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High-magnitude headers are not associated with structural and functional brain changes in active high-level football (soccer) players

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ABSTRACT

Objectives To date, consistent evidence for consequences of heading in football (soccer) on the structure and function of the brain is lacking, but first studies indicate a potential effect of specific high-magnitude headers. The purpose of this longitudinal, prospective study was to investigate whether potential structural and/or functional alterations within the brain were associated with (high-magnitude) heading.

Methods 3T MRI sequences were obtained from active high-level male players before and after an observation period of 17.2 months (median). Cortical thickness and grey matter (GM) volume were investigated on a whole-brain level. Functional connectivity (FC) was analysed in the default mode network (DMN) and salience network (SN). During the observation period, each training and each match was videotaped and evaluated regarding the heading exposure. Significant structural and functional findings were subsequently correlated with specific header characteristics.

Results 14 included participants (mean age: 20.36±3.34 years) played 5822 headers. GM volume remained unchanged, whereas cortical thickness decreased minimally from pre-measurement to post-measurement in a left precentral region (mean change: 0.048±0.128 mm; clusterwise p=0.0416). Within the SN, FC increased in one cluster (false discovery rate corrected p=0.026). FC remained stable within the DMN and between DMN and SN. Change from pre-measurement to post-measurement for the significant results did not correlate with heading variables.

Conclusion Our findings may indicate no cumulative effect of heading during the observation period. As these results contrast with cross-sectional findings, more longitudinal, prospective studies with a greater sample size are urgently needed to understand potential heading effects.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although some studies described an association between heading exposure in football with structural and functional brain changes, results are overall still conflicting and longitudinal and prospective studies are still scarce. As head impacts with higher magnitudes may rather be associated with alterations of brain architecture, headers with higher velocities and accelerations are of specific interest in the exploration of possible effects on brain function and structure.

WHAT THIS STUDY ADDS

⇒ The objective and prospective analysis provides a most accurate estimation of heading exposure. The correlation analyses revealed no association between the number of long-distance headers and heading duels with significant macrostructural and functional findings, indicating no influence of such high-magnitude headers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Although no significant correlations between structural and functional brain changes and heading variables were detected, recent publications indicate an effect of high-magnitude headers on white matter integrity and a neurocognitive domain. Hence, a characterisation of headers should be included in analyses of potential heading effects and this study may serve as a foundation for such research. Additionally, this may indicate the need to include multiple modalities to capture the broader perspective rather than relying on a single test or modality.

INTRODUCTION

A concussion seems to disrupt the connections of two resting-state brain networks, the default mode network (DMN) and the salience network (SN).[1] This is underlined by functional connectivity (FC) alterations within and between these networks in resting state after sustaining a concussion.[2 3] Changes in the FC in DMN and SN regions described in non-concussed collision and contact sports athletes[4–7] led to the assumption that exposure to repetitive head impacts (RHIs) contributes to FC alterations. The hypothesis of RHI-induced brain changes was supported by findings of altered macrostructural parameters in various collision and contact sports athletes.[8 9] Compared with non-contact sports athletes, mixed martial arts athletes exhibited cortical thinning over 1 year.[8] A trend towards lower total brain volume and a significantly lower grey matter (GM) volume in one cluster was found in American football players compared with volleyball players.[9] Such macrostructural changes may be associated with neurocognitive impairments and neurodegenerative processes. Hence, (short-term) effects of RHI exposure on neurocognitive performance are discussed and have been reported in studies on several (former) collision and contact sports athletes.[10 11] Similarly, a highly debated potential long-term consequence of RHI exposure is the development of neurodegenerative diseases and ultimately chronic traumatic encephalopathy,[12 13] although evidence for a causal relationship is limited. The discussion of these potential short-term or long-term effects emphasises the necessity to investigate and potentially detect subtle structural and/or functional brain changes. Heading in football is of specific interest as the head is purposefully used to play the ball. Some studies reported associations between heading exposure and differences in cortical thickness[14 15] or GM volume.[16] As stated above, such changes may be associated with neurodegenerative consequences. In addition, cortical thinning in football players was associated with a worse performance in a neurocognitive test representing processing speed and visual memory.[14] However, in these studies, self-reports were used for assessing heading exposure. Additionally, associations between greater heading exposure and increased FC were described.[17 18] Alterations in brain network organisation in high school female football players have been described,[19] but topological properties of brain networks in relation to headers have not been examined yet.

