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Review

A Systematic Review of the Effects of Football Playing on Changes in Serum Brain-Derived Neurotrophic Factor Level

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Abstract: Background: Consistent evidence suggests that exercise improves cognition and decision making, with preliminary evidence suggesting that brain-derived neurotrophic factors (BDNFs) may mediate these effects on high-intensity interval activities, such as in football playing. We conducted a systematic review of studies on football players or football task interventions that evaluated the causality of exercise or its relationship with changes in the basal BDNF level. Methods: The search was conducted in PubMed, SPORTDiscus, Cochrane, and FECYT (Web of Sciences, CCC, DIIDW, KJD, MEDLINE, RSCI, and SCIELO) according to the guidelines for performing systematic reviews in the sport sciences field. Results: From the 44 studies initially identified, seven studies were fully reviewed, and their outcome measures were extracted and analysed. In the scientific study of football, the studies published thus far have explored the relationship of serum BDNF levels and other cognitive function factors with the genetic expression of polymorphisms, the anthropometric and fitness conditions, the acute exercise effect of the match, and the typical actions of the match such as heading. Conclusions: The heterogeneity of designs and variables evaluated in studies related to BDNF exercise or interaction and football playing does not allow us to conclusively determine that there is a relationship with the cause or effect of genetic, anthropometric, or conditional factors that derive from an increase in BDNF due to actions during the playing of football.

Keywords: BDNF; neuroplasticity; VEGF; soccer; cognitive function; team sports

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a highly expressed protein molecule that is synthesised in neurons [1]. It has been used as a reliable marker of brain function, cognitive function, and memory; more recently, evidence suggests a role in glucose homeostasis and lipid metabolism [2]. Studies in healthy people and those with pathologies have shown that BDNF seems to promote neurogenesis, synaptic plasticity, and neuroprotection due to its immunomodulatory action [3]. Specifically, sport and exercise science research has shown that this member of the family of neurotrophins responds to physical activity [1].

The release of BDNF into the bloodstream could lead to some neuro- and immunoprotective effects, such as neurodegeneration inhibition, hippocampal neural plasticity, neurogenesis, axonal growth, and synaptogenesis [4,5]. Low basal BDNF levels have been associated with long-time exercise training and physically trained athletes [6,7]. However,

some questions around the discussion of the role of BNDF in physiological cascade events during exercise remain unanswered. Moderate intensity, aerobic exercise could increase basal and post-exercise BNDF levels [8]. During acute aerobic exercise activity, basal BNDF levels increase and upregulate cellular processing of BDNF (e.g., synthesis, release, absorption, and degradation) in well trained, healthy men. In addition, BDNF can be released due to the activity of reactive oxygen species resulting from mitochondrial activity in neurons [9], calcium increase in neurons [10], and lactate synthesis [11]. Subsequently, an increased amount of BDNFs could be released into the bloodstream and absorbed more efficiently by central and peripheral tissues, provoking a cascade of neurotrophic and neuroprotective effects [12].

Nerve growth factor (NGF) and BDNF are members of the neurotrophin family that are reliable markers of brain damage when released into the circulation. Blows/contusions to the head or ball-striking with the head are relevant to increased NGF and BDNF [13]. By considering other reference biomarkers (blood or lactate), the information on the relevance of BNDF on executive functions or neuropsychological responses would be much more complete; however, its influence on attention/concentration, arousal, or decision-making processes is widely assumed [14].

High-intensity training can activate higher BDNF production in the brain than continuous exercise and could increase brain H_2O_2 and TNF-a levels [15,16]. Acute high-intensity exercise also leads to an increase in circulating endocannabinoids [17], crucial in sport-related recovery [18], and an increase in BDNF [17]. In this sense, football playing is characterised by intermittent, repetitive, and high-intensity actions [19]. In addition, actions, such as accelerations and decelerations, as well as peak speed and repeated sprint ability are crucial for performance [20,21]. The role of these movements should be explored in future studies regarding the potential differences in BDNF release rates due to the intensity and number of actions.

Although evidence of the effect of intense exercise on serum BDNF level has recently been shown [17], information regarding how this neurotrophin acts in athletes who regularly perform high-intensity actions is limited. In addition, in competitive sports, it is necessary to consider other factors, such as the stressful effects of competition and injury potential, among other factors that could influence the behaviour of serum BDNF level. Some cognitive (e.g., anger expression and mental fatigue) and behavioural (e.g., coping skills, competitive anxiety, and mental toughness) characteristics of football players [22,23] could also influence changes in serum BDNF level [24]. The available evidence indicates that exercise is an effective strategy for enhancing BDNF activity, with promising preliminary evidence in high-intensity exercise [1]; however, there is a lack of data available regarding football playing. Consequently, in this systematic review, we aimed to describe the current knowledge regarding the acute and long-term effects of football playing on serum BDNF level.

2. Materials and Methods

2.1. Design

This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25] and the guideline for performing systematic reviews in sport sciences [26]. After conducting the search, the studies were classified by year, identifying those that met the inclusion criteria for final consideration and extraction (see Figure 1). Two authors independently reviewed the manuscripts based on risk of bias. The systematic review was conducted considering previously established guidelines, taking into consideration the delimitation of the research question, identification of relevant evidence, evaluation of the quality of the studies, summary of the results, and their interpretation [27].

