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High magnitude exposure to repetitive head impacts alters female adolescent brain activity for lower extremity motor control

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.brainres.2024.148785.

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Abstract

Contact and collision sport participation among adolescent athletes has raised concerns about the potential negative effects of cumulative repetitive head impacts (RHIs) on brain function. Impairments from RHIs and sports-related concussions (SRC) may propagate into lingering neuromuscular control. However, the neural mechanisms that link RHIs to altered motor control processes remain unknown. The purpose of this study was to isolate changes in neural activity for a lower extremity motor control task associated with the frequency and magnitude of RHI exposure. A cohort of fifteen high school female soccer players participated in a prospective longitudinal study and underwent pre- and post-season functional magnetic resonance imaging (fMRI). During fMRI, athletes completed simultaneous bilateral ankle, knee, and hip flexion/extension movements against resistance (bilateral leg press) to characterize neural activity associated with lower extremity motor control. RHI data were binned into continuous categories between 20 g – 120 g (defined by progressively greater intervals) with the number of impacts independently modeled within the fMRI analyses. Results revealed that differential exposure to high magnitude RHIs ($\geq 90\ g$ - $< 110\ g$ and $\geq 110\ g$) was associated with acute changes in neural activity for the bilateral leg press (broadly inclusive of motor, visual, and cognitive regions; all $p < 0.05$ & $z > 3.1$). Greater exposure to high magnitude RHIs may impair lower extremity motor control through maladaptive neural mechanisms. Future work is warranted to extend these mechanistic findings and examine the linkages between RHI exposure and neural activity as it relates to subsequent neuromuscular control deficits.

Keywords

fMRI; Bilateral Motor Control; Repetitive Head Impacts; Female Adolescent Athletes

1. Introduction

Sports-related concussion (SRC) is a significant public health concern, particularly among adolescent populations. With an estimated 1.9 million SRCs occurring annually (Bryan et al., 2016; Meehan et al., 2011), SRCs are one of the leading causes of mild traumatic brain injuries among adolescent athletes (Ali et al., 2019). SRCs can result in altered brain structure, brain function, and clinical symptoms such as headaches, confusion, and cognitive impairment (Hallock et al., 2023). Though athletes on average return to sport (RTS) within one month of SRC (Patricios et al., 2023) there is some evidence that alterations in brain structure, brain function, and cognition remain (Churchill et al., 2017a; Churchill et al., 2017b; Dettwiler et al., 2014; Hallock et al., 2023; Zuleger et al., 2023). The prolonged effects of SRC on the central nervous system (CNS) are theorized to negatively impact neuromuscular control (Wilkerson et al., 2017) and increase the risk for lower extremity injury after RTS (Howell et al., 2018; McPherson et al., 2019). Specifically, following SRC, and upon RTS, athletes exhibit lingering neuromuscular control impairments in dual-task gait and balance (Howell et al., 2017; Howell et al., 2020; Howell et al., 2018; Howell et al., 2015), landing kinematics, and joint stiffness (Dubose et al., 2017; Lapointe et al., 2018). Furthermore, the odds of sustaining a lower extremity injury have been noted to be as high as 3.39 times higher in athletes following SRC relative to non-concussed athletes (Herman et al., 2017), with reports of female athletes showing an elevated risk of lower extremity injury following SRC (Biese et al., 2021), in conjunction with prolonged recovery and more severe concussions compared to their male counterparts (McGroarty et al., 2020). Although SRCs are associated with CNS alterations, neuromuscular control deficits, and subsequent lower extremity injury, SRCs are less prevalent in sports than repetitive head impacts (RHIs). Interestingly, RHIs may have similar effects on the CNS as SRCs, despite a lack of overt clinical concussion symptoms associated with RHIs.

Prolonged exposure to RHIs has been associated with changes in brain structure and brain function. Specifically, greater RHI exposure is associated with changes in white matter structural integrity (Koerte et al., 2023), altered task-related neural activity (Jain et al., 2023; Talavage et al., 2014), altered functional connectivity (a measure of brain function in resting-state conditions) (Abbas et al., 2015; Cassoudesalle et al., 2020), and increased corticomotor inhibition within the primary motor cortex (Di Virgilio et al., 2016); all consistent with SRC (Churchill et al., 2017b; De Beaumont et al., 2007; Meier et al., 2020; Zuleger et al., 2023). While SRCs and RHIs may share an overlap in the effects on the CNS, the extent to which RHIs affect the CNS, as well as downstream neuromuscular function and lower extremity injury risk, likely varies based on the relative magnitude (measured *g* forces) and frequency (number of hits sustained) of the hits. For example, findings from a recent prospective longitudinal trial in high school football athletes revealed that pre- to post-season changes in the diffusion and anisotropic properties of white matter were associated with greater exposure to high magnitude RHIs (>110 *g* – 140 *g*) (Diekfuss et al., 2021). Additionally, athletes who sustained a higher distribution of per-practice impacts exceeding > 80 *g* exhibited greater increases in resting state connectivity within the default mode network, suggesting that the frequency of high magnitude impacts is associated with observable changes in brain function (Slobounov et al., 2017). With prior literature demonstrating both structural and functional brain changes associated with relatively high magnitude head impacts and SRC associated with both brain changes and neuromuscular function, further investigation with neuroimaging is needed to examine the association of differential exposure to RHIs with CNS and neuromuscular function.

One method for evaluating CNS and neuromuscular function following RHI exposure is via fMRI while participants complete motor control tasks. fMRI has been used to demonstrate time varying changes in brain metabolism. The primary consequence of changes in neural activity can be detected based on local cerebral blood flow and changes in oxygenation concentration. Blood oxygenation level dependent (BOLD) imaging allows for the measure of cerebral blood follow to delineate regional changes in neuronal activity signaling either an increase or decrease in activation (Poldrack et al., 2011) (henceforth referred to as 'neural activity' changes). Early investigations have aimed to probed motor control during fMRI acquisition but have been constrained to upper extremity fine motor control (e.g., finger tapping) due to methodological limitations associated with head motion artifacts. However, technological advances over the past decade permit the assessment of gross lower extremity motor control during brain fMRI (Anand et al., 2021; Criss et al., 2022; Fontes et al., 2015; Grooms et al., 2022a; Grooms et al., 2019; Grooms et al., 2015; Mehta et al., 2009, 2012; Slutsky-Ganesh et al., 2023; Zuleger et al., 2023). Utilizing a previously published simultaneous bilateral ankle, knee, and hip flexion–extension control (henceforth deemed "bilateral leg press), (Grooms et al., 2022a; Slutsky-Ganesh et al., 2023) is of particular interest as bilateral coordinated movements are vital to neuromuscular function during sports participation, and this motor task has demonstrated the ability to differentiate neural activity changes in athletes with a history of SRC (Zuleger et al., 2023). Therefore, the purpose of this study was to isolate changes in neural activity associated with the frequency of RHIs at different *g* force magnitudes (20 *g* – 120 *g*; six separate, progressively greater *g* force intervals) in female adolescent athletes during a single season of soccer. Based on prior literature, we hypothesized that season-long exposure to high magnitude *g* force RHIs would be associated with changes in neural activity during the fMRI bilateral leg press.