Recently, headers with a longer flight distance compared with ones with shorter distances have been shown to be associated with increased response times[20] and may influence the white matter (WM) integrity of the brain.[21] Balls that travel longer distances have higher accelerations than those from shorter distances,[22] potentially explaining the findings. Similarly, head-to-head impacts, which may happen in heading duels, have higher accelerations than other impacts to the head.[23] Such headers with higher velocities and accelerations may induce different brain alterations than headers with lower accelerations. Consequently, the number of long-distance headers (ie, headers that occurred after the ball travelled more than 20 m) and heading duels should be in the focus of analyses of heading effects.

Cross-sectional study designs applying retrospective methods to assess heading exposure,[14–16] focusing on exposure in matches,[18] and different cohorts limit the generalisability of previous study results. Therefore, this longitudinal, prospective cohort study aimed to investigate structural and functional MRI parameters, heading exposure and especially focus on a potential association between structural and/or functional brain changes and heading variables in active, high-level male players.

METHODS

Patient and public involvement

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

Study design and procedure

German, active football players over 18 years were included between November 2017 and July 2018. All athletes were part of the professional, U21 or U19 team. Exclusion criteria were (1) pathological or abnormal findings on structural imaging; (2) psychiatric or neurological disorder; (3) any self-reported learning disabilities; (4) contraindication to MRI; (5) any other native language than German, English, French or Spanish; and (6) sustaining a concussion during the study period. The data presented here are based on players who had completed pre-test and post-test brain MRI scanning.

At the initial visit, the medical history, including concussion history, was documented with a questionnaire and a neurological screening. Brain MRI scans were obtained and repeated during the follow-up visits in May 2019, which was shortly after the end of the season.

Heading

The video observation for heading data started after the initial individual MRI scan to ensure that only headers performed thereafter were included in the evaluation. Observation ended in May 2019. During the observation period, each training and each match was videotaped. Videos were analysed independently by two trained research assistants. The evaluation of headers and header characteristics was based on a previously published protocol.[24] For organisational reasons, it was necessary to deviate from the original protocol regarding the variables 'flight distance of the ball' and 'heading duel'. The flight distance was categorised as follows: *<5 m*, *5–20*m and *>20*m. The cut-off for the long-distance headers was chosen due to studies reporting greater mean peak linear and angular accelerations for balls already coming from distances of 10 m.[22] Kern *et al* similarly categorised all headers from a distance >20 m as long-distance and high-magnitude headers.[25] A heading duel was defined as two players having <1 m distance between each other. This definition is stricter than in the original protocol. Unclear situations were discussed and evaluated by both assistants.

MRI

Whole-brain MRI was obtained with a 3T Philips Ingenia scanner with a 32-channel head coil. MRI data processing and analyses were computed on a high-performance computing cluster.

Structural data quality was checked visually and automatically with MRIqc (V.0.15.2rc1).[26] FreeSurfer's (V.6.0.0) longitudinal stream[27] was used for structural MRI processing. T1-weighted scans were preprocessed using the recon-all pipeline, including T2-weighted fluid-attenuated inversion recovery sequences for improved surface reconstructions.

Functional MRI data were analysed using the CONN FC toolbox (V.20b)[28] for the Statistical Parametric Mapping software 12 (Wellcome Centre for Human Neuroimaging, London, UK) implemented in MATLAB R2020a (MathWorks Inc., Natick, Massachusetts, USA). The default preprocessing pipeline for volume-based analyses was applied.

Detailed information on data acquisition settings, preprocessing and processing steps is presented in online supplemental file 1.

Statistics

Demographical and heading data were processed with the SPSS Statistics software package (V.29.0, IBM, Armonk, New York, USA). Mean age and SD are reported. The total heading number is presented as median with 25% and 75% quartiles. For the different categories for the flight distance of the ball and heading duel, the total number of each category and the percentage of the category relative to the total heading number are reported.