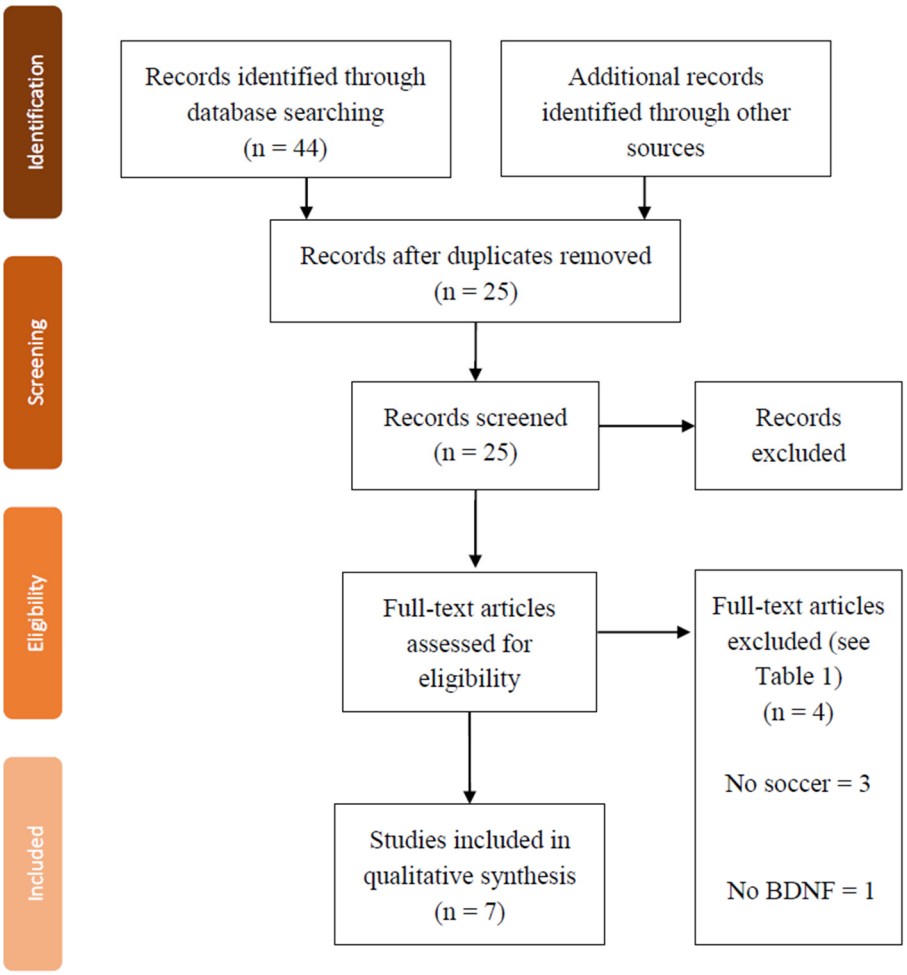

Figure 1. Flow diagram of the study, see Table 1.

Table 1. Inclusion and exclusion criteria.

Item	Inclusion Criteria	Exclusion Criteria
Population	Soccer players of any age and sex without injury or illness reported	Athletes from other sports (basketball, futsal, etc.)
Intervention/exposure	Measures were performed during soccer training or competition	Measures were performed in another context
Comparison/control	Not necessary	-
Outcome	Values related to BDNF were reported	No BDNF-related values were provided
Study design	-	-
Other	Only original and full-text studies written in English	Written in a language other than English. Article types other than the original (e.g., reviews, letters to editors, trial registrations, proposals for protocols, editorials, book chapters, and conference abstracts).

BDNF, brain-derived neurotrophic factor.

2.2. Eligibility Criteria

The title, abstract, and reference list of each paper were screened to locate potentially relevant studies. Additionally, the authors reviewed, in detail, the full version of the included studies to identify papers that met the selection criteria. An additional search within the reference lists of the included studies was conducted to retrieve further relevant studies. The inclusion and exclusion criteria are detailed in Table 1.

2.3. Information Sources and Search

PubMed, SPORTDiscus, Cochrane, and FECYT (Web of Sciences, CCC, DIIDW, KJD, MEDLINE, RSCI, and SCIELO), were searched for relevant publications before 24 November 2021. Keywords and synonyms were entered as various combinations in the title and abstract, or keywords based on other previously published reviews and meta-analyses on BDNF and exercise [28,29]. The selection was determined based on PRISMA's PICOS considering population (soccer OR football) AND outcome (BDNF OR "brain-derived neurotrophic factor" OR neurotrophin). Additionally, the reference lists of the retrieved studies were manually searched by two authors (M.R.-G. and D.R.-V.) to identify potential eligible studies not captured by the electronic searches. Possible errata were explored for each included study. Inconsistencies between the examinations and the selection of studies were resolved by consensus between the authors.

2.4. Data Extraction

Data extraction was prepared in a Microsoft Excel sheet (Microsoft Corporation, Redmond, WA, USA) following the Cochrane Consumers and Communication Review Group's data extraction template [30]. An Excel sheet was used to assess inclusion requirements and subsequently tested for all selected studies. The full text was screened, and articles were excluded due to the population not following inclusion criteria (e.g., Australian football and rugby). All records were stored in the sheet.

2.5. Data Items

Study data were extracted following specific guidelines for systematic reviews and meta-analyses on the effects of exercise on BDNF and executive function [31]. The following information was extracted from the included original studies: aim, sample characteristics, study design, methodological key information, output variables, and main outcomes.

2.6. Methodological Assessment

The methodological assessment process was performed using an adapted version of the STROBE assessment criteria [32], looking at studies eligible for inclusion. Each article was assessed based on 10 specific criteria (see Table 1). Any disagreement was discussed and solved by a consensus decision. Each item was evaluated using numerical characterisation (1 = completed and 2 = non-completed). As suggested by O'Reilly et al. [32], each study rating was qualitatively interpreted using the following law: a study had a risk of bias or low quality with a lower punctuation than 7 points, while those studies with greater punctuations (i.e., $\geq$7) were considered to be low risk of bias or high-quality studies.

3. Results

3.1. Study Identification and Selection

The results of the database search identified a total of 44 titles. These studies were exported to reference manager software (EndNote™ X9, Clarivate Analytics, Philadelphia, PA, USA). Duplicates (19 references) were subsequently removed either automatically or manually. The remaining 25 articles were screened for their relevance based on titles and abstracts, resulting in the removal of a further 14 studies. Following the screening procedure, 11 papers were selected for in-depth reading and analysis. After reading full texts and removing four studies that did not meet the population required characteristics, seven studies were included in the qualitative synthesis (Figure 1).