2. Results

2.1. Demographics

The fifteen female athletes that were included in the final analysis of the study were between the ages of 14 and 17 years old (15.7 ± 1.0 years; 165.8 ± 5.7 cm; 59.7 ± 11.1 kg; 21.7 ± 3.8 BMI). Athletes were in grades 9–12, and part of the same high school soccer team.

2.2. fMRI neuroimaging quality assessment

To support the evaluation of neuroimaging data quality of the fMRI bilateral leg press (see MRI processing and analysis), we report both the mean (+1 SD) absolute and relative head motion for pre- and post-season timepoints. The average absolute head motion displacement for pre- and post-season neuroimaging was 0.42 ± 0.19 mm and 0.35 ± 0.14 mm, respectively. Where the average relative head motion displacement for the pre- and post-season neuroimaging was 0.10 ± 0.03 mm and 0.09 ± 0.03 mm, respectively.

2.3. Repetitive head impacts following a season of soccer

A total of 2,647 impacts were recorded ≥ 20 *g* during the regular soccer season (combined practice and games) across the 15 female soccer athletes included in this study. Following application of the hit-run filter, a total of 2,066 head impacts were identified (total impacts removed = 581). The magnitude and frequency of head impacts sustained at various *g* force thresholds for each individual athletes can be found in Table 1. Additionally, we examined, the number of impacts sustained only during practice and only during games. The number of impacts sustained during practice that were ≥ 20 *g*'s was 863. Following the application of the hit-run filter a total of 601 impacts were identified (practice impacts removed = 262). The number of impacts sustained during games were 1,784, and following hit run filtering application were 1,465 (game impacts removed = 319). The average number of filtered impacts ≥ 20 *g*'s for practice and games were 40.1 ± 20.8, and 97.7 ± 61.3 respectfully. With a total of 24 games played during the season, the average number of impacts ≥ 20 *g* per game was 4.07. The number of impacts sustained in practice and games separately following the hit-run filter application can be found in Tables 2 and 3, and additional impacts prior to the hit-run filter for the total (games and practice: Table S1), practice only (Table S2), and games only (Table S3) for each subject can be found in the supplementary document.

2.4. Functional neural activity changes as a function of g forces over a season

After modeling the frequency of *g* force hits acquired from each athlete's accelerometer data as a covariate of interest, results revealed pre- to post-season changes in neural activity during the bilateral leg press task were associated with the number of impacts sustained at ≥ 90 *g* - <110 *g* and ≥ 110 *g* (all *z*'s > 3.1 and *p*'s < 0.05). Specifically, greater RHI exposure at ≥ 90 *g* - <110 *g* was associated with task-related decreased activity in both the left and the right orbitofrontal cortex (Fig. 2). Further, greater RHI exposure at ≥ 110 *g* was associated with decreased task-related activity in the paracingulate gyrus, extending into the cingulate gyrus, and precentral gyrus. Greater RHI exposure ≥ 110 *g* was also associated with increased task-related activity in the left occipital fusiform gyrus, extending into cerebellar crus I, and the lingual gyrus (Fig. 3). Information on the voxel size, *p-value*, and peak voxel location at each *g* force magnitude is presented in Table 4.

There were no significant relationships between the frequency of RHI exposure sustained at lower magnitude g force categories (≥20 *g* - < 30 *g*; ≥30 *g* - <50 *g*; ≥50 *g* - <70 *g*; ≥70 *g* - <90 *g*) and changes in neural activity during the bilateral leg press (all *z*'s < 3.1 and *p*'s > 0.05).

3. Discussion

The purpose of this study was to isolate changes in neural activity for lower extremity motor control associated with the frequency of RHIs at various *g* force magnitudes experienced during a single season high school soccer. To accomplish our study's purpose, we utilized a previously published task-based fMRI paradigm (bilateral leg press) (Grooms et al., 2022a; Slutsky-Ganesh et al., 2023; Zuleger et al., 2023) to characterize the relationship between differential exposure to RHIs and pre- to post-season changes in neural activity for lower extremity motor control. Binned *g* force-based analyses revealed that exposure to high, but not low, magnitude impacts was associated with pre- to post-season changes in neural activity for the bilateral lower extremity motor control task. Specifically, region-specific associations were found between high magnitude RHI exposure (≥90 *g* - <110 *g* and ≥ 110 g) and alterations in neural activity within regions critical for motor control, vision, and cognition.

3.1. RHI exposure Xpatch technology

Xpatch sensors recorded a total of 2,647 impacts ≥ 20 *g* across both practices and games. The application of the hit-run filter removed a total of 581 impacts, resulting in a total of 2,066. The application of this hit-run filter has shown increased validity of 44.6 % with video-verification compared to the default methods employed by the sensor technology, yielding only 22 % accuracy for identify impacts. (DiCesare et al., 2020). When splitting the data by practice and games we noted a total of 601 and 1,456 impacts following hit-run filter application, respectively. The removal of 581 impacts from the combined practice and games data was mainly seen at lower impact levels impacts with 39.1 % removed from impacts between ≥ 20 g - < 30 g and 34.9 % removed from impacts between ≥ 30 g - < 50 g. The removal of impacts at lower g forces indicate the presence of false positives specific to these magnitudes, supporting the use of additional filtration methods, such as the ‘hit run filter’ on impact data.

When examining the breakdown of impacts sustained in just game play, a total of 1,465 impacts were sustained, with an average of 97.7 ± 61.3 across the players. Within the season, players played a total of 24 games resulting in an average 4.07 impacts per game, which is consistent with previously published work demonstrating impacts per athletic exposure ranged from 2.9 to 5.7 without video verification (McCuen et al., 2015; Reynolds et al., 2017) in female soccer athletes.