Surface-based analysis of cortical thickness, as the closest distance between the GM/WM boundary and the GM/cerebrospinal fluid boundary,[29] and cortical GM volume was done by a paired analysis. After sampling the individual's pre-surface and post-surface onto the average surface ('fsaverage'), the difference between the individual pre-measurement and post-measurement was computed in the average surface space and concatenated into one file, which was spatially smoothed by 10 mm full-width half-maximum. A general linear model (GLM) was applied to test whether the mean difference differed from zero. Age was included as a nuisance regressor in all analyses. Estimated intracranial volume was added as a control variable in the GM volume analysis. A permutation simulation was used for clusterwise correction for multiple comparisons with 1000 iterations and a cluster-forming threshold of $p<0.0001$ (unsigned). Clusters were declared significant with a cluster-wise $p<0.05$.

A region of interest (ROI)-to-ROI approach in the CONN toolbox was applied to evaluate the FC of the DMN and SN. CONN's default network seeds for the SN (anterior cingulate cortex (ACC), left and right anterior insula, left and right rostral prefrontal cortex (rPFC) and left and right supramarginal gyri (SMG)) and the DMN (medial prefrontal cortex, left and right lateral parietal lobes and the posterior cingulate cortex) were included in the analysis. Based on previous literature, the precuneus was added as a DMN seed region.[30 31]

In the first-level analysis, individual and session-specific ROI-to-ROI matrices were created by a weighted GLM. In the matrices, each element is the Fisher-transformed bivariate correlation coefficient between a pair of ROI blood oxygenation level-dependent time series. The group analysis (second-level) included the 5 DMN and 7 SN seeds, resulting in an analysis of 12 seeds with 66 connections (see online supplemental table S1 for all ROI-to-ROI connections). Non-parametric spatial pairwise clustering[32] with an uncorrected connection threshold of $p<0.01$ and cluster-level false discovery rate (FDR) corrected p cluster threshold of $p<0.05$ was applied.

Using the ROIs as nodes and the correlation values between the ROIs as edges, graph theory measures were evaluated within the ROI-to-ROI analysis. First-level and second-level analysis settings were kept as in the ROI-to-ROI approach. For the adjacency matrix threshold, cost was set to 0.15 two-sided. The analysis threshold was $p<0.05$ p-FDR corrected (two-sided). Global and local efficiency, betweenness centrality, cost, degree, average path length and clustering coefficient were analysed. The parameters are explained in online supplemental material 2.

A potential effect of heading was evaluated for significant structural and functional MRI findings within the SPSS Statistics software package (V.29.0, IBM). The change from pre-measurement to post-measurement of significant results was calculated by subtracting the post-test values from the pre-test values. This difference and the calculated percentage change were correlated with heading variables by applying Pearson's or Spearman's rank correlation for normally or non-normally distributed variables, respectively. Normal distributions were tested with Shapiro-Wilk. Associations were analysed for the total heading number and the number of long-distance headers and heading duels. Bonferroni was applied to correct for multiple testing. Correction of multiple testing was done with a permutation simulation (structural imaging), FDR (functional imaging) or Bonferroni (correlation analyses).

RESULTS

30 football players were included in the study. Eight players changed clubs or teams before the study's end. Another eight players did not complete both MRI scans, resulting in a final cohort of 14 athletes (mean age 20.4±3.3 years; flow diagram in online supplemental figure S1). None of the athletes sustained a concussion during the study period. The documentation of concussion history revealed that one player sustained three concussions and four players sustained one concussion. Nine players did not report having had a concussion. The observation period ranged between 9.5 and 17.8 months (median: 17.2), in which 5822 headers were documented. The total heading number per player ranged from 146 (in 9.5 months) to 943 (in 17.8 months). Headers were mostly played after a short distance and without a heading duel. Table 1 summarises the information about the heading exposure.

Table 1 Total numbers and percentages for the total heading amount, the flight distance of the ball and heading duels for 14 players

	Total number	Percentage from total (5822)
Total heading number	5822	100
Minimum–maximum	146–943	n/a
Median (25–75% quartiles)	340 (241.75–534.5)	n/a
Flight distance of the ball		
<5 m	3248	55.79
5–20 m	1246	21.40
>20 m	1328	22.81
No information	0	0
Heading duel		
Header without duel	3007	51.65
Header with duel	739	12.69
No information	2076	35.66

n/a, not applicable.