3.2. Methodological Quality

The overall methodological quality scores of the studies can be found in Table 2, which were evaluated by two authors individually. Overall, three studies had scores of 10 points assigned for the 10 items evaluated, two studies scored 9 points, one study scored 8 points, and one study scored 7 points.

Table 2. Methodological assessment of the included studies.

Reference	1	2	3	4	5	6	7	8	9	10	Quality
Murtagh et al. [33]	X	X	X	X	X	X	X	X	X	X	10
Babaei et al. [6]	X	X	X	-	X	X	X	-	X	-	7
Bamaç et al. [34]	X	X	X	X	X	X	X	X	X	-	9
Roh et al. [35]	X	X	X	X	X	X	X	X	X	-	9
Yang, Jung-Su et al. [36]	X	X	X	X	X	X	X	-	X	-	8
Williams et al. [37]	X	X	X	X	X	X	X	X	X	X	10
Hunter et al. [38]	X	X	X	X	X	X	X	X	X	X	10

Note: In the abstract, provide an informative and balanced summary of what was done and what was found (item 1); state specific objectives, including any prespecified hypotheses (item 2); provide the eligibility criteria, and the sources and methods of selection of participants (item 3); for each variable of interest, provide sources of data and details of methods of assessment (measurement), and describe comparability of assessment methods if there is more than one group (item 4); explain how quantitative variables were handled in the analyses, and, if applicable, describe which groupings were chosen and why (item 5); provide characteristics of study participants (item 6); summarize key results with reference to study objectives (item 7); discuss limitations of the study, considering sources of potential bias or imprecision, as well as discuss both direction and magnitude of any potential bias (item 8); give a cautious overall interpretation of results considering objectives, limitations, a multiplicity of analyses, results from similar studies, and other relevant evidence (item 9); provide the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (item 10).

3.3. Characteristics of Individual Studies

Details of the characteristics of the studies that reported BDNF in football are summarized in Table 3. A total of 946 football players of different levels participated in the studies (25 college, 34 master, 16 adolescent, and 864 professional/elite players) and 42 persons were assigned to control groups. Four studies also used a cross-sectional and comparative design, one study used a counterbalanced crossover intervention on a longitudinal follow-up, and one study used a quasi-experimental approach.

In addition, studies explored the association of serum BDNF level or polymorphisms expression with physical or technical testing (n = 3), memory or cognitive function (n = 3), and environmental conditions (e.g., temperature) (n = 1). Physical tests performed were countermovement jump (n = 1), heading (n = 2), agility test (n= 1), and sprints (n = 1). Among the cognitive tests were Stroop (n = 3) and Sternberg (n = 1). The polymorphisms, genes, and blood level biomarkers were: ACTN3 (n = 1), Val66Met (n = 1), PPARA (n = 1), NOS3 (n = 1), IGF-1 (n = 2), plasma fTRP (n = 1), AGT and NGF (n = 2).

3.4. Main Outcomes of Studies

Figure 2 shows a summary of results of the seven studies included in this systematic review, highlighting the most relevant outcomes of each investigation. The results of cross-sectional studies showed that 60 and 100 min of football playing acutely increased BDNF, NGF, and IGF-1 levels [36–39]. In addition, aerobic (e.g., shuttle run) and anaerobic (e.g., Rast Test) tasks provoked an increase in serum BDNF level. The players with BDNF CC homozygote polymorphism expression could sprint faster and jump farther than the players who were A and T allele carriers [33].

Football activity has been shown to improve neurocognitive functions (e.g., Stroop test scores) [37–39] and memory performance [6,37]. The higher the serum BDNF level identified, the better the memory was [6]. Finally, repeated heading leading to microtrauma provoked an increase in serum BDNF level [34] and less impaired remyelination [38]. In addition, exercise activity in the heat has been shown to provoke lower BDNF release and better cognitive function scores [35].

Table 3. Characteristics of studies based on sample, design, and outcomes.

Ref.	Aim	Sample	Design	Methodological Information	Output Variables	Main Outcomes
Murtagh et al. [33]	Association of multiple single nucleotide polymorphisms (SNPs) with athlete status and power/speed performance in elite male youth football players (ESP) and control participants (CON) at different stages of maturity	535 elite football players (8–23 years) and 151 healthy adults (9–26 years)	Cross-sectional comparative	Relationship between allele and genotype frequency distribution and the field tests performance	Genotype and allele frequency distribution Bilateral vertical and horizontal countermovement jump 10–20 m Sprints 505 Agility test	Elite football players presented higher ACTN3 (XX), PPARA (C allele), AGT (GG), and NOS3 (T allele) frequency distribution. Football players with BDNF (CC) homozygotes sprint quicker and jump farther than players who are A allele and T allele carriers.
Babaei et al. [6]	Evaluate the basal BDNF level and memory performance, also the responsiveness of BDNF regulation system to acute aerobic and anaerobic training in athletes and sedentary groups	Study 1: 25 Master football players (45–65 years) and 22 sedentary adults Study 2: 19 Master football players (45–65 years) and 20 sedentary adults	Study 1: Cross-sectional comparative Study 2: Quasi-experimental	Study 1 (Longitudinal comparative): Basal serum BDNF, platelets, and memory performance comparison between groups Study 2: Test results change after a single bout of aerobic (shuttle run, n = 20) and anaerobic n = 19, Rast test exercise	BDNF Platelets Memory task	Study 1: Athletes had higher basal BDNF levels, better memory. Study 2: An increase in BDNF level after aerobic and anaerobic tasks in both groups
Bamaç et al. [34]	Determine the effects of heading training on serum nerve growth factor (NGF) and BDNF levels in football players	17 Professional male football players (age 24 ± 4.4 years)	Cross-sectional comparative	Players performed 15 headings after corner kicks (30–35 m far) in about 20–25 min	BDNF NGF	BDNF and NGF levels increased after repeated heading training due to microtrauma
Roh et al. [35]	Investigate the effects of fluid ingestion during exercise in different environments on the serum brain-derived neurotrophic factor and cognition among athletes	Ten collegiate male football and rugby players	Cross-sectional comparative	Players performed running tests (60 min each) in four conditions: a. Thermoneutral temperature at 18 °C b. High ambient temperature at 32 °C without fluid ingestion c. High ambient temperature at 32 °C with water ingestion d. High ambient temperature at 32 °C with sports drink ingestion	BDNF Stroop Colour and Word Test scores IGF-1 Plasma f-TRP	Running performed in a thermoneutral environment improved cognitive function and presented higher BDNF levels than those performed in hot environments. Liquid intake may counteract the negative heat effects on BDNF exertion.