3.2. Functional changes in neural activity and high magnitude RHI exposure

Modeling head impact data with the fMRI analyses revealed acute changes in neural activity associated with greater exposure to high (≥90 *g* - <110 *g* > 110 g), but not low (20 *g* – <90 *g*) magnitude impacts. Most notably, elevated exposure to high magnitude impacts emerged as altered activity across three primary domains: motor, visual, and cognition. Increases in neural activity associated with high magnitude exposure may manifest as adaptive, neurologic compensatory mechanisms to maintain or regulate motor control in response to insult, where the presence of decreased activity may represent disruption or dysregulation of the system. The presence of both compensatory and disruptive associated neural activity changes related to high magnitude exposure lends support for the potential redistribution of motor, visual, and cognitive neural resources to maintain bilateral, lower extremity motor control. Furthermore, the present data provide mechanistic support that alterations in regions responsible for sensorimotor integration and higher-level cognitive processing may be present in athletes following a single season of RHI exposure.

3.3. Motor alterations following exposure to high magnitude RHIs

Greater exposure to high magnitude RHIs was associated with decreased activity in the precentral gyrus. The precentral gyrus, or primary motor cortex (M1), is essential for the execution and control of voluntary movements (Banker & Tadi, 2023). Reductions in M1 activity during the bilateral leg press could indicate impaired motor execution, resultant of high magnitude RHI exposure. Diminished cortical activity during the task could manifest as less neural drive to lower extremity muscles, which is further supported by prior evidence from the TMS literature. Specifically, exposure to a single bout of soccer heading (mean impact; 13.1 ± 1.9 *g*) increased intracortical inhibition, measured via cortical silent periods (cSP) within M1(Di Virgilio et al., 2016). Moreover, these observable changes were measured immediately following 20 consecutive impacts over 10 min. The findings from this study, along with the prior TMS evidence showing increased intracortical inhibition, may suggest that a reduction in neural activity during the motor control task may signal disruption of the motor cortex following high magnitude exposure. There is, however, a paucity of literature investigating motor cortex alterations following RHI exposure. Therefore, further work is warranted.

3.4. Visual system alterations following exposure to high magnitude RHIs

High magnitude RHIs were also associated with pre- to post-season neural activity changes in visual-related regions, including the occipital fusiform gyrus, extending into the left crus I of the cerebellum, and the lingual gyrus. Alterations in visual-related brain regions may be indicative of system-level changes to visual processing associated with high magnitude exposure, thereby increasing visual-related neural activity for desired integration with motor control. Although visual processing was not directly evaluated in the present study (e.g., oculomotor performance), the increase in activity could be secondary to sensory compensation and activation for cross-modal processing to enhance limb position accuracy. Prior literature indicates that head impact exposure is associated with poor visual and sensory task performance (Harpham et al., 2014), along with altered oculomotor and neuro-ophthalmologic responses following RHI exposure (Kiefer et al., 2018). The consequences of altered activity in visual regions include potential difficulties in translating visual cues into appropriate motor responses and/or greater reliance on visual information to complete motor movements. Greater reliance on visual-related neural activity has been observed in individuals who have experienced or are at high risk for, lower extremity injury (Chaput et al., 2022; Grooms et al., 2022b; Grooms et al., 2017).

Initially hypothesized as neural reweighting (i.e., greater neural activity in visual-motor vs. sensory-motor activity for motor control following lower extremity injury (Grooms et al., 2017), emergent data indicates that alterations in visual regions, such as the lingual gyrus, also contribute to cross-modal processing and may uniquely contribute to future injury risk. Cross-modal brain functioning within the context of lower extremity motor control is broadly defined as regions important for integrating visual and proprioceptive information. Altered visual/cross-modal processing activity related to high magnitude exposure may similarly underlie impaired neuromuscular control and sensorimotor coordination more broadly, thus elevating an athlete’s future risk for lower extremity musculoskeletal injury; similar to that of an SRC increasing the future risk for lower extremity injury (Herman et al., 2017).

3.5. Cognitive alterations following exposure to high magnitude RHIs

High magnitude impacts were associated with task-related decreases in activation within the orbitofrontal cortex (OFC), and the paracingulate gyrus, extending into the cingulate gyrus. The identified brain regions are involved in complex higher-level cognitive and behavioral processing, decision-making, attention, and sensory integration (Kringelbach, 2005; Leech & Sharp, 2014; Rolls, 2004). Prior work has reported both cognitive changes (Koerte et al., 2017; McAllister et al., 2012) and brain alterations associated with cognitive measures following RHI exposure (Talavage et al., 2014). The cingulate is a well-connected brain region with connection to motor and supplementary motor regions (Asemi et al., 2015), additionally, the most anterior aspect of the cingulate gyrus is thought to be responsible for modulating visually coordinated behaviors in adolescents (Asemi et al., 2015). Prior cytoarchitectural imaging work has revealed the existence of three motor areas along the cingulate sulcus that are somaotopically organized, with representation of the foot across all three motor zones (Amiez & Petrides, 2014) suggesting that the cingulate may play an important role in both joint proprioception/motor control (Smith, 2021). The cumulative effects of high magnitude RHIs and resultant disruptions in the cognitive system may contribute to decreased precision, speed, and accuracy of movements, affecting an athlete's ability to execute more complex maneuvers, making them more susceptible to injuries.

