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ORIGINAL ARTICLE

CLINICAL STUDIES

Post-Concussive Vestibular Dysfunction Is Related to Injury to the Inferior Vestibular Nerve

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Abstract

Symptoms of vestibular dysfunction such as dizziness and vertigo are common after sports-related concussions (SRC) and associated with a worse outcome and a prolonged recovery. Vestibular dysfunction after SRC can be because of an impairment of the peripheral or central neural parts of the vestibular system. The aim of the present study was to establish the cause of vestibular impairment in athletes with SRC who have persisting post-concussive symptoms (PPCS). We recruited 42 participants—21 athletes with previous SRCs and PPCS ≥ 6 months and 21 healthy athletic age- and sex-matched controls—who underwent symptom rating, a detailed test battery of vestibular function and 7T magnetic resonance imaging with diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) of cerebellar white matter tracts, and T1-weighted imaging for cerebellar volumetrics. Vestibular dysfunction was observed in 13 SRC athletes and three controls ($p=0.001$). Athletes with vestibular dysfunction reported more pronounced symptoms on the Dizziness Handicap Inventory (DHI; $p<0.001$) and the Hospital Anxiety and Depression Scale (HADS; $p<0.001$). No significant differences in DTI metrics were found, while in DKI two metrics were observed in the superior and/or inferior cerebellar tracts. Cerebellar gray and white matter volumes were similar in athletes with SRC and controls. Compared with controls, pathological video head impulse test results (vHIT; $p<0.001$) and cervical vestibular evoked myogenic potentials (cVEMP; $p=0.002$) were observed in athletes with SRC, indicating peripheral vestibular dysfunction and specifically suggesting injury to the inferior vestibular nerve. In athletes with persisting symptoms after SRC, vestibular dysfunction is associated with injury to the inferior vestibular nerve.

Keywords: concussion; inferior vestibular nerve; persisting post-concussion symptoms; 7T MRI; sports-related concussion; vestibular dysfunction

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Introduction

Contact sport athletes are at high risk of sustaining head impacts that may lead to a sports-related concussion (SRC).¹ The incidence of SRC has increased during the last decades.^{2–6} While symptoms typically gradually subside within seven to 14 days,^{7–10} some athletes show prolonged persisting symptoms, and some never recover fully.^{8,11} When three symptoms last three months, this has commonly been defined as a post-concussion syndrome (PCS). Because of difficulties defining the syndrome,^{12–15} the descriptive term persistent post-concussive symptoms (PPCS), referring to symptoms persisting beyond the normal recovery period, is increasingly used. Vestibular dysfunction, manifested as vertigo, dizziness, unsteadiness, and visual impairment, are common in PPCS^{16,17} and, when present, associated with a worse outcome and a prolonged recovery.^{18–22}

The vestibular system is an intricate sensorimotor system responsible for detection of self-motion, head and body positioning, motor responses, and multi-sensory integration with the main purposes of gaze stability and maintaining balance.^{23,24} It includes peripheral structures of the inner ear and vestibular nerves, as well as central structures including cerebellar tracts, brainstem, and supratentorial regions.²⁵ The cause of persisting vestibular symptoms has not been established. While some SRC studies indicate a central origin,^{26–28} others suggest a peripheral cause,^{29,30} and recently a combination of vestibular lesions was suggested.³¹

Our aim was to establish whether vestibular dysfunction in athletes with SRC who have PPCS is of central, peripheral, or combined origin. We used morphological, diffusion tensor imaging (DTI), and diffusion kurtosis imaging (DKI) 7T magnetic resonance imaging (MRI) of the cerebellum, a detailed vestibular testing protocol, and self-reporting questionnaires addressing symptoms of post-concussion dizziness, anxiety, and depression.

Methods

Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Ethics Committee, Lund, Sweden (Dnr 2017/1049). All participants received oral and written information and signed a written consent.

Study population

Athletes ≥ 18 years old with a history of at least one SRC and experiencing symptoms exceeding six months, and healthy control athletes with no previous SRC and exercising three times per week were included. Subjects with a previous or current self-reported neurological or psychiatric disorder were not eligible for inclusion.

Athletes with SRC were recruited via rehabilitation physicians, team physicians, physiotherapists, contacts within Swedish sports societies, and via word-of-mouth. Controls were recruited by advertisement or personal con-

tacts and were age- and sex-matched to the athletes with SRC. One researcher (AG) interviewed potential study participants and included those who fit the inclusion criteria.

Symptom evaluation forms

SCAT5. The Sport Concussion Assessment Tool, 5th edition,³² has a graded symptom checklist evaluating 22 symptoms, where “0” is unaffected and “6” is maximum severity giving a maximum symptom severity score of 132. The questionnaire was self-administrated by the athletes with SRC.

DHI. The Dizziness Handicap Inventory is a self-reported questionnaire assessing the physical, functional, and emotional components of vestibular dysfunction. The total score is 0–100, where a high score indicates a high level of self-perceived handicap of vestibular dysfunction.³³ The DHI is one of the most widely used scales for measuring the impact of dizziness on quality of life.³⁴

HADS. The Hospital Anxiety Depression Scale is a self-reported measure of anxiety (HADS-A) and depression (HADS-D). The questionnaire has seven statements for anxiety and seven for depression, with a total score of 0–42 points. A high score implies a high level of self-perceived symptoms.^{35,36}

7T MRI

The MRI was performed with an actively shielded 7T scanner (Achieva, Philips, Best, Netherlands) equipped with a two-channel transmit and 32 channel receive phased-array head coil (Nova Medical, Wilmington, MA). B1 inhomogeneities were reduced by using dielectric pads (Teeuwisse, Brink, & Webb, 2012). The MRI protocol consisted of three-dimensional T1-weighted imaging, DTI, and DKI. Further details are provided in Supplementary Methods 1.

Volumetrics. Anatomical regions of interest were segmented from the T1w images using FreeSurfer³⁷ and cerebellar white and gray volumes were analyzed (Fig. 1a). An expert reader (ENK) inspected and corrected the material for misclassification.³⁸

DTI and DKI. The DTI and DKI processing included denoising,³⁹ correction for Gibbs-ringing artefacts,⁴⁰ brain extraction and correction of distortions from head motion and eddy currents,^{41,42} and median filtering (for DKI only). The DTI parameters were estimated through DTIFIT in FSL⁴³ and DKI parameters through dipy and its module DiffusionKurtosisModel.⁴⁴ Tract segmentation was performed using TractSeg.^{45–47} Three cerebellar tracts were selected for analysis: the inferior (left and right merged), middle, and superior (left and right merged) cerebellar tract (Fig. 1b). The fractional anisotropy (FA)

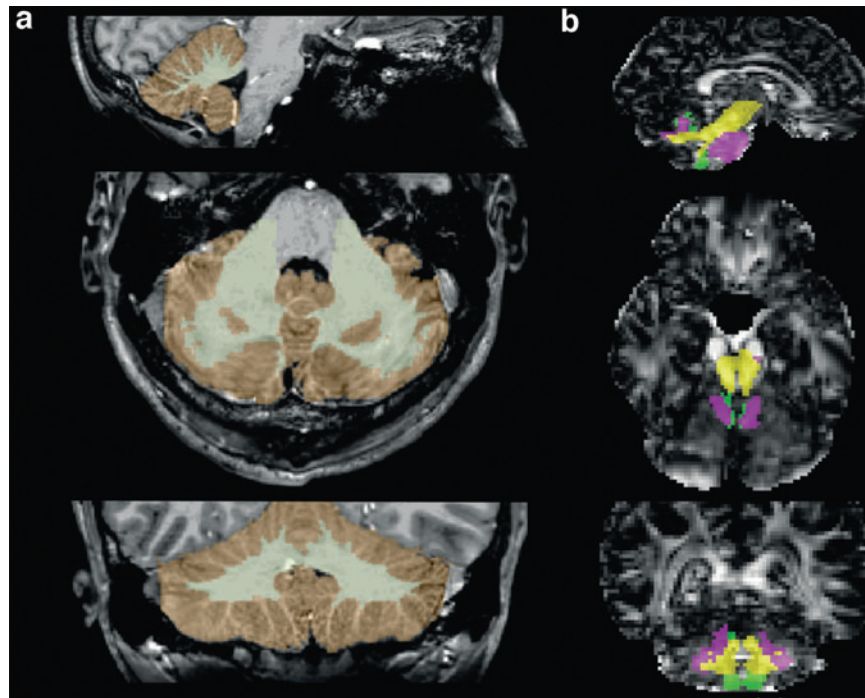


FIG. 1. Volumetrics, diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) of the cerebellum. Sagittal (upper row), axial (middle row), and coronal (lower row) views of the cerebellum are shown. (a) Cerebellar segmentation. Visualization of the performance of semi-automatic FreeSurfer approach for cerebellar white matter and gray matter segmentation. White matter is depicted with yellow color and gray matter with brown color. (b) Segmentation of white matter cerebellar tracts. Visualization of the performance of TractSeg in DKI. The superior cerebellar tract is depicted in yellow, the middle cerebellar tract in purple, and the inferior cerebellar tract in green. The cerebellar tracts are depicted on top of the fractional anisotropy image. A similar segmentation of the cerebellar tracts was also performed with TractSeg in DTI.

and mean diffusivity (MD) were analyzed for DTI and mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK) for DKI.

Vestibular tests

The vestibular tests included video head impulse test (vHIT), caloric test, cervical vestibular evoked myogenic potentials (cVEMP), videonystagmography (VNG), posturography, pursuit eye movements (PEM), and an audiogram. Before testing, the subjects were examined to exclude middle ear pathology, eventual ear wax was removed, and an audiogram was obtained. Tests were performed by two experienced audiologists according to manufacturer's instructions.

A blinded assessment by a physician specialized in neurotology (MM) was made. Tests were graded as normal or pathological whereafter an overall assessment was performed and deficits were classified as peripheral, central, or of combined origin. Peripheral signs included impairments of vHIT, caloric test, cVEMP, and a peripheral pattern of the VNG. Central signs included a central pattern of the VNG (i.e., gaze shifting nystagmus, continu-

ous positional nystagmus), PEM, and posturography. If both peripheral and central test-deficits were found, the pathology was classified as combined. For additional details see Supplementary Methods 2.

vHIT. The vHIT evaluates the vestibulo-ocular reflex (VOR), which depends on the integrity of the vestibular nerve and the semicircular canals.⁴⁸ Three vHITs were performed, one for each pair of semicircular canals.^{49,50} Evaluation was performed by calculating gains in the VOR, but mainly by classifying responses as normal or abnormal, because of the risk of possible shortcomings in calculations within the measuring system, especially for the vertical canals.⁵¹

Caloric testing. The caloric test evaluates unilateral peripheral deficits of the lateral semicircular canals and the function of the VOR. A shift in temperature of the endolymph in the semicircular canals stimulates the ampulla, causing an imbalance of the left and right VOR, resulting in nystagmus.^{52–54} Pathological outcome was defined as a reaction differing 25% or more from the opposite side.

cVEMP. The cVEMP is a test of the ipsilateral saccule and, hence, the inferior branch of the vestibular nerve. Central deficits delay the myogenic response, while peripheral deficits give an absent or reduced response.⁵⁵ Evaluation was performed both by inspecting the recorded curve and by assessing calculated amplitudes, latencies, and asymmetries. The overall responses were classified as normal or abnormal, for one or both sides, according to standardized laboratory procedures.

Videonystagmography. The VNG registers the eye movement during different gaze directions, body positionings, and head movements. The response pattern was classified as normal, peripheral, or central. Nystagmus with a peripheral pattern beats toward the contralateral side, improves with gaze toward the lesion, worsens with gaze away from the lesion, and suppresses with visual fixation. A central pattern can be solely vertical or torsional, is not affected by fixation, and can change direction with the gaze.⁵⁶

Posturography. The posturography tests integration of somatosensory, visual, and gravitational signals, and therefore studies the collective vestibular system. The recorded body sway was analyzed for frequency peaks and the variance of the forces actuated against the support surface during the body sway.⁵⁷

PEM. In the PEM-test, the ability to fixate and track a visually moving object is evaluated. Visual information travels to the middle temporal area and frontal eye field of the cerebrum, to the oculomotor regions of the brainstem, projects to the striatum and cerebellum, back to the brainstem before controlling eye movement.⁵⁸ Hence, it is a test of comprehensive visual function and depends on several central structures, including the cerebellum. Abnormal PEM was defined as prominently reduced velocity versus the stimuli, saccadic, or loss of pursuit.

Statistics

The data were analyzed using SPSS 25 (SPSS Inc., version 25, IBM Corporation, Armonk, NY). The signifi-

cance threshold was set to 0.05 for all tests but the DTI and DKI where a Bonferroni correction was made to adjust for the three cerebellar tracts, and the significance threshold was set to 0.017. The metrics test different features, why they were not corrected for multiple comparison.⁵⁹

Time is reported as mean values with \pm standard deviations (SD), or with a time-range interval. The vestibular tests were reported dichotomously. Data were analyzed for normal or skewed distribution using a Shapiro-Wilk test and histograms. Normally distributed data were compared using means and analyzed with *t* tests and analysis of variance regression analysis. Skewed or categorical data were presented as median and interquartile range (IQR) and analyzed with a Mann-Whitney *U* test for pairwise comparisons and with a chi-square test for categorical and binominal values.

Results

Study population

Forty-two subjects were included: 21 athletes with previous SRCs and persisting symptoms and 21 healthy age- and sex-matched controls. One patient did not complete the MRI. Demographics are listed in Table 1. Mean age was 26 (range 18–43) years, and 60% were males.

Symptom evaluation forms

On SCAT5, athletes with SRC reported a median 20 symptoms (IQR 20–22) and symptom severity 64 (IQR 44.5–81.5). Fatigue was reported by everyone, and the least common symptoms, nausea or vomiting, by 60%. Symptoms of vestibular disturbance were reported by a vast majority (Fig. 2). Number of SRCs, age, or sex did not correlate with SCAT5 symptom severity, $p=0.347$, $p=0.204$, and $p=0.343$, respectively.

Athletes with SRC reported higher scores on DHI compared with controls (Table 2). The number of previous SRCs, age or sex did not correlate with the DHI score, $p=0.356$, $p=0.147$ and $p=0.603$, respectively.

Table 1. Demographics

	SRC athletes, n = 21	Controls, n = 21
Male sex, % (n), $p=0.346$	67% (14)	52%, (11)
Age, mean (SD), $p=0.404$	26 (6.5) years	25 (4.2) years
Sports (n)	Ice hockey (7), soccer (4), karate (4), handball (2), indoor hockey (2), wrestling (1), and endurance riding (1)	Running, weightlifting, cycling, and swimming
Years of sports practice, mean (SD)	18 (5) years	-
Number of SRCs, mean (range)	5 (1–20)	-
Age at first SRC, mean (SD)	18 (5) years	-
Time from first SRC, mean (SD)	9 (7) years	-
Time from last SRC, mean (SD)	2.5 (3) years	-

Demographics of athletes with sports-related concussion (SRC) and controls.

Demographic details on the 42 participants of the present study—21 athletes with SRC and 21 athletic controls; the majority were males and of young age. The sports that the athletes with SRC were involved in are listed in declining order; because controls usually were involved in multiple athletic activities specific numbers are not listed. SD, standard deviation.

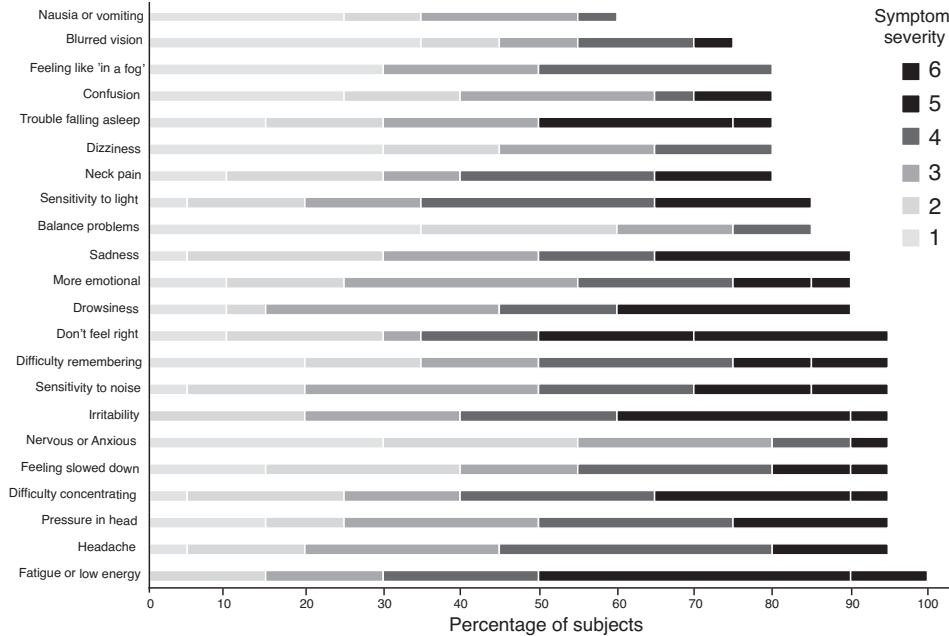


FIG. 2. Sport Concussion Assessment Tool (SCAT). The SCAT was used for symptom grading of symptoms where the most common symptom was fatigue or low energy, reported by 100% of the athletes with sports-related concussion (SRC). Balance problems were reported by 85% and dizziness by 80% of athletes with SRC. Symptom severity was reported in seven scales where 0 is that the symptom is absent, 1 represents a mild degree of suffering from the symptom, and 6 the maximum suffering from the symptom.

Athletes with SRC reported elevated rating on HADS anxiety and depression subscale compared with controls (Table 2). The number of SRCs, age, or sex did not correlate with the HADS score, $p=0.316$, $p=0.684$, and $p=0.817$, respectively.

7T MRI: volumetrics, DTI, and DKI

Because of artefacts, two athletes and three controls were excluded from the volumetric segmentations and one control from the DKI. The DTI data were missing for one ath-

Table 2. Hospital Anxiety and Depression Scale and Dizziness Handicap Inventory

	<i>SRC athletes, median (IQR) n=21</i>	<i>Controls, median (IQR) n=21</i>	<i>p</i>
DHI	40 (27–55)	0 (0–0)	< 0.001
Physical	14 (9–20)	0 (0–0)	
Emotional	12 (5–19)	0 (0–0)	
Functional	14 (5–20)	0 (0–0)	
HADS	16 (11.5–19)	4 (2.5–6)	< 0.001
Anxiety	9 (5.5–11.5)	3 (2–4.5)	
Depression	7 (5–8.5)	1 (0–2)	

Hospital Anxiety and Depression Scale (HADS) and Dizziness Handicap Inventory (DHI). Median scores and interquartile range (IQR) for the DHI for physical, emotional, and functional subgroups and the HADS for anxiety and depression. Total scores of the DHI and DHI differ significantly comparing athletes with sports-related concussion (SRC) with controls, $p<0.001$ and $p<0.001$. The significance threshold was set to 0.05; significant values are bolded.

lete and DKI data from two athletes. Images were reviewed by an independent neuroradiologist and a researcher (IBB), and no structural abnormalities were observed.

Cerebellar white matter volume was 27.3 ± 4.0 mL in athletes with SRC and 28.5 ± 4.8 mL in controls; grey matter volume was 114 ± 12.2 mL in athletes and 116 ± 14.9 mL in controls, similar between groups ($p=0.441$ and $p=0.722$, respectively; Fig. 3), and there was no correlation with vestibular dysfunction ($p=0.361$ and $p=0.774$, respectively). The DKI metrics revealed a decrease in MK in the superior and inferior cerebellar tract and in RK in the superior cerebellar tract for athletes with SRC compared with controls (Table 3). No DTI or DKI metric showed significant correlation with vestibular dysfunction. TractSeg analysis found similar cerebellar tract volumes in athletes with SRC and controls using DTI and DKI (data not shown).

Vestibular tests

Vestibular dysfunction was present in three of 21 controls and 13 of 21 athletes with SRC ($p=0.001$; Fig. 4). Vestibular dysfunction of peripheral ($n=1$), central ($n=1$), or combined ($n=1$) origin was diagnosed in controls and of peripheral ($n=9$) or combined ($n=4$) origin in athletes with SRC (Fig. 4). All participants had an normal audiogram, except one athlete with SRC who had left-sided peripheral vestibular dysfunction although right-sided hearing impairment.

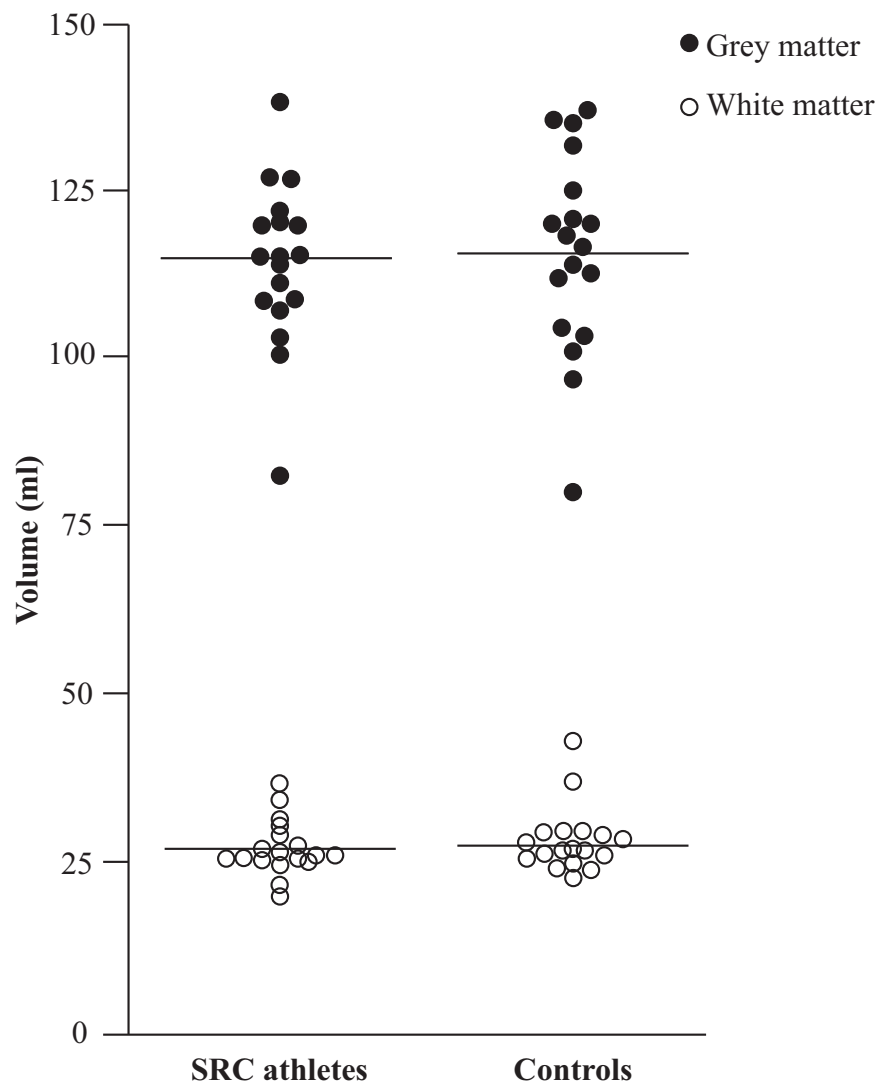


FIG. 3. Cerebellar volumes. Cerebellar volumes of grey and white matter in 18 SRC athletes and 18 controls. Mean volumes are noted with a line. Athletes with sports-related concussion (SRC) had a white matter volume of 27.3 mL and controls of 28.5 mL ($p=0.441$); athletes with SRC had a grey matter volume of 114 mL and controls of 116 mL ($p=0.722$). The volumes did not differ between the groups.

Table 3. Diffusion Weighed Imaging

DTI		SRC athletes median (IQR) n=19	Controls median (IQR) n=21	P
FA	Superior cerebellar peduncle	0.427 (0.412–0.442)	0.424 (0.397–0.448)	0.968
	Middle cerebellar peduncle	0.471 (0.448–0.488)	0.482 (0.460–0.497)	0.180
	Inferior cerebellar peduncle	0.430 (0.412–0.456)	0.433 (0.393–0.462)	0.888
MD	Superior cerebellar peduncle	0.742 (0.706–0.809)	0.740 (0.725–0.774)	0.695
	Middle cerebellar peduncle	0.745 (0.727–0.765)	0.743 (0.723–0.777)	0.715
	Inferior cerebellar peduncle	0.739 (0.686–0.829)	0.715 (0.674–0.774)	0.448
DKI		SRC athletes median (IQR) n=18	Controls median (IQR) n=20	P
MK	Superior cerebellar peduncle	0.923 (0.821–0.960)	0.972 (0.927–1.013)	0.010
	Middle cerebellar peduncle	0.942 (0.834–1.016)	0.980 (0.948–1.022)	0.090
	Inferior cerebellar peduncle	0.898 (0.860–0.953)	0.962 (0.934–0.993)	0.010
AK	Superior cerebellar peduncle	0.846 (0.822–0.882)	0.851 (0.829–0.891)	0.726
	Middle cerebellar peduncle	0.933 (0.906–0.955)	0.934 (0.920–0.955)	0.792
RK	Inferior cerebellar peduncle	0.952 (0.912–0.975)	0.945 (0.934–0.984)	0.748
	Superior cerebellar peduncle	0.878 (0.651–1.014)	1.032 (0.912–1.083)	0.006
	Middle cerebellar peduncle	0.873 (0.693–1.070)	0.999 (0.910–1.082)	0.070
	Inferior cerebellar peduncle	0.829 (0.686–0.945)	0.950 (0.851–1.023)	0.021

7T magnetic resonance imaging diffusion weighed imaging. Diffusion tensor imaging (DTI) metrics for fractional anisotropy (FA) and mean diffusion (MD), and diffusion kurtosis imaging (DKI) metrics for mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK), in the superior, middle, and inferior cerebellar peduncles. The significance threshold was set to 0.017 after Bonferroni correction; significant values are bolded. SRC, sports-related concussion.

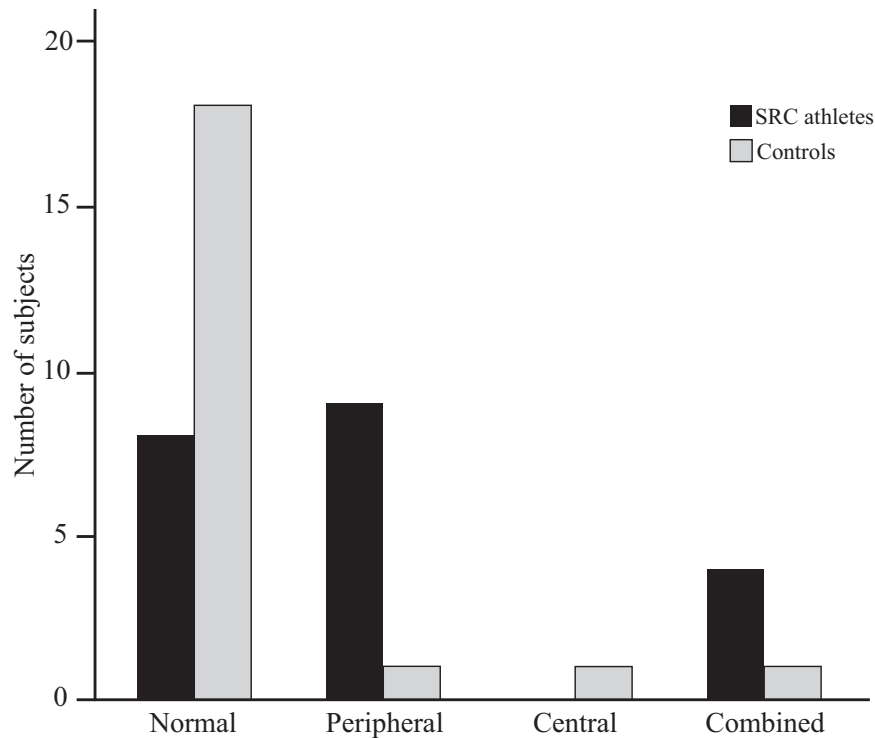


FIG. 4. Type of vestibular pathology. Vestibular dysfunction classified as normal (non-existing), peripheral, central, or combined in athletes with sports-related concussion (SRC) and controls. Among the athletes with SRC, nine had a peripheral and four a combined deficit where none had a central pathology. Among controls, one diagnosis was peripheral, one central, and one combined pathology.

The athletes with SRC had worse results in vHIT and cVEMP; all test-results are listed in Table 4. The combination of pathology on the posterior semicircular canal in vHIT and the ipsilateral cVEMP argues for an injury to the inferior vestibular nerve because responses are dependent on the integrity of the posterior semicircular canal (vHIT) or the saccule (cVEMP), both innervated

by the inferior vestibular nerve. Vestibular dysfunction did not correlate with the number of previous SRCs ($p=0.971$), age ($p=0.141$), sex ($p=0.758$) or SCAT-5 symptom severity ($p=0.418$).

Subjects with vestibular dysfunction assessed higher scores on DHI (median 35, IQR 4.5–47 vs. median 0, IQR 0–20.5, $p=0.019$) and HADS (median 15, IQR

Table 4. Vestibular Tests

Test name	Test structures	SRC athletes, n=21 Abnormal test results		Controls, n=21 Abnormal test results		P
		Number of subjects	Percent of subjects	Number of subjects	Percent of subjects	
vHIT	Peripheral system - Vestibular nerve, semicircular canals	10	52%	0	0%	< 0.001
Caloric test	Peripheral system - Semicircular canals	5	24%	4	1%	0.707
cVEMP	Peripheral system - Inferior vestibular nerve, Saccule	8	38%	0	0%	0.002
VNG	Central or peripheral system	3	14%	0	0%	0.072
Posturography	Collective vestibular system	8	38%	3	14%	0.079
PEM	Central system	4	19%	2	10%	0.378

Vestibular tests.

The results of vestibular tests for athletes with sports-related concussion (SRC) and controls. The results for the specific tests video head impulse test (vHIT), caloric test, cervical evoked myogenic potentials (cVEMP), videonystagmography (VNG), posturography, and pursuit eye movements (PEM) are reported as number and percent with pathological findings. The results of vHIT and cVEMP differ significantly between athletes with SRC and controls. The significance threshold was set to 0.05; significant values are bolded.

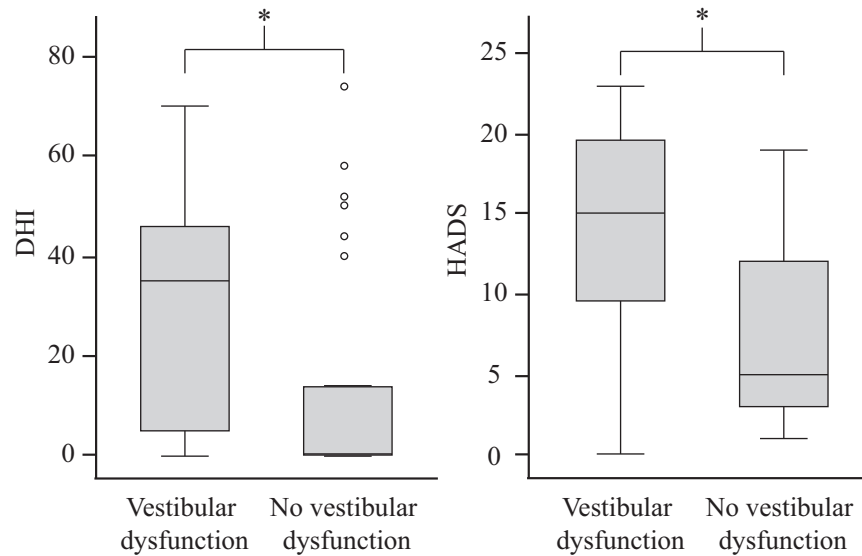


FIG. 5. Dizziness Handicap Inventory (DHI) and Hospital Anxiety and Depression Scale (HADS). Total scores of the DHI and HADS in athletes with and without vestibular dysfunction. If a vestibular pathology existed, subjects scored higher on DHI ($p=0.019$) and HADS ($p=0.004$) than athletes without vestibular dysfunction. $*p<0.05$.

9.25–19.75 vs. median 5, IQR 3–12.25, $p=0.004$) compared with subjects without vestibular dysfunction (Fig. 5).

Discussion

In this study, our focus was to investigate the vestibular system of athletes with persisting symptoms for ≥ 6 months after SRC. Athletes with SRC had a high burden of self-perceived symptoms and a negative impact on health because of dizziness, depression, and anxiety. The main finding was that athletes with SRC had a peripheral vestibular deficit, specifically dysfunction of the inferior vestibular nerve, whereas there was no difference in cerebellar gray and white matter as evaluated by 7T MRI.

In the present study, 80% and 85% of athletes with SRC reported dizziness and imbalance, respectively, which are symptoms of vestibular dysfunction. The included athletes with SRC had a high level of self-perceived symptoms on SCAT, DHI, and HADS, and subjects with vestibular dysfunction had higher levels of symptoms on DHI and HADS. These findings are in line with previous studies showing that vestibular dysfunction negatively affects SRC outcome.^{18–22} The DHI was developed to measure self-perceived handicap from symptoms of vestibular dysfunction and how they impact quality of life (QoL).^{33,34} After SRC, athletes commonly have increased levels of anxiety and depression,⁶⁰ and PPCS can lead to a lower QoL.⁶¹

White matter pathology is considered a major contributor to the sequelae of SRC,⁶² and a central cause of the vestibular dysfunction has been suggested. Two previous studies observed no abnormality in functional tests of the peripheral vestibular structures, including cVEMP and vHIT, at 10–14 days post-SRC. While the central vestibular systems were not tested, a central cause was suggested.^{27,28} Similarly, peