, Research and Resources Memory Center (CM2R), University Hospital of Strasbourg, Strasbourg, France
- ⁶Neuropsychology Department, University Hospital Centre Strasbourg, Strasbourg, France
- ⁷Fédération Française de Football, Paris, France
- ⁸School of Osteopathy, College COS Strasbourg, Strasbourg, France
- ⁹Medical Sport Center of Strasbourg, CMSM, Strasbourg, France
- ¹⁰Racing club Strasbourg, Strasbourg, France

Contributors SaK, FL, FB and StK conceived the idea of the study. StK, FL, JG, FB, MB, AB, CK, JM, EO, FP, FG, CD, VN, RW and SaK formed the working group that wrote the study protocol. JG performed statistical analysis for the sample size calculation. All coauthors have approved the protocol and will participate in the study.

Funding This work was supported by Strasbourg University Hospital (HUS), Philipps and GE Healthcare; Grant Number PRI 2020-HUS No 8077. Philipps and GE Healthcare were not involved in the conception or design of this study protocol.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Sabrina Kepka <http://orcid.org/0000-0002-7406-5005>

REFERENCES

- 1 Levy ML, Kasasbeh AS, Baird LC, et al. Concussions in soccer: a current understanding. *World Neurosurg* 2012;78:535–44.
- 2 Decq P, Brauge D, Calmat A, et al. Diagnosis clinical criteria of sport related concussion: toward an operational criteria definition in France. *Neurochirurgie* 2021;67:222–30.
- 3 McCrory P, Meeuwisse W, Dvorák J, et al. Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med* 2017;51:838–47.
- 4 Bailes JE, Petraglia AL, Omalu BI, et al. Role of subconcussion in repetitive mild traumatic brain injury. *J Neurosurg* 2013;119:1235–45.
- 5 Smith DW, Bailes JE, Fisher JA, et al. Internal jugular vein compression mitigates traumatic axonal injury in a rat model by reducing the intracranial slosh effect. *Neurosurgery* 2012;70:740–6.
- 6 Gysland SM, Mihalik JP, Register-Mihalik JK, et al. The relationship between subconcussive impacts and concussion history on clinical measures of neurologic function in collegiate football players. *Ann Biomed Eng* 2012;40:14–22.
- 7 Rodrigues AC, Lima MDM, de Souza LC, et al. No evidence of association between soccer heading and cognitive performance in professional soccer players: cross-sectional results. *Front Neurol* 2019;10:209.
- 8 Spiotta AM, Bartsch AJ, Benzel EC. Heading in soccer: dangerous play? *Neurosurgery* 2012;70:1–11.
- 9 McKee AC, Alosco ML, Huber BR. Repetitive head impacts and chronic traumatic encephalopathy. *Neurosurg Clin N Am* 2016;27:529–35.
- 10 Stern RA, Daneshmand DH, Baugh CM, et al. Clinical presentation of chronic traumatic encephalopathy. *Neurology* 2013;81:1122–9.
- 11 Ling H, Morris HR, Neal JW, et al. Mixed pathologies including chronic traumatic encephalopathy account for dementia in retired association football (soccer) players. *Acta Neuropathol* 2017;133:337–52.

- 12 Grinberg LT, Anghinah R, Nascimento CF, *et al.* Chronic traumatic encephalopathy presenting as Alzheimer's disease in a retired soccer player. *J Alzheimers Dis* 2016;54:169–74.
- 13 Mez J, Daneshvar DH, Kiernan PT, *et al.* Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA* 2017;318:360–70.
- 14 Abbas K, Shenk TE, Poole VN, *et al.* Effects of repetitive subconcussive brain injury on the functional connectivity of default mode network in high school football athletes. *Dev Neuropsychol* 2015;40:51–6.
- 15 Koerte IK, Ertl-Wagner B, Reiser M, *et al.* White matter integrity in the brains of professional soccer players without a symptomatic concussion. *JAMA* 2012;308:1859–61.
- 16 Manley G, Gardner AJ, Schneider KJ, *et al.* A systematic review of potential long-term effects of sport-related concussion. *Br J Sports Med* 2017;51:969–77.
- 17 Ng TS, Lin AP, Koerte IK, *et al.* Neuroimaging in repetitive brain trauma. *Alzheimers Res Ther* 2014;6:10.
- 18 Coughlin JM, Wang Y, Munro CA, *et al.* Neuroinflammation and brain atrophy in former NFL players: an in vivo multimodal imaging pilot study. *Neurobiol Dis* 2015;74:58–65.
- 19 Hart J, Kraut MA, Womack KB, *et al.* Neuroimaging of cognitive dysfunction and depression in aging retired National football League players: a cross-sectional study. *JAMA Neurol* 2013;70:326–35.
- 20 Casson IR, Viano DC, Haacke EM, *et al.* Is there chronic brain damage in retired NFL players? Neuroradiology, neuropsychology, and neurology examinations of 45 retired players. *Sports Health* 2014;6:384–95.
- 21 Lin AP, Ramadan S, Stern RA, *et al.* Changes in the neurochemistry of athletes with repetitive brain trauma: preliminary results using localized correlated spectroscopy. *Alzheimers Res Ther* 2015;7:13.
- 22 Baugh CM, Kiernan PT, Kroshus E, *et al.* Frequency of head-impact-related outcomes by position in NCAA division I collegiate football players. *J Neurotrauma* 2015;32:314–26.
- 23 Morales JS, Valenzuela PL, Saco-Ledo G, *et al.* Mortality risk from neurodegenerative disease in sports associated with repetitive head impacts: preliminary findings from a systematic review and meta-analysis. *Sports Med* 2022;52:835–46.
- 24 Sandmo SB, Filipic P, Cente M, *et al.* Neurofilament light and tau in serum after head-impact exposure in soccer. *Brain Inj* 2020;34:602–9.
- 25 Straume-Naesheim TM, Andersen TE, Dvorak J, *et al.* Effects of heading exposure and previous concussions on neuropsychological performance among Norwegian elite footballers. *Br J Sports Med* 2005;39 Suppl 1:i70–7.
- 26 Matser JT, Kessels AGH, Jordan BD, *et al.* Chronic traumatic brain injury in professional soccer players. *Neurology* 1998;51:791–6.
- 27 McCunn R, Beaudouin F, Stewart K, *et al.* Heading in football: incidence, biomechanical characteristics and the association with acute cognitive function—a three-part systematic review. *Sports Med* 2021;51:2147–63.
- 28 Strauss SB, Fleysher R, Ifrah C, *et al.* Framing potential for adverse effects of repetitive subconcussive impacts in soccer in the context of athlete and non-athlete controls. *Brain Imaging Behav* 2021;15:882–95.
- 29 Snowden T, Reid H, Kennedy S, *et al.* Heading in the right direction: a critical review of studies examining the effects of heading in soccer players. *J Neurotrauma* 2021;38:169–88.
- 30 Nasreddine ZS, Phillips NA, Bédirian V, *et al.* The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.
- 31 Van der Linden M G. L'évaluation des troubles de la mémoire. In: *De Boeck Supérieur*, 2004.
- 32 Meyers JE, Meyers KR. Rey complex figure test under four different administration procedures. *Clin Neuropsychol* 1995;9:63–7.
- 33 Bright P, Hale E, Gooch VJ, *et al.* The National adult reading test: restandardisation against the Wechsler adult intelligence Scale—Fourth edition. *Neuropsychol Rehabil* 2018;28:1019–27.
- 34 Godefroy O G. Fonctions exécutives et pathologies neurologiques et psychiatriques. In: *De Boeck Supérieur*, 2012.
- 35 Zimmermann P, Fimm B. Testbatterie zur Aufmerksamkeitsprüfung - Version 2.2: (TAP) ; [Handbuch]. Psytest. Available: <https://www.psytest.net/de/testbatterien/tap/bestellen>
- 36 Baron-Cohen S, Wheelwright S, Hill J, *et al.* The "Reading the Mind in the Eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry* 2001;42:241–51.
- 37 Lovstad M, Sigurdardottir S, Andersson S, *et al.* Behavior rating inventory of executive function adult version in patients with neurological and neuropsychiatric conditions: symptom levels and relationship to emotional distress. *J Int Neuropsychol Soc* 2016;22:682–94.
- 38 Smith SM, Zhang Y, Jenkinson M, *et al.* Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 2002;17:479–89.
- 39 Fischl B, Salat DH, Busa E, *et al.* Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002;33:341–55.
- 40 Ashburner J, Friston KJ. Voxel-based morphometry—the methods. *Neuroimage* 2000;11:805–21.
- 41 Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect* 2012;2:125–41.
- 42 Jordan SE, Green GA, Galanty HL, *et al.* Acute and chronic brain injury in United States national team soccer players. *Am J Sports Med* 1996;24:205–10.
- 43 Mussack T, Dvorak J, Graf-Baumann T, *et al.* Serum S-100B protein levels in young amateur soccer players after controlled heading and normal exercise. *Eur J Med Res* 2003;8:457–64.
- 44 Zetterberg H, Jonsson M, Rasulzada A, *et al.* No neurochemical evidence for brain injury caused by heading in soccer. *Br J Sports Med* 2007;41:574–7.
- 45 Downs DS, Abwender D. Neuropsychological impairment in soccer athletes. *J Sports Med Phys Fitness* 2002;42:103–7.
- 46 Matser JT, Kessels AG, Jordan BD, *et al.* Chronic traumatic brain injury in professional soccer players. *Neurology* 1998;51:791–6.
- 47 Stephens R, Rutherford A, Potter D, *et al.* Neuropsychological impairment as a consequence of football (soccer) play and football heading: a preliminary analysis and report on school students (13–16 years). *Child Neuropsychol* 2005;11:513–26.
- 48 Myer GD, Barber Foss K, Thomas S, *et al.* Altered brain microstructure in association with repetitive subconcussive head impacts and the potential protective effect of jugular vein compression: a longitudinal study of female soccer athletes. *Br J Sports Med* 2019;53:1539–51.
- 49 Blyth RJ, Alcock M, Tumilty DS. Why are female soccer players experiencing a concussion more often than their male counterparts? A scoping review. *Phys Ther Sport* 2021;52:54–68.
- 50 Deck C, Bourdet N, Meyer F, *et al.* Protection performance of bicycle helmets. *J Safety Res* 2019;71:67–77.
- 51 Sahoo D, Robbe C, Deck C, *et al.* Head injury assessment of non-lethal projectile impacts: a combined experimental/computational method. *Injury* 2016;47:2424–41.
- 52 Bliven E, Rouhier A, Tsai S, *et al.* Evaluation of a novel bicycle helmet concept in oblique impact testing. *Accid Anal Prev* 2019;124:58–65.