3.6. Lower magnitude RHIs across a season of soccer

Results revealed no significant relationships between relative exposure to lower magnitude impacts (≥20 *g* - < 90 *g* categories) and changes in neural activity during the bilateral leg press. The absence of RHI-associated neural activity changes at lower loads, combined with data indicating most RHIs occurred below 90 *g*'s (>95 % of all impacts), may indicate that the accumulated impacts at lower magnitudes may have less of an effect on neural functioning for lower extremity motor control. However, we are not suggesting that RHI exposure at lower magnitudes is not affecting the CNS more broadly (see the following review for prior work supporting the presence of structural and functional alterations following RHI exposure (Rodrigues et al., 2016), but that the frequency of lower impacts experienced by the present cohort of athletes was not directly influencing brain function for gross lower extremity motor control. Moreover, the absence of neural correlates associated with the frequency of exposure to lower magnitude impacts may be due to an overestimation of the Xpatch sensor technology (i.e., more 'noisy' data at lower magnitudes). Specifically, prior work by Wu and colleagues highlights the effects of skin displacement upon impacts. The Xpatch sensor technology demonstrated 2–4 mm of skin displacement and estimated linear acceleration forces at 15 ± 7 g's compared to the mouthguard which had recordings at 9 ± 2. Leading to an 18 % normalized root mean square error. Further, upon transformation of kinematic measures to an estimated center of gravity, based off mouthguard location, the normalized root mean square error was 120 % (Wu et al., 2016). Thus, we hypothesize that our methods may not have been sensitive to low exposure like the work by Di Virgilio et al., because of a) limitations in sensor technology at lower impact levels (i.e., higher rates of false positives) and/or b) low level impacts may not be longitudinally related to changes throughout the entire cortex (as measured via fMRI), for motor control.

3.7. Clinical applications

With our results showing high magnitude RHI exposure is associated with pre- to post-season neural activity alterations during an fMRI bilateral leg task, there is a need for comprehensive strategies to address the potential consequences of RHIs in adolescent soccer athletes. Implementing injury prevention protocols, that could potentially mitigate subsequent motor control deficits in athletes, may also reduce future lower extremity injuries. Specifically, prior work demonstrated the effectiveness of neuromuscular training (NMT) in those with acute concussion and showed reductions in subsequent injury incidence for up to one year (Howell et al., 2022). While NMT interventions have yet to be explored in athletes following RHI exposure, implementing NMT protocols throughout an athlete's competitive career may aid in mitigating neurological compensation mechanisms and subsequent motor deficits following RHI exposure. Additionally, the findings from this study contribute to our understanding of the complex relationship between RHI exposure, brain physiology, and motor control in adolescent athletes. Multidisciplinary approaches that integrate neuroscience and sports medicine to safeguard the brain health and motor function of young soccer players are vital to prevent future injuries. Further research is essential to elucidate the underlying mechanisms and to develop targeted interventions to minimize the long-term impact of head impacts on motor control in this population.

3.8. Limitations

As with any study, this investigation is not without limitations. First, this investigation was limited by the absence of behavioral data. Our data indicate that increased exposure to high magnitude impacts alters neural activity during the fMRI motor control tasks; however, we acknowledge that further work is needed to verify that the observed relationships were in fact adaptive or maladaptive in nature. Specifically, future work that includes behavioral measures that can quantify measurable outcomes to support the interpretation of the present fMRI data (i.e., in-scanner biomechanics, lab-based landing biomechanics, cognitive assessments, and injury surveillance) is warranted. Second, despite the application of a hit-run filter on the head acceleration data, prior work has noted that the identification and categorization of low magnitude head impacts may lead to an over and/or underestimation (O'Connor et al., 2017) of head acceleration events, leading to the misidentification of RHIs (i.e., false positives). Moreover, as previously stated, additional work has shown overestimations of both linear and rotational acceleration events with skin patch accelerometer devices (Wu et al., 2016). For this reason, the results of the present work should be interpreted cautiously, particularly our null findings at the lower magnitudes. Additionally, results from previous work confirm the need for video-confirmation of impacts in sensor research to remove nonimpact recorded data (Nevins et al., 2019; Patton et al., 2020; Press & Rowson, 2017). Future work should implement video-verification methods to determine the true number of head impacts, and/or implement machine learning algorithms that are trained and validated via video verification, which may enhance sensitivity in detecting relationships between RHI exposure and associated neural activity changes (DiCesare et al., 2020), particularly at low magnitudes, whereby we found no significant relationships. Third, post-concussion changes to motor control are also hypothesized to be due to axonal injury (Wilkerson et al., 2017), thus, complementing the present functional neuroimaging work with sequences that can observe microstructural integrity (DWI), could further delineate the mechanisms underlying SRC-related changes to the CNS that impair neuromuscular control. Finally, the study population of interest was limited to a small sample of female adolescent soccer athletes and, therefore, has limited generalizability to both sexes. While much of the prior RHI investigations have been done in male athletes (Broglio et al., 2017), a comparison between the magnitude and frequency of impacts across a single season in a sport with both sexes may yield differential neural activity changes during the fMRI bilateral leg press task. Future studies should consider sex as a biological variable to examine brain related changes following RHI exposure in adolescent athletes, as it relates to motor control.

3.9. Conclusion

Results from the current study revealed that during a single season of soccer, the accumulation of RHI exposures was associated with pre- to post-season changes in brain function for female adolescent athletes. Specifically, alterations in brain activation during a bilateral leg press task were identified in cognitive, visual, and motor regions. Neural alterations may cascade as impaired sensorimotor performance and elevate an athlete's future injury risk, like what has been reported for SRC. However, we emphasize that the presently identified relationships between greater exposure RHIs and alterations to neural activity for motor control may only reflect acute changes and/or be more transitory in nature (post season scans done within two weeks of final RHI). Future research with longer term follow ups and sensor video-verification are needed to evaluate the longitudinal trajectory of pre- to post-season brain alterations associated with the accumulation of RHI, and whether RHI-related acute and/or chronic brain alterations for motor control contribute to future lower extremity injury.

4. Experimental procedures

4.1. Participants

Twenty-eight female soccer athletes between the 2015–2016 season were recruited to participate in this study, which included prospective longitudinal neuroimaging and season-long head impact monitoring. We focused on females for this investigation given the elevated severity of symptom reporting compared to males, as well as their higher propensity to experience future lower extremity injury following SRC than males (Biese et al., 2021; McGroarty et al., 2020). Further, adolescent females are generally underrepresented within the head impact and neuroimaging literature compared to males. Athletes and their parents completed informed assent and consent, respectively, prior to enrollment in the study. Of the twenty-eight athletes, seven athletes were ineligible to undergo fMRI scanning due to dental hardware (i.e., braces), two athletes did not return for post-season imaging, and one athlete sustained an anterior cruciate ligament injury (ACL) during the season and was excluded from the study. Additionally, following examination of the athlete's neuroimaging quality assurance reports, three athletes had data that was deemed unusable (i.e., corrupted image files and/or motion-degraded data) resulting in a total n of 15.