There were no structural differences within DMN or SN regions. Cortical thickness changed in one cluster in the left precentral region (mean change=0.048±0.128 mm; cluster size=64.6 mm^2; clusterwise p=0.0416 (90% CI 0.0298 to 0.0533); figure 1). The positive change implies higher cortical thickness at the pre-measurement. No other clusters were found for cortical thickness or GM volume.

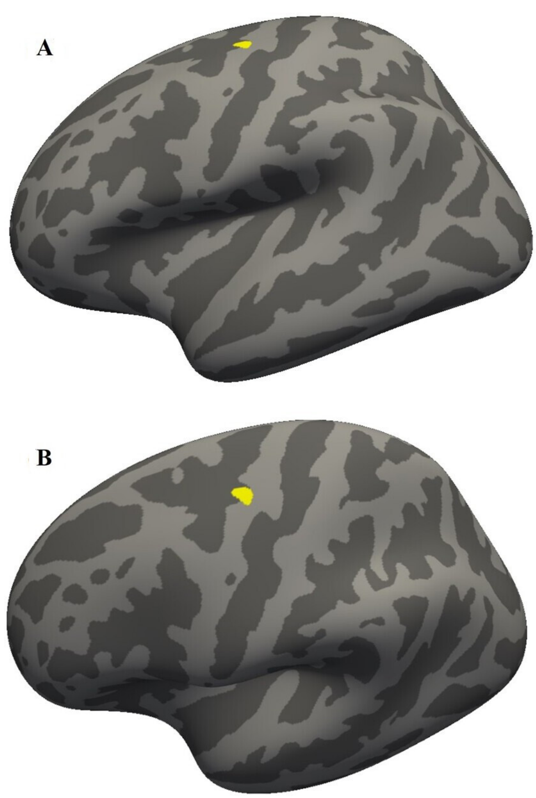

Figure 1 Precentral cluster in the left hemisphere (yellow) showing a decrease in cortical thickness over the observation period (A: lateral view; B: lateral view with tilted hemisphere).

The ROI-to-ROI analysis yielded one cluster within the SN (p-FDR=0.026), comprised the right SMG, left rPFC and ACC (figure 2, table 2). The negative mean change represents higher FC in the post-measurement. There were no alterations within the DMN or for connections between DMN and SN. Graph theory parameters did not change between pre-measurement and post-measurement.

The change for the significant cortical thickness and FC findings did not correlate with the different heading variables (table 3; online supplemental figures S2–S4). Similarly, the calculated percentage change was not correlated with any heading variables (online supplemental table S2).

DISCUSSION

This study aimed to examine changes in functional and structural brain architecture in relation to heading exposure in active, high-level male football players. 5822 headers were documented for 14 players in all training sessions and matches during the observation period. Headers were mostly played after the ball travelled a short distance and occurred without a heading duel. Cortical thickness decreased minimally in a left precentral cluster. No changes in GM volume were detected, and the FC remained stable within the DMN and between DMN and SN. A cluster comprising three regions within the SN showed increased FC in the post-test. Graph theory analysis did not reveal alterations. Subsequent correlation analyses did not identify any associations between heading variables and the calculated change for the described significant findings. Specifically, long-distance headers and headers played in duels did not correlate with functional or structural brain changes.

Heading

The total amount presented here is higher than previously reported. For female collegiate cohorts with a similar sample size as in the present study, between 1307 headers in 149 sessions[22] and 329 headers in 96 sessions[33] were documented. The difference may be due to a longer observation period in our study. Additionally, heading exposure differs between males and females, increases with age[34] and seems to be highest in adults on the highest level of play.[35]

Most headers occurred after the ball came from a distance of <5 m and without a heading duel. Both findings are in line with previous literature on youth cohorts.[36 37] However, due to a data transmission error, the information on heading duels was missing for 35.66% of all headers in the present investigation (table 1). Although this is a limitation, one study on youth cohorts reported that only 10% and 2% of all headers in matches and training sessions, respectively, involved a duel.[36] In