Table 3. *Cont.*

Ref.	Aim	Sample	Design	Methodological Information	Output Variables	Main Outcomes
Yang, Jung-Su et al. [36]	Investigate the effects of acute football match on serum levels of neurotrophins and neurocognitive function	15 Healthy male adolescents	Cross-sectional comparative	Participants were evaluated three times: before, after treatment and two hours after treatment; the two treatments (100 min) were football match vs. self-study	BDNF NGF IGF-1 Stroop Colour and Word Test	Stroop test scores, BDNF, NGF, and IGF-1 increased after the football match and were higher than self-study conditions
Williams et al. [37]	Examine the effect of an acute bout of outdoor football activity on information processing, inhibitory control, working memory, and circulating BDNF in adolescents	36 Adolescents (16 girls)	Counterbalanced crossover	Two conditions were 60 min football session and 60 min sitting	BDNF levels Stroop Test Sternberg Paradigm	BDNF level was not affected by football activity or physical fitness The high-fit group presented better Stroop task and Sternberg paradigm results
Hunter et al. [38]	Examine the potential effect modifying role of the BDNF Val66Met polymorphism on the association of football heading with white matter microstructure	312 Football players	Longitudinal follow-up comparative	Met allele expression and reported sub-concussive heading in football was assessed throughout two years	BDNF Val66Met polymorphism Self-reported total heading in the prior 12 months Diffusion tensor imaging	BDNF Val66Met (+) football players with long-term exposure to high levels of heading exhibit less low radial diffusivity (impaired remyelination)

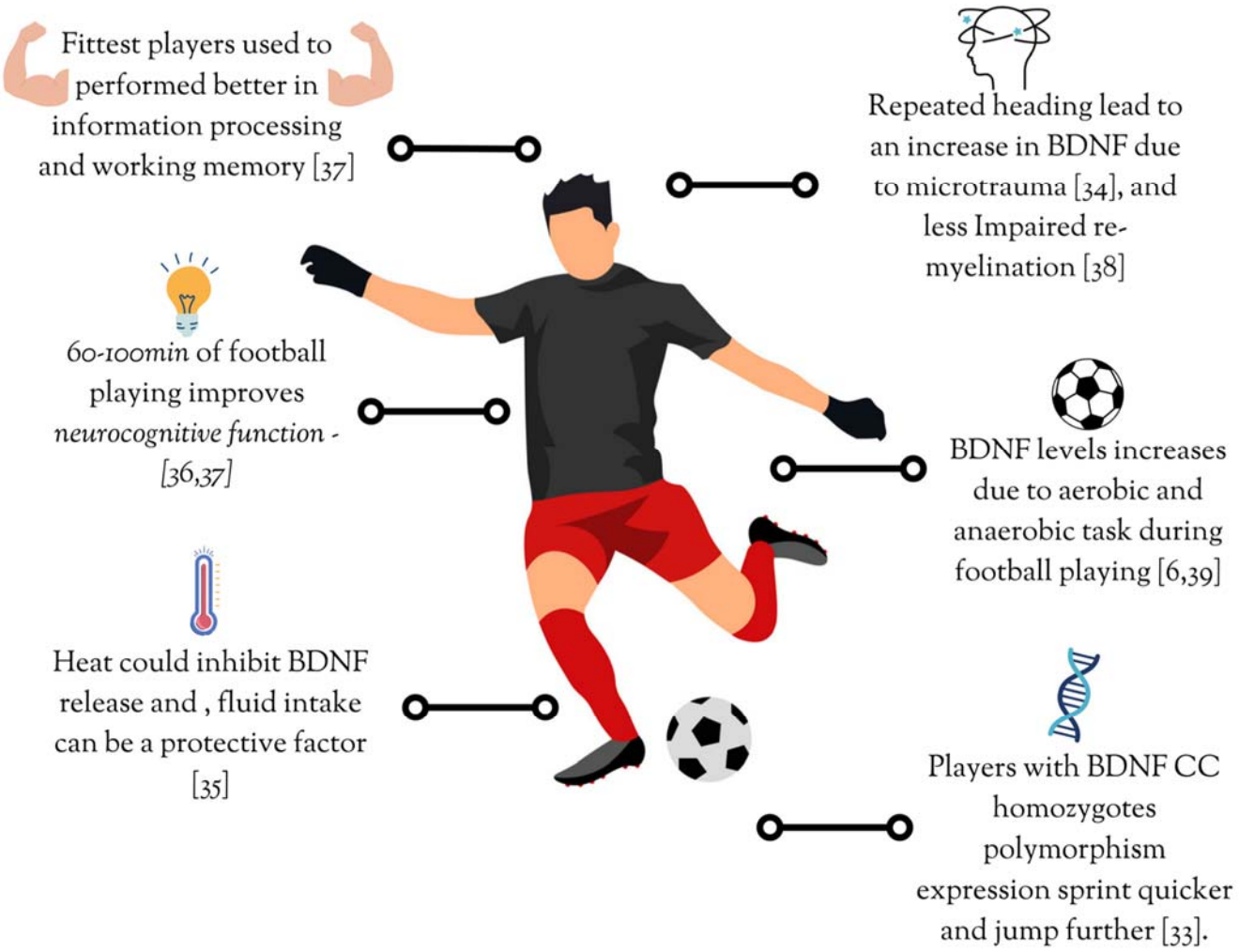

Figure 2. Main outcomes of studies analysing the effects of football playing on brain-derived neurotrophic factor levels [6,33,39].