4.2. Head impact surveillance[1]

Head impact data were recorded for all athletes across one competitive soccer season between 2016 and 2017 during both regular season games and practices. To follow best practice in reporting of head impact sensors, we relied on the Consensus Head Acceleration Measurement Practices (CHAMP) checklist (Arbogast et al., 2022) to support

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[1] We aimed to follow best practices in reporting of head impact sensors, using the CHAM checklist (Arbogast et al., 2022). However, if any aspect of the CHAMP guidelines is not reported, that is due to that information being unavailable (data collection occurred prior to publication of CHAMP guidelines) and/or was not performed (e.g., validation of head impacts via video verification to support machine learning approaches).

the documentation of head impact surveillance methods. The frequency and magnitude of sustained head impacts were collected using a 6 degree-of-freedom accelerometer (X2 Biosystems, Seattle, Washington, USA) attached to the mastoid process behind the left ear. The X2 system has a tri-axial linear accelerometer (±200 g) and tri-axial gyroscope (±2000 deg/sec) that are sampled at 1 kHz and 850 Hz. respectively, for linear acceleration and rotational velocity. Prior to first use, all X2 accelerometers were tested for basic functionality (battery life) and were calibrated and validated according to the manufacturer's specification. All accelerometers were placed and monitored by a designated research specialist (KBF) to ensure proper application and function. The X2 system recorded impacts when an acceleration event of > 10 g was detected. Each event was recorded over a 100 ms window, in which data was collected for 10 ms prior to when and 90 ms after the linear acceleration exceeded the threshold. Following a practice or game, the devices were removed and turned off, data was downloaded from each device, and then uploaded to a cloud-based server. From there, data was downloaded via proprietary software (X2 Injury Management System, X2 Biosystem, Seattle, WA). Despite validation of the accelerometer device in female competitive soccer sports (Chrisman et al., 2016; McCuen et al., 2015; Press & Rowson, 2017), recorded accelerometer data are susceptible to the presence of false-positive recordings (e.g., from taking the accelerometer off and putting it down, falling off the participant), and in one study the authors reported that linear and rotational acceleration magnitudes were overestimated using a skin patch sensor (Wu et al., 2016). To mitigate the influence of false-positive recordings, and or spurious impacts, we first ensured that only impacts recorded within the time window of games and practice were recorded (between the recorded start and end times and timestamps of the sensors) and only acceleration events ≥ 20 *g* were considered for the neuroimaging analyses.

Post-processing involved aggregation of the data for each participant across both practices and games, with subsequent removal of impacts that occurred within 5 min of the recorded stop time to avoid spurious events that were recorded due to handling of the sensors by personnel. Further, any impacts exceeding 200 *g* were excluded. Additionally, data underwent 'hit-run' filter, which has been previously described in the literature (Diekfuss et al., 2021; Dudley et al., 2020). The 'hit-run' filter method aimed to identify periods of time in which impacts may be overestimated. Specifically, accelerometer data was flagged when an athlete received three or more consecutive hits > 20 g that were less than 10 s apart and occurred within a 30-second time interval (these impact events were considered improbable occurrences in soccer). In a recent study with a similar cohort of female adolescent soccer athletes, the application of the "hit-run" filter showed an improved accuracy of 44.6 % for quantification of impact exposure which were video verified. Despite the absence of video-verification in the current study we opted for this approach as the standard "threshold" based method which is the default employed by the sensor when an acceleration event exceeds the threshold above a certain *g* force as this has only shown 22 % accuracy for quantification impact exposure with video verification (DiCesare et al., 2020). The total number of head impacts sustained across all athletes is reported before and after the hit-run filter application. Adapted from prior literature in male high school football players (Diekfuss et al., 2021), RHI data in this study were binned into six threshold categories defined by progressively greater g increments (≥20 *g* - < 30 *g*; ≥30 *g* - <50 *g*; ≥50 *g* - <70 *g*; ≥70 *g* - <90 *g*; ≥90 *g*

- <110 *g*; ≥110 *g*). The number of impacts within each of the six threshold categories were used as covariates of interest as continuous variables in the higher-level fMRI analyses (see below).

4.3. Bilateral motor control paradigm and bilateral leg press device.

We utilized an MRI-compatible, bilateral leg press device to engage motor control neural activity during neuroimaging (Grooms et al., 2022a; Slutsky-Ganesh et al., 2023; Zuleger et al., 2023). Related movement-based fMRI approaches have shown a high interclass correlation (ICC) for inducing neural activity in somatosensory, sensorimotor, and motor planning regions (Grooms et al., 2019), allowing for reliable neural activity assessment concurrent with motor behavior (i.e., resistance-based bilateral leg press movements) (Fig. 1). As previously described, the bilateral leg press is comprised of two independent horizontal sliding foot pedals, with resistance applied via elastic resistance bands anchored at the center of the board (between the athlete’s adductor brevis) and at the lateral aspect of each athlete’s greater trochanters The resistance bands wrapped around the foot pedals and are secured to fixation points, allowing for standardized resistance during the leg press (manufactured peak rated force ~ 9.1 kg) (Grooms et al., 2022a; Slutsky-Ganesh et al., 2023; Zuleger et al., 2023).

Prior to entering the real MR environment, all athletes underwent an experimenter-guided, brief familiarization period in a mock MRI environment standardized and completed at pre and post season). The purpose of this familiarization period was to ensure participants were comfortable with the tasks and understood the constraints associated with fMRI prior to entering the real MR environment (reduce claustrophobia, discuss safety precautions that would be in place, etc.). Specifically, using the same MRI-compatible leg press, the athletes were instructed to perform the bilateral leg press task (flexion/extension against resistance) while maintaining limited head motion (in a mock head coil within a mock scanner outside of the MR environment). Athletes were instructed to move both legs simultaneously to the sound of a 1.2 Hz metronome. Specifically, athletes were asked to match knee flexion and extension movements with each beat of the metronome. During the familiarization period, the athlete was monitored by a trained research scientist who first instructed them through the movements and provided instruction for maintaining limited head motion (Grooms et al., 2022a; Slutsky-Ganesh et al., 2023; Zuleger et al., 2023). The familiarization period was standardized to all athletes and occurred prior to the real MRI.

Following the familiarization period, athletes were taken to the MRI to complete the testing protocol (i.e., in the ‘real’ MR environment). All athletes were placed in a supine position. Athletes received visual and auditory cues for when to initiate movement trials via a television monitor (NordicNeuroLab, Bergen, Norway) and headphones, respectively. To reduce head motion artifacts, the upper body of each athlete was securely fastened to the MRI table via two Velcro straps placed diagonally from the shoulder to the hip. Body restraints and additional padding around the head were used to isolate movement to the lower legs.