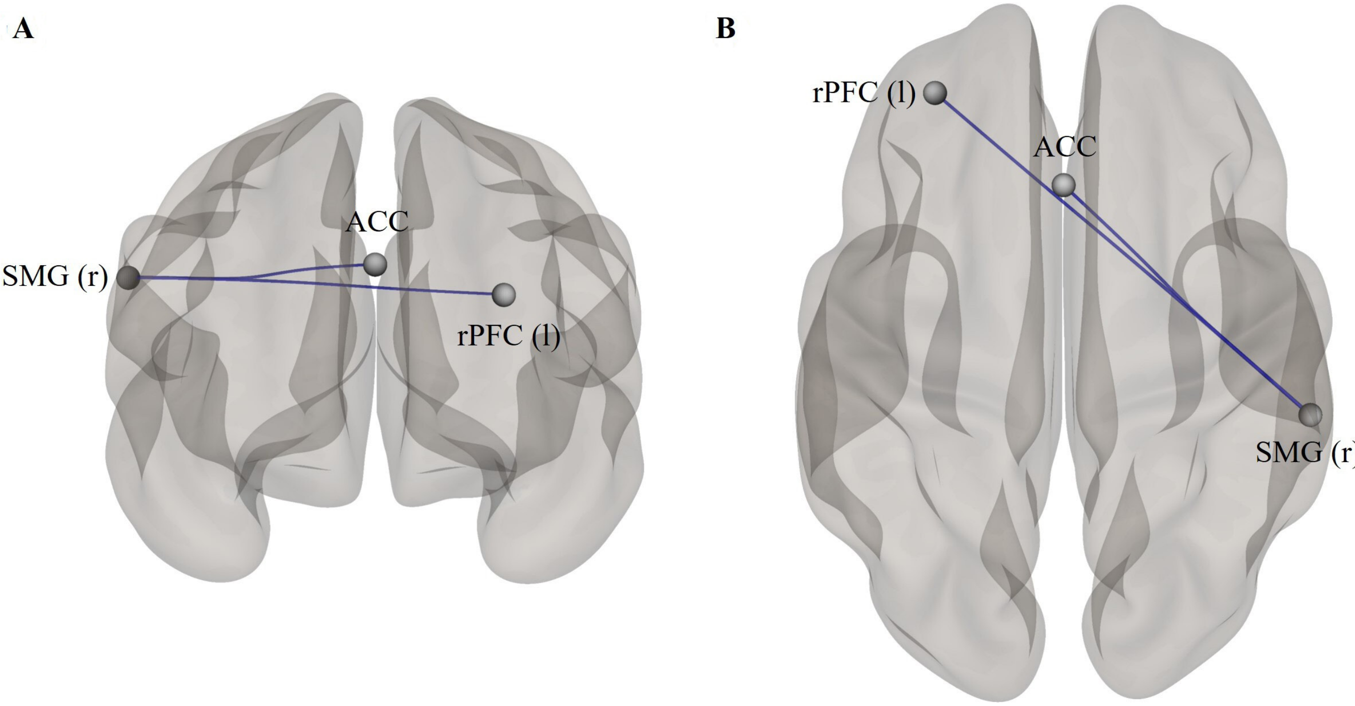

Figure 2 Increased functional connectivity in the post-measurement within the salience network between the right supramarginal gyrus (SMG (r)) and the anterior cingulate cortex (ACC) and between the SMG (r) and the left rostral prefrontal cortex (rPFC (l)) in the anterior view (A) and the superior view (B).

addition, >50% of all headers occurred without a header duel in our cohort, which is similar to previous results in training sessions or matches,[36 37] indicating an accurate measurement of exposure.

Structural imaging

The reported decrease in cortical thickness in a left precentral cluster is in line with a study showing greater cortical thinning in retired male professional football players compared with a matched control group.[14] However, only one significant cluster was detected, and the cluster revealing cortical thinning is smaller than the previously found multiple clusters in several brain regions.[14] Reduced cortical thickness is associated with several neurodegenerative diseases, such as different forms of dementia[38 39] or Parkinson's.[40] Therefore, a highly speculative interpretation of our finding may be an early presence of such neurodegenerative processes. Similarly, developmental or normal ageing processes may have led to the decrease in cortical thickness. However, the clinical meaning of this finding may be questionable and is rather unknown, as the mean decrease of cortical thickness was only 0.048 mm.