4. Discussion

In this systematic review, we examined studies on football players or football task interventions that evaluated the causality of exercise or its relationship with changes in basal BDNF level. Few studies showed the effect of a football match on BDNF concentrations [36,37]. On the one hand, one study found a significant increase in serum BDNF level after a 90 min match in 15-year-old adolescents [39]. On the other hand, after a 60 min football match, it was reported that the BDNF level was not altered in 12-year-old adolescents [37]. Other studies have been conducted with football players as subjects, which evaluated the responses of their neurotrophic factor to different types of training [6,35], the effect of frequent heading [34], as well as the influence of polymorphism on expression [33,38].

BDNF concentrations increase immediately after physical aerobic, anaerobic, and high-intensity exercise [35,39]. Some meta-analyses have reported that this response is conditioned by factors, such as the duration and intensity of the efforts, the type of exercise, frequency, and duration of the intervention, as well as gender [40,41]. Exercise intensity must be at least 65% of VO2max to show a linear relationship with BDNF concentration [41]. The BDNF level can increase by around 60% in the blood at the peripheral level as an acute response and there is a greater release in activities that exceed 30 min [40].

The physical fitness of the participants has also been found to affect the release of BDNF, although the results were different. In 12-year-olds with high fitness, no change in serum BDNF levels was observed [37]. The physical and physiological adaptations generated by training programs can also affect BDNF responses [8]. Interestingly, in some studies, lower concentrations of BDNF have been observed in football players [6] or adults who perform more physical activities than sedentary adults [7]. Low concentrations of this neurotrophic factor have been found in football players; an inverse correlation was even found between VO2max and BDNF, i.e., BDNF levels were higher in those with a low cardiorespiratory capacity [6]. When a sample of non-athletic men was analysed, it was found that those people who presented a vigorous level of physical activity had low BDNF levels [7].

BDNF contributes to an improvement in cognitive responses; in football players, it has been evaluated using a memory test and information processing and the domain of inhibitory control. The evidence suggests that there is better performance in the Stroop Colour Word test [36]. The physical fitness of adolescent football players can also be considered to be a factor that modulates these cognitive responses after a match [37]. A study indicated that environmental conditions could affect the release of neurotransmitters, and therefore could influence cognitive functions [35]. It has also been concluded that the immediate effects of BDNF release after anaerobic training on master football players did not seem to imply memory capacity [6]. Indeed, the outcomes of this review suggest that football playing improves neurocognitive function [38,39]. The fittest players performed better in information processing and working memory tasks [36], suggesting a role of BDNF release in cognitive function during these sporting activities.

It has been reported that both aerobic and resistance exercises trigger the peripheral release of BDNF [40]; however, it has been found that transient increases in peripheral BDNF are more prone with aerobic exercise than with resistance exercise [12]. Little evidence has evaluated changes in BDNF in high-intensity activities [2]. However, in male adults (not football players), it has been shown that the execution of short series of high-intensity exercises (90% HRmax) alternated with similar periods of rest (1:1) can lead to a greater release of serum BDNF than continuous high-intensity exercise (70% HRmax) [16]. During a protocol of 1 min of effort at 100% VO2peak and 1 min of rest (1:1), a significant increase in BDNF level was observed immediately at the end of the exercise, although it decreased 60 min later [15].

During anaerobic exercises of high intensity, BDNF can be released to counteract the lack of oxygenation in the brain. Between 70 and 80% of the surrounding BDNF is contributed by the brain [42]. Likewise, it has been stated that lactate can promote the release of BDNF [43], and therefore BDNF concentration increases after high-intensity exercise, even after maintaining its level in post-exercise rest periods [14]. Serum BDNF levels after physical efforts may decrease due to their use in lipid metabolism that occurs at the peripheral level [42].

Another factor that can modulate BDNF secretion is hydration status and neuromuscular fatigue [35]. On the one hand, serum BDNF levels increased in a small group of young football and rugby players, who ran for 60 min at 75% of the heart rate reserve in a thermoneutral environment (18 °C), as well as in a high-temperature environment (32 °C), drinking water or sports drinks for hydration. On the other hand, when this same group was prohibited hydration in a high-temperature environment (32 °C), serum BDNF levels decreased immediately after the run [35]. Coaches and athletes should address that heat could inhibit BDNF release and that fluid intake can be a protective factor [37]; therefore, hydration protocols should be defined during training and competition to allow regular acute BDNF responses.

BDNF polymorphisms have been evaluated [33,38]. Considering the implications of gene expression on BDNF release levels, two studies in football players suggested that players with BDNF CC homozygote polymorphism expression sprinted quicker and jumped farther [33]. A study assessed BDNF (rs6265) CC (also known as Val 66 Met)

and its relationship with physical tests, and found that the homozygous BDNF (CC) was associated with faster running speed and jumping capacity [33]. In contrast, in a recent study, the Val 66 Met gene was shown to be associated with poor motor performance in basketball players [44].

In another study, the relationship between BDNF Val 66 Met polymorphism with repeated heading was explored, and showed that players with Met (+) showed an association between high exposure to heading and low radial diffusivity [38], which indicated an affectation in the myelination of the axons, which could be reflected even in functional tests [38]. A previous systematic review has also shown that this polymorphism (BDNF Val 66 Met) could affect the release and concentration of BDNF [40]. Although it has been known that BDNF stimulates myelination, a high frequency of heading can affect it [38].