The bilateral leg press movement trial was an fMRI block design, in which athletes would move for 30 s and then rest for 30 s, resulting in 4–30 s movement blocks and 5–30 s rest blocks (Fig. 1). Athletes started the task in a resting position with their legs fully extended. The start of the movement trial was cued via a countdown (2–1-Start displayed on the television screen). Athletes completed flexion and extension movements while trying to maintain their pace with the sound of the metronome. At the end of the 30 s movement block athletes were again shown a countdown (2–1-Stop) instructing them to stop moving for the period. The athlete then returned to the resting position for the next 30 s. This cycle was repeated four times.

4.4. MRI acquisition

All neuroimaging data were collected using a 3 T Philips Ingenia MRI scanner with a 32-channel phased-array head coil. Data were collected using the same scanner for both the pre- and post-season neuroimaging sessions. All post-season neuroimaging data was collected within two weeks of the end of the regular soccer season. Structural T1w MP-RAGE images were collected on the athletes using the following parameters: (TR/TE = 8.1/3.7 ms; T1 = 1070 ms; isotropic resolution = 1 mm^3; FOV = 256×256; reconstructed matrix = 256×256). The functional T2* bilateral motor control data was recorded with the following parameters (TR/TE = 2000/35 ms; voxel size = 3.75 × 3.75 × 5 mm; FOV = 240×240; reconstructed matrix = 64×64; slice thickness = 5; SENSE acceleration factor = 2).

4.5. MRI processing and analysis.

All imaging data was run through a quality assurance pipeline, magnetic resonance imaging quality control (MRIQC), to determine if artifacts were present in the data (Esteban et al., 2017). MRIQC is an open-source software package used to examine image quality metrics from both structural and functional neuroimaging data (Esteban et al., 2017). Image quality metrics (IQM) are grouped into four categories that characterize the impact of noise, spatial distribution, presence of artifacts, and tissue distributions. Individualized reports were created for each athlete’s structural and functional data. Once the IQMs were extracted, a single group report was generated to plot each IQM, allowing for the identification of outliers for each measured metric. After examination, there were no notable artifacts or issues with the data acquired, however, data from three subjects were removed at this stage due to an indication of excessive head motion (>1mm absolute head motion). Specifically, we determined if excessive head motion was present by evaluating absolute and relative head motion mean displacements during both the pre- and post-season fMRI scans (i.e., as one component of data quality assurance). Absolute head motion is the highest head motion recorded during fMRI collection, while the relative head motion compares head motion with the previous time-point estimations to quantify the highest change in head motion between volumes acquired. Given head motion artifact can influence fMRI data quality, we have reported these data, as well as our criteria to ensure high quality data (i.e., > 1 mm was deemed unusable), to ensure rigor and transparency as per best practices set forth by the neuroimaging community (Nichols et al., 2017).

All fMRI data was processed using FMRIB’s Software Library (FSL) (Jenkinson et al., 2012). Data preprocessing included brain extraction, slice timing correction, intensity normalization, motion correction using MCFLIRT (Jenkinson et al., 2002), and spatial smoothing (6 mm FWHM). Each athlete’s functional data was linearly registered to their anatomical T1-weighted scan, and non-linearly registered to standardized space (Montreal Neurological Institute template: MNI-152). Following registration, head motion artifacts were detected and removed using independent component analysis for automated removal of motion artifacts (ICA-AROMA) (Pruim et al., 2015). Using FSLs Fast segmentation, gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) masks were generated from each participant's structural data. CSF and WM regressors were generated and set to a threshold level of one to create a conservative mask. Using the MNI-152 template, the WM and CSF were set to a threshold of one and registered to the raw functional data for each athlete. The files with the applied threshold from each athlete were masked to the MNI masks to remove any overlapping voxels within the grey matter. Time series were generated for the CSF/WM from each athlete's raw and unsmoothed functional data. Regressor files were then input into the model as confounding explanatory variables to restrict BOLD activation to only the gray matter.

Following ICA-AROMA, all data underwent visual inspection to evaluate removed motion components using the interface for batch processing data using ICA-AROMA (INFOBAR) (Anand et al., 2020). Additional quality assurance testing included checking the brain registration, presence of a stable baseline, BOLD signal model fit, and absolute head motion set to a threshold of ≤ 1 mm. Following quality assurance testing, the data were then subjected to a high-pass filter in FSL using a 100 s cutoff. The individual subject (first-level) analysis was completed using the FSLs FEAT tool (Woolrich et al., 2001). All time- series analyses for pre- and post-season data were conducted using FILM prewhitening and local autocorrelation correction, along with a 30 s block design (30 s rest/30 move) with a cluster-wise corrected threshold of $z > 3.1$ and $p < 0.05$.