The present study did not find any GM volume changes over the observation period in football players. Similarly, no volumetric changes were found in American football players previously in a study with a rather short observation time.[41] However, as our study had a similar cohort regarding age, level of play and sample size, and a longer observation period, our results may substantiate the finding.[41]

Functional imaging

The unchanged FC within the DMN and between DMN and SN indicates a lack of functional alterations in the DMN throughout the observation period. Although this may be in contrast to a finding of increased FC between posterior DMN seeds and frontal medial and temporal gyri in semi-professional football players,[18] similar results of unchanged FC over one season within the DMN were described for American football and ice hockey athletes.[41 42] As the cohorts of the latter two studies were

Table 2 Mean change, SD, uncorrected and corrected p values, and *t*-statistics for the significant FC findings within the salience network

Connection	Mean change in FC	SD	Uncorrected p value	FDR-corrected p value	*t*(12)
Right SMG–left rPFC	−0.0563	0.297	0.0004	0.025	−4.87
Right SMG–ACC	−0.0076	0.45	0.0016	0.054	−4.05

ACC, anterior cingulate cortex; FC, functional connectivity; FDR, false discovery rate; rPFC, rostral prefrontal cortex; SMG, supramarginal gyrus.

Table 3 Results of the correlation analyses between heading variables and the calculated change from pre-test to post-test for the significant cortical thickness and FC findings

	Total heading number	Total number of long-distance headers	Total number of heading duels
Change in cortical thickness (precentral left)			
Correlation coefficient	−0.152*	−0.165*	0.064*
95% CI	−0.642 to 0.426	−0.65 to 0.415	−0.496 to 0.586
r^2	0.023104	0.027225	0.004096
P value	0.605	0.573	0.829
Change in FC (right SMG–ACC)			
Correlation coefficient	0.003	0.011	0.182*
95% CI	−0.529 to 0.532	−0.522 to 0.539	−0.4 to 0.66
r^2	0.000009	0.000121	0.033124
P value	0.993	0.969	0.533
Change in FC (right SMG–left rPFC)			
Correlation coefficient	−0.099	−0.085	−0.046*
95% CI	−0.598 to 0.456	−0.589 to 0.467	−0.575 to 0.51
r^2	0.009801	0.007225	0.002116
P value	0.737	0.774	0.876

Bonferroni corrected p=0.017.
*Spearman's rank correlation.
ACC, anterior cingulate cortex; FC, functional connectivity; rPFC, rostral prefrontal cortex; SMG, supramarginal gyrus.

comparable to our sample, our results may underline these previous findings. Bigger samples are urgently needed to substantiate these results, especially as they differ from more frequently reported FC alterations in the DMN in a cohort with less well-defined header exposure[18] and in cohorts with RHI exposure.[4 6]

Within the SN, two connections showed higher FC in the post-measurement. The SN is primarily responsible for switching between the internally directed processes from the DMN and the externally directed processes from the central executive network.[43] Our result may therefore indicate a higher sensitivity or increased effort required to detect and filter stimuli and switch between internal and external processes. First studies showed increased FC in the SN in patients with insomnia[44] or an association between increased depressive symptoms and FC changes in the SN in children.[45] Further investigation is required to determine whether such associations or clinical implications may be detected in our cohort or football players in general. To date, a (clinical) relevance and potential effects are unknown. One recent study found FC decreases within this network post-season in high school American football players.[7] This finding differs from our results. As the American football players were 16.5 years old and the study period was 4.5 months, the age difference to our cohort and the longer observation period may explain the difference. Increased resting-state FC may represent an adaptive plasticity resulting from brain injuries.[46] As 5 of the 14 players reported having had a concussion prior to the study, this may be a potential explanation for the finding. However, the majority of players did not have a concussion, and it is questionable whether concussion history may have influenced the results. Increased FC may similarly indicate a compensatory mechanism to overcome structural or functional alterations.[46–48] How this might apply to our results needs to be further elucidated, especially as there were no alterations in network organisation and properties assessed by graph theory parameters in the included ROIs and networks. This indicates stable topological properties and efficient communication within and between the two networks, although an increased FC within the SN was found. Analyses of graph theory parameters are still scarce in football players but should be considered in future studies as such analysis approaches may help in understanding brain network topology.