Given the characteristics of football, players have frequent contacts between the ball and their heads. Although this area has not been as well addressed in studies and the conclusions are not precise, an association has been reported between head butting and structural level affectations determined by neuroimaging techniques, as well as in the release or restrictions of neurotransmitters [13]. Repeated heading can cause increases in serum BDNF associated with microtrauma [34]. Increased peripheral BDNF and NGF levels have been associated with the recovery of possible damage generated by trauma in the central nervous system caused by contact with the ball [13,34]. Considering these results, soccer players should be monitored for the amount and severity of headings they perform during training to avoid microtrauma and subsequent inhibition of BDNF release. These actions should be considered, especially in young populations and masters, who have fewer protective factors.

Finally, from a cognitive and decision-making point of view during the match, adequate levels of BDNF in soccer players could provoke a better predisposition to avoid aggressive and anger misexpression and emotion control [22,23]. In addition, players may have better coping skills and preferable management of competitive anxiety [22,23]. Understanding the influence of changes in BDNF level on the cognition and behaviour of football players is critical [24], particularly during sessions of learning new technical, tactical, and behavioural skills, as well as during the sensitive stages of the development of young players.

Guidelines for Future Research

There is clearly a lack of evidence regarding the study of the effects of football competition or training on the expression of BDNF. The heterogeneity of the few studies analysed in this review does not allow for definitive conclusions regarding the impact of football playing on the expression of this neurotrophic factor. Consequently, it is difficult to understand the effects that the habitual practice of football (training or competition) can generate at the neurophysiological level.

Considering that this systematic review has presented the evidence described so far on this topic, this information can serve as a basic guide for future approaches to research problems. Future studies should focus on understanding the physiological cascade of BDNF expression in high-intensity sports, such as team sports. Additionally, understanding the relationship between players' external and internal loads and the physiological and cognitive behaviour of BDNF is critical to guide practical interventions.

The absence of longitudinal studies on this topic limits the comprehension of the chronic effects associated with football on BDNF concentrations at the peripheral and brain levels. In addition, it is necessary to determine its influence on cognitive tasks, and its practical implications in the field. It is also crucial to explore the effects of the different types of football training tasks (e.g., multitasking, analytic, and global) on the release of BDNF. These studies must consider differences by sex, competitive level (e.g., professionals or amateur), age (e.g., master, elite, or youth), environmental conditions (e.g., heat or cold), and other contextual factors (e.g., public presence, pressure due to elimination, stress and

anxiety, programming phase, or load balanced recovery) that could influence the release of BDNF at the acute level, and also its long-term implications.

More evidence is needed regarding the effects that exposure to highly stressful settings may have at cognitive (e.g., mental fatigue, sleep disorders), physical (e.g., trauma injuries, repetitive mechanical injuries, concussion), emotional (e.g., sports-related anxiety), and physiological (e.g., heat stress) levels on the dynamics of BDNF release in athletes.

It is key to understand the physiological dynamics of the release of BDNF in high-impact activities, high metabolic load, and the high-load intensity characteristics of football. Finally, the interrelation between the neurophysiological behaviour of BDNF and the genetic expression of the specific polymorphism related to this neurotrophin, anthropometric factors, and other structural and functional factors that may specifically influence football players, must be established.

5. Conclusions

Although interest in studying the effects of physical exercise on the acute release of BDNF and its chronic implications is growing, this is a grey area in team sports science knowledge. Likewise, the heterogeneity of designs and variables evaluated in studies related to the effects of football-playing on BDNF expression does not allow to conclude with certainty the interrelation and its impact on cognitive and neurophysiological function. Based on the evidence published thus far, this review provides a series of considerations for the design of future research in the field of sports science performance analysis in sport and sports medicine, specifically in football.

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References

1. Szuhany, K.L.; Bugatti, M.; Otto, M.W. A Meta-Analytic Review of the Effects of Exercise on Brain-Derived Neurotrophic Factor. *J. Psychiatr. Res.* **2015**, *60*, 56–64. [CrossRef]
2. Jiménez-Maldonado, A.; Rentería, I.; García-Suárez, P.C.; Moncada-Jiménez, J.; Freire-Royes, L.F. The Impact of High-Intensity Interval *Train.* on Brain Derived Neurotrophic Factor in Brain: A Mini-Review. *Front. Neurosci.* **2018**, *12*, 1–9. [CrossRef]
3. Bathina, S.; Das, U.N. Brain-Derived Neurotrophic Factor and Its Clinical Implications. *Arch. Med. Sci.* **2015**, *11*, 1164–1178. [CrossRef]
4. Fernandes, J.; Arida, R.M.; Gomez-Pinilla, F. Physical Exercise as an Epigenetic Modulator of Brain Plasticity and Cognition. *Neurosci. Biobehav. Rev.* **2017**, *80*, 443–456. [CrossRef]
5. Tapia-Arancibia, L.; Aliaga, E.; Silhol, M.; Arancibia, S. New Insights into Brain BDNF Function in Normal Aging and Alzheimer Disease. *Brain Res. Rev.* **2008**, *59*, 201–220. [CrossRef] [PubMed]
6. Babaei, P.; Damirchi, A.; Mehdipoor, M.; Tehrani, B.S. Long Term Habitual Exercise Is Associated with Lower Resting Level of Serum BDNF. *Neurosci. Lett.* **2014**, *566*, 304–308. [CrossRef]
7. Nofuji, Y.; Suwa, M.; Moriyama, Y.; Nakano, H.; Ichimiya, A.; Nishichi, R.; Sasaki, H.; Radak, Z.; Kumagai, S. Decreased Serum Brain-Derived Neurotrophic Factor in Trained Men. *Neurosci. Lett.* **2008**, *437*, 29–32. [CrossRef] [PubMed]
8. Zoladz, J.A.; Pilc, A.; Majerczak, J.; Grandys, M.; Zapart-Bukowska, J.; Duda, K. Endurance Training Increases Plasma Brain-Derived Neurotrophic Factor Concentration in Young Healthy Men. *J. Physiol. Pharmacol.* **2008**, *59* (Suppl. 7), 119–132.

9. Radak, Z.; Suzuki, K.; Higuchi, M.; Balogh, L.; Boldogh, I.; Koltai, E. Physical Exercise, Reactive Oxygen Species and Neuroprotection. *Free Radic. Biol. Med.* **2016**, *98*, 187–196. [CrossRef] [PubMed]
10. Kahlert, S.; Zündorf, G.; Reiser, G. Glutamate-Mediated Influx of Extracellular Ca^{2+} Is Coupled with Reactive Oxygen Species Generation in Cultured Hippocampal Neurons but Not in Astrocytes. *J. Neurosci. Res.* **2005**, *79*, 262–271. [CrossRef] [PubMed]
11. Bergersen, L.H. Lactate Transport and Signaling in the Brain: Potential Therapeutic Targets and Roles in Body—Brain Interaction. *J. Cereb. Blood Flow Metab.* **2015**, *35*, 176–185. [CrossRef] [PubMed]
12. Knaepen, K.; Goekint, M.; Heyman, E.M.; Meeusen, R. Neuroplasticity—Exercise-Induced Response of Peripheral Brain-Derived Neurotrophic Factor: A Systematic Review of Experimental Studies in Human Subjects. *Sports Med.* **2010**, *40*, 765–801. [CrossRef] [PubMed]
13. Rodrigues, A.C.; Lasmar, R.P.; Caramelli, P. Effects of Soccer Heading on Brain Structure and Function. *Front Neurol.* **2016**, *7*, 38. [CrossRef]
14. Hashimoto, T.; Fukui, K.; Takeuchi, H.; Yokota, S.; Kikuchi, Y.; Tomita, H.; Taki, Y.; Kawashima, R. Effects of the BDNF Val66Met Polymorphism on Gray Matter Volume in Typically Developing Children and Adolescents. *Cerebral Cortex* **2016**, *26*, 1795–1803. [CrossRef]
15. Cabral-Santos, C.; Castrillón, C.I.M.; Miranda, R.A.T.; Monteiro, P.A.; Inoue, D.S.; Campos, E.Z.; Hofmann, P.; Lira, F.S. Inflammatory Cytokines and BDNF Response to High-Intensity Intermittent Exercise: Effect the Exercise Volume. *Front. Physiol.* **2016**, *7*, 1–8. [CrossRef]
16. Saucedo Marquez, C.M.; Vanaudenaerde, B.; Troosters, T.; Wenderoth, N. High-Intensity Interval Training Evokes Larger Serum BDNF Levels Compared with Intense Continuous Exercise. *J. Appl. Physiol.* **2015**, *119*, 1363–1373. [CrossRef] [PubMed]
17. Heyman, E.; Gamelin, F.-X.; Goekint, M.; Piscitelli, F.; Roelands, B.; Leclair, E.; Di Marzo, V.; Meeusen, R. Intense Exercise Increases Circulating Endocannabinoid and BDNF Levels in Humans—Possible Implications for Reward and Depression. *Psychoneuroendocrinology* **2012**, *37*, 844–851. [CrossRef] [PubMed]
18. Rojas-Valverde, D. Potential Role of Cannabidiol (CBD) on Sport Recovery: A Narrative Review. *Front. Physiol.* **2021**, *12*, 722550. [CrossRef]
19. Iaia, F.M.; Ermanno, R.; Bangsbo, J. High-Intensity Training in Football. *Int. J. Sports Physiol. Perform.* **2009**, *4*, 291–306. [CrossRef]
20. Schimpchen, J.; Gopaladesikan, S.; Meyer, T. The Intermittent Nature of Player Physical Output in Professional Football Matches: An Analysis of Sequences of Peak Intensity and Associated Fatigue Responses. *Eur. J. Sport Sci.* **2021**, *21*, 793–802. [CrossRef]
21. Oliva-Lozano, J.M.; Rojas-Valverde, D.; Gómez-Carmona, C.D.; Fortes, V.; Pino-Ortega, J. Impact of Contextual Variables on The Representative External Load Profile of Spanish Professional Soccer Match-Play: A Full Season Study. *Eur. J. Sport Sci.* **2020**, *21*, 497–506. [CrossRef] [PubMed]
22. Junge, A.; Dvorak, J.; Rösch, D.; Graf-Baumann, T.; Chomiak, J.; Peterson, L. Psychological and Sport-Specific Characteristics of Football Players. *Am. J. Sports Med.* **2000**, *28*, S22–S28. [CrossRef]
23. Terpstra, A.R.; Vasquez, B.P.; Colella, B.; Tartaglia, M.C.; Tator, C.H.; Mikulis, D.; Davis, K.D.; Wennberg, R.; Green, R.E.A. Comprehensive Neuropsychiatric and Cognitive Characterization of Former Professional Football Players: Implications for Neurorehabilitation. *Front. Neurol.* **2019**, *10*, 712. [CrossRef] [PubMed]
24. Piepmeier, A.T.; Etnier, J.L. Brain-Derived Neurotrophic Factor (BDNF) as a Potential Mechanism of the Effects of Acute Exercise on Cognitive Performance. *J. Sport Health Sci.* **2015**, *4*, 14–23. [CrossRef]
25. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
26. Rico-González, M.; Pino-Ortega, J.; Clemente, F.; Los Arcos, A. Guidelines for Performing Systematic Reviews in Sports Science. *Biol. Sport* **2022**, *39*, 463–471. [CrossRef]
27. Khan, K.S.; Kunz, R.; Kleijnen, J.; Antes, G. Five Steps to Conducting a Systematic Review. *J. R. Soc. Med.* **2003**, *96*, 118–121. [CrossRef]
28. Fernández-Rodríguez, R.; Álvarez-Bueno, C.; Martínez-Ortega, I.A.; Martínez-Vizcaíno, V.; Mesas, A.E.; Notario-Pacheco, B. Immediate Effect of High-Intensity Exercise on Brain-Derived Neurotrophic Factor in Healthy Young Adults: A Systematic Review and Meta-Analysis. *J. Sport Health Sci.* **2021**, in press. [CrossRef]
29. de Azevedo, K.P.M.; de Oliveira, V.H.; de Medeiros, G.C.B.S.; de Sousa Mata, Á.N.; García, D.Á.; Martínez, D.G.; Leitão, J.C.; Knackfuss, M.I.; Piuvezam, G. The Effects of Exercise on BDNF Levels in Adolescents: A Systematic Review with Meta-Analysis. *Int. J. Environ. Res. Public Health* **2020**, *17*, 6056. [CrossRef]
30. Prictor, M.; Hill, S. Cochrane Consumers and Communication Review Group: Leading the Field on Health Communication Evidence. *J. Evid.-Based Med.* **2013**, *6*, 216–220. [CrossRef] [PubMed]
31. de Azevedo, K.P.M.; de Oliveira Segundo, V.H.; de Medeiros, G.C.B.S.; de Sousa Mata, Á.N.; García, D.Á.; de Carvalho Leitão, J.C.G.; Knackfuss, M.I.; Piuvezam, G. Effects of Exercise on the Levels of BDNF and Executive Function in Adolescents. *Medicine* **2019**, *98*, e16445. [CrossRef]
32. O'Reilly, M.; Caulfield, B.; Ward, T.; Johnston, W.; Doherty, C. Wearable Inertial Sensor Systems for Lower Limb Exercise Detection and Evaluation: A Systematic Review. *Sports Med.* **2018**, *48*, 1221–1246. [CrossRef]

33. Murtagh, C.F.; Brownlee, T.E.; Rienzi, E.; Roquero, S.; Moreno, S.; Huertas, G.; Lugioratto, G.; Baumert, P.; Turner, D.C.; Lee, D.; et al. The Genetic Profile of Elite Youth Soccer Players and Its Association with Power and Speed Depends on Maturity Status. *PLoS ONE* **2020**, *15*, e0234458. [CrossRef]
34. Bamaç, B.; Tamer, G.S.; Colak, T.; Colak, E.; Seyrek, E.; Duman, C.; Colak, S.; Ozbek, A. Effects of repeatedly heading a soccer ball on serum levels of two neurotrophic factors of brain tissue, BDNF and NGF, in professional soccer players. *Biol. Sport* **2011**, *28*, 177–181. [CrossRef]
35. Roh, H.-T.; So, W.-Y.; Cho, S.-Y.; Suh, S.-H. Effects of Fluid Ingestion on Brain-Derived Neurotrophic Factor and Cognition during Exercise in the Heat. *J. Hum. Kinet.* **2017**, *58*, 73–86. [CrossRef]
36. Yang, J.S.; Yoo, S.H.; Cho, S.Y.; Roh, H.T. Effects of Acute Soccer Game on Serum Levels of Neurotrophins and Neurocognitive Functions in Male Adolescents. *J. Life Sci.* **2012**, *22*, 1444–1450. [CrossRef]
37. Williams, R.A.; Cooper, S.B.; Dring, K.J.; Hatch, L.; Morris, J.G.; Sunderland, C.; Nevill, M.E. Effect of Football Activity and Physical Fitness on Information Processing, Inhibitory Control and Working Memory in Adolescents. *BMC Public Health* **2020**, *20*, 1398. [CrossRef] [PubMed]
38. Hunter, L.E.; Freudenberg-Hua, Y.; Davies, P.; Kim, M.; Fleysher, R.; Stewart, W.F.; Lipton, R.B.; Lipton, M.L. BDNF Val66Met Positive Players Demonstrate Diffusion Tensor Imaging Consistent with Impaired Myelination Associated with High Levels of Soccer Heading: Indication of a Potential Gene-Environment Interaction Mechanism. *Front. Neurol.* **2019**, *10*, 1297. [CrossRef]
39. Yang, C.; Li, Y.; Du, M.; Chen, Z. Recent Advances in Ultrasound-Triggered Therapy. *J. Drug Target* **2019**, *27*, 33–50. [CrossRef]
40. Dinoff, A.; Herrmann, N.; Swardfager, W.; Lanctôt, K.L. The Effect of Acute Exercise on Blood Concentrations of Brain-Derived Neurotrophic Factor in Healthy Adults: A Meta-Analysis. *Eur. J. Neurosci.* **2017**, *46*, 1635–1646. [CrossRef]
41. Feter, N.; Alt, R.; Dias, M.G.; Rombaldi, A.J. How Do Different Physical Exercise Parameters Modulate Brain-Derived Neurotrophic Factor in Healthy and Non-Healthy Adults? A Systematic Review, Meta-Analysis and Meta-Regression. *Sci. Sports* **2019**, *34*, 293–304. [CrossRef]
42. Rasmussen, P.; Brassard, P.; Adser, H.; Pedersen, M.V.; Leick, L.; Hart, E.; Secher, N.H.; Pedersen, B.K.; Pilegaard, H. Evidence for a Release of Brain-Derived Neurotrophic Factor from the Brain during Exercise. *Exp. Physiol.* **2009**, *94*, 1062–1069. [CrossRef] [PubMed]
43. Schiffer, T.; Schulte, S.; Sperlich, B.; Achtzehn, S.; Fricke, H.; Strüder, H.K. Lactate Infusion at Rest Increases BDNF Blood Concentration in Humans. *Neurosci. Lett.* **2011**, *488*, 234–237. [CrossRef] [PubMed]
44. Deveci, S.Ş.; Matur, Z.; Kesim, Y.Y.; Senturk, G.G.; Sargın-Kurt, G.G.; Ugur, S.A.; Öge, A.E. Effect of the Brain-Derived Neurotrophic Factor Gene Val66Met Polymorphism on Sensory-Motor Integration during a Complex Motor Learning Exercise. *Brain Res.* **2020**, *1732*, 146652. [CrossRef]