4.6. Statistics

Individual pre- and post-season fMRI results were then analyzed using fixed-effects analysis (second level). The fixed-effects model option is applied for within-subject multi-session analysis. This allowed for the generation of Z maps that show pre- to post-season neural activity changes for each individual athlete. Generated comparisons of parameter estimate files were then input into the higher-level analysis (third level) using a mixed-effects model (Flame 1 + 2). The frequency of impacts for each *g* force category was demeaned and added as a covariate of interest to determine the association between differential *g* force frequency and changes in neural activity (six independent models). All higher-level analyses were computed across the entire brain with multiple comparison corrections using cluster-based thresholding of $z > 3.1$ and $p < 0.05$. The application of a gray matter mask was applied to restrict significant clusters within gray matter voxels. Statistically significant brain regions were located using FSL's atlasquery with a threshold set to 10 %, and the Harvard-Oxford Cortical Structural Atlas and Cerebellar Atlas in MNI152 space. All demographic, head motion, and head impact data were analyzed descriptively using SPSS software (Version 28.0; IBN Corp., Armonk, NY, USA).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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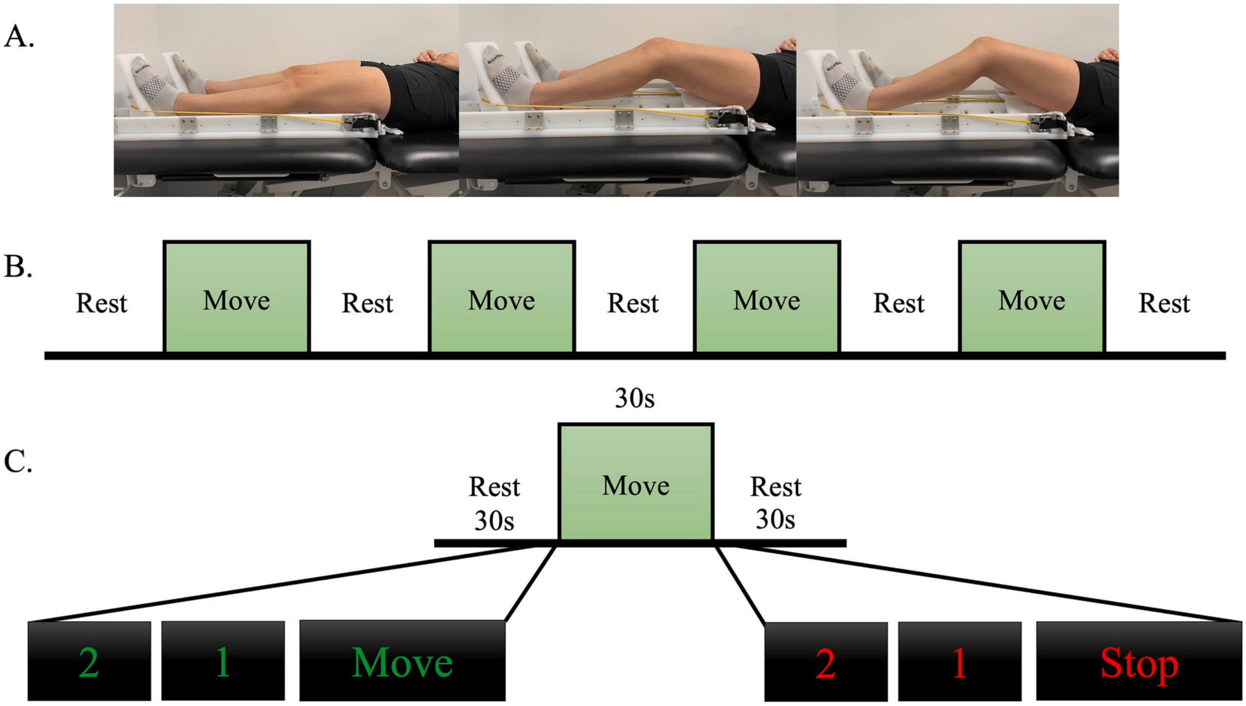

Fig. 1.

Functional magnetic resonance imaging assay for motor control. A) Using an MRI-compatible lower extremity leg press device athletes were trained to move both independent horizontal sliding foot pedals to perform the bilateral leg press movement. B) The fMRI paradigm is a block design with 4 movement blocks and 5 rest blocks. C) Rest and move blocks were a total of 30 s each. At the start of each movement block, athletes with provided with a countdown (2–1-start) to initiate the bilateral leg press, which was followed by a countdown (2–1-stop). *Abbreviations:* MRI; magnetic resonance imaging; fMRI; functional magnetic resonance imaging.

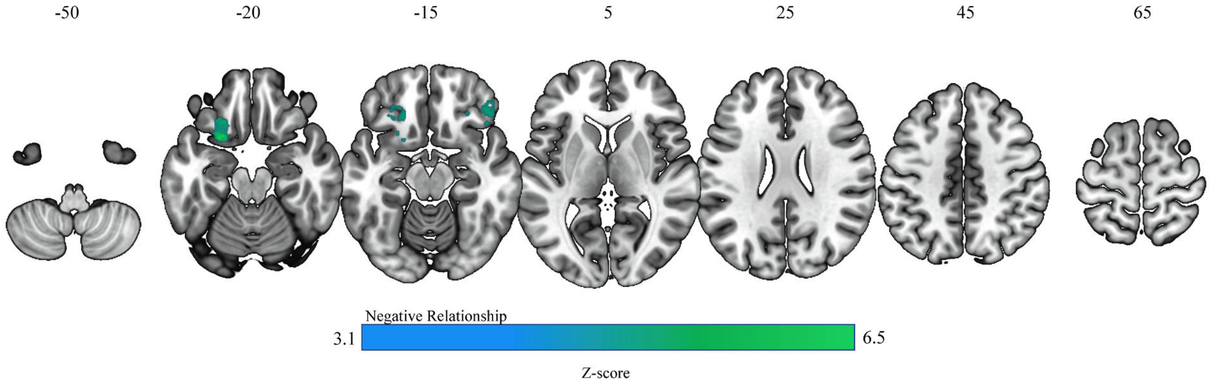

Fig. 2.

Functional neural activity during the bilateral leg task is associated with the number of RHIs between ≥ 90 *g* - <110 *g*. Following a season of soccer athletes showed decreased activity (negative relationship, shown in blue/green) associated with the frequency of exposure at ≥ 90 *g* - <110 *g* in the left orbitofrontal cortex (MNI coordinates: x = 64, y = 71, z = 23; Voxels: 429; $p < 0.001$; Z max = 5.72) and right orbitofrontal cortex/frontal pole (MNI coordinates: x = 20, y = 82, z = 33; Voxels: 272; $p = 0.001$; Z max = 6.17).

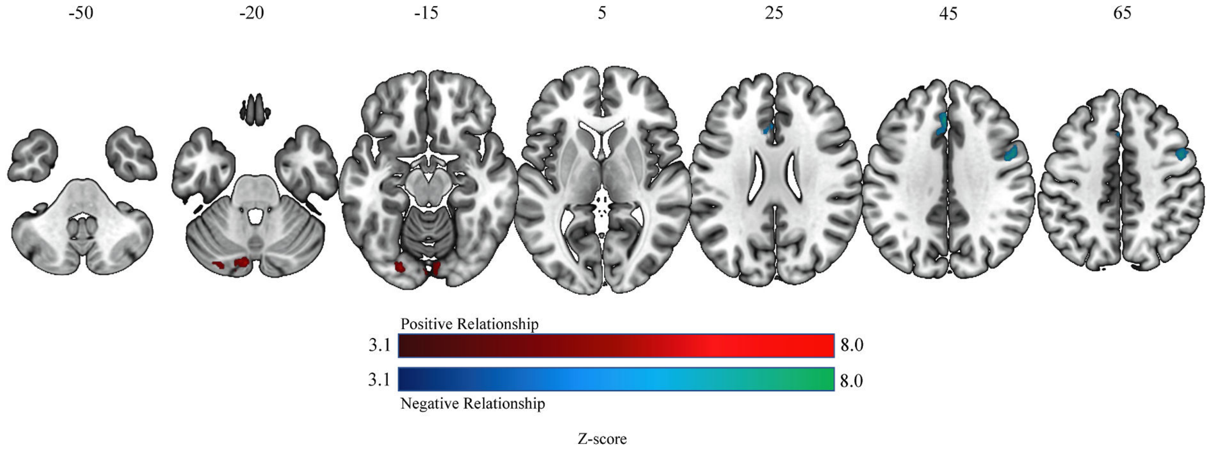

Fig. 3.

Functional brain activity during the bilateral leg task is associated with the number of RHIs at ≥ 110 g. Athletes following a season of soccer showed increased activity (shown in red) in the occipital fusiform gyrus extending into the left crus I (MNI coordinates: x = 57, y = 19, z = 27; Voxels: 208; p = 0.006; Z max = 7.48) and the lingual gyrus (MNI coordinates: x = 41, y = 22, z = 28; Voxels: 130; p = 0.042; Z max = 5.84). Impacts at ≥ 110 g were also associated with decreased activity (shown in blue/green) in the paracingulate gyrus/cingulate gyrus (anterior division) (MNI coordinates: x = 46, y = 76, z = 53; Voxels: 152; p = 0.024; Z max = 6.49) and the precentral gyrus (MNI coordinates: x = 19, y = 67, z = 53; Voxels: 134; p = 0.038 Z max = 5.79). Please note that the z-score color map range is set to z > 3.1 for both positive relationships with RHI (red color bar: z > 3.1 to 8.0) and negative relationships with RHI (blue to green color bar: z > 3.1 to 8.0).

Table 1

Number of Head Impacts Sustained (Total Practice and Games) at Each g Force Category.

Subject ID	**≥20 *g* – < 30 *g***	**≥30 *g* – < 50 *g***	**≥50 *g* – < 70 *g***	**>70 g – < 90 g**	**≥90 *g* – < 110 *g***	**≥110 *g***
Sub-001	103	91	31	6	3	1
Sub-002	110	68	23	11	3	1
Sub-003	58	34	10	0	5	4
Sub-004	48	19	6	2	1	1
Sub-005	34	30	4	1	3	1
Sub-006	47	37	6	6	4	1
Sub-007	34	29	6	3	2	1
Sub-008	53	36	8	5	2	2
Sub-009	18	11	6	0	1	0
Sub-010	123	63	9	6	2	0
Sub-011	138	94	27	2	2	2
Sub-012	97	46	14	3	1	3
Sub-013	145	53	13	7	6	1
Sub-014	88	23	14	2	2	1
Sub-015	27	14	5	2	1	0

Notes: Impacts from both practice and games were combined and included in the fMRI analysis.

Table 2

Number of Head Impacts Sustained Across a Single Soccer Season (Practice Only).

Subject ID	**≥20 *g* – < 30 *g***	**≥30 *g* – < 50 *g***	**≥50 *g* – < 70 *g***	**>70 g – < 90 g**	**≥90 *g* – < 110 *g***	**≥110 *g***
Sub-001	13	8	3	2	0	0
Sub-002	25	14	2	2	1	0
Sub-003	35	22	5	0	1	0
Sub-004	19	4	4	1	1	1
Sub-005	14	9	1	0	1	0
Sub-006	13	8	2	2	2	0
Sub-007	19	11	4	1	2	1
Sub-008	19	8	2	3	0	0
Sub-009	7	5	1	0	0	0
Sub-010	38	15	5	2	1	0
Sub-011	45	31	9	0	1	1
Sub-012	19	7	1	2	0	0
Sub-013	44	17	5	1	1	1
Sub-014	34	8	4	1	0	1
Sub-015	3	2	4	0	0	0

Table 3

Number of Head Impacts Sustained Across a Single Soccer Season (Games Only).

Subject ID	**≥20 *g* – < 30 *g***	**≥30 *g* – < 50 *g***	**≥50 *g* – < 70 *g***	**>70 g – < 90 g**	**≥90 *g* – < 110 *g***	**≥110 *g***
Sub-001	90	83	28	4	3	1
Sub-002	85	54	21	9	2	1
Sub-003	23	12	5	0	4	4
Sub-004	29	15	2	1	0	0
Sub-005	20	21	3	1	2	1
Sub-006	34	29	4	4	2	1
Sub-007	15	18	2	2	0	0
Sub-008	34	28	6	2	2	2
Sub-009	11	6	5	0	1	0
Sub-010	85	48	4	4	1	0
Sub-011	93	63	18	2	1	1
Sub-012	78	39	13	1	1	3
Sub-013	101	36	8	6	5	0
Sub-014	54	15	10	1	2	0
Sub-015	24	12	1	2	1	0

Table 4

Changes in Neural Activity Following Repetitive Head Impacts at Various *g* forces.

***g* force Magnitude**	**Brain Region**	**Clusters**	**Voxel Size**	**Z max**	***p* value**	**Peak Voxel Location (MNI-152)**		
						X	**Y**	**Z**
≥90 *g* - <110 *g* (Negative)	Orbitofrontal Cortex/Temporal Pole (L)	1	429	5.72	$p < 0.001$	64	71	23
	Orbitofrontal Cortex/Frontal Pole (R)	2	272	6.17	$p = 0.001$	20	82	33
≥110 *g* (Positive)	Occipital Fusiform Gyrus/ Left Crus I (L)	1	207	7.48	$p = 0.006$	57	19	27
	Lingual Gyrus (B)	2	130	5.84	$p = 0.042$	41	22	28
≥110 *g* (Negative)	Paracingulate Gyrus/ Cingulate Gyrus (anterior) (L)	1	152	6.49	$p = 0.024$	46	76	53
	Precentral Gyrus (R)	2	134	5.79	$p = 0.038$	19	67	53

Abbreviations: MNI, Montreal Neurological Institute; R, Right side; L, Left side.

Note: Reported clusters were significant following multiple comparisons corrections using cluster-based thresholding of $z > 3.1$ and $p < 0.05$.