Associations between alterations and heading

The missing association between cortical thickness change and the total heading number is in contrast to previous study results reporting a decrease with heading[14] or differences between groups with different heading exposure.[15] Similarly, the missing correlation between the total amount and FC changes contrasts with results demonstrating increased FC with greater heading exposure.[17 18] As the total heading amount did not correlate with structural and functional brain changes, higher impact headers were specifically analysed.

Effects of long-distance headers on WM integrity[21] and a response time task[20] have been published previously. These are associated with greater accelerations,[22] similarly found for head-to-head impacts,[23] which may occur in heading duels. The correlation analyses between the number of long-distance headers and headers in heading duels with calculated changes in cortical thickness and FC, however, did not reveal significant associations. The small sample size and length of observation may have contributed to this negative finding, but a study on American football players with a similar sample size and a shorter observation period revealed greater increases in the FC of the DMN with a higher number of high-magnitude head impacts.[41] This disparity may indicate that effects of RHIs between different sports (eg, football and American football) may not be the same. Compared with football, linear and rotational accelerations were higher for head impacts experienced in lacrosse and highest in American football.[49] This difference in kinematics underlines potential differences between contact and collision sports. Hence, findings in one sport may not necessarily be transferable to another one.

Clinical/research implications

As similar correlation analyses between structural and functional MRI parameters and heading variables have not yet been conducted, our study may inform future research. The calculated change of significant findings was not associated with the total heading number or the number of long-distance headers and heading duels. As other studies showed effects of the amount of long-distance headers,[20 21] focusing on the total heading number may potentially mask effects of specific headers in addition to the large interindividual variability. To evaluate possible effects of high-magnitude headers, more studies that differentiate between the total amount and specific headers are needed.

Limitations

The sample was small, and specific subgroup analyses (eg, based on position) could not be conducted. The inclusion of high-level male players further limits the generalisability of results. Although considered the gold standard,[50] the video observation excluded the possibility of investigating biomechanical and kinematic data, such as linear or rotational accelerations of the headers and impact speed. Additionally, there was no distinction between voluntary and involuntary head impacts. Individual player incidence rates per athlete exposure or training/playing hours could not be calculated due to missing information on observed sessions and exposure times. This also excluded the possibility to calculate time between last training or match and post-test measurement. Inter-rater reliability could not be calculated for the video analysis, which should be added in future studies.

Factors such as concussion history, years of experience, neck strength or anthropometrics were not included in the analyses. As these may potentially influence the results or explain findings, these factors could be of interest in future research. Similarly, as heading exposure differs between playing positions,[24] adding the position may be a relevant aspect to consider. Lastly, the study period may not have been sufficiently long to detect brain alterations or the real effects of heading. It is therefore recommended that future studies consider extending the observation period and incorporating intermediate tests.

CONCLUSION

Video observation and analysis of all training sessions and matches in 14 high-level, active male football players over 17.2 months allowed an accurate representation of heading exposure. MRI analyses of scans before and after the observation period revealed a minimal decrease of cortical thickness in a precentral cluster, and increased FC within the SN. The calculated change for the significant results did not correlate with heading variables, suggesting no cumulative effects of heading, specifically not with respect to long-distance headers and headers played in heading duels. However, due to the limitations of the study, these findings may be limited to the cohort or dependent on the study period. As various potentially influencing factors were not included in the analysis, an analysis model including these factors and different modalities and tests is urgently needed to ultimately assess the actual effects of heading.

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Contributors NF-D, GHW, CS, JF and CR contributed to the study design. NF-D, GHW, CS, JF, CT, LM and CR performed the data collection. FKM, NF-D, RR and CR did the initial analysis and interpretation of data. FKM and CR wrote the first edition of the full manuscript. All authors participated in the critical revision of the manuscript, as well as approval of the final submitted version of the manuscript. CR is the guarantor of the work.

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Associations (UEFA). All other authors declare no conflicts of interest relevant to the manuscript.

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Data availability statement The data that support the findings of the study are not publicly available due to potential traceability of participants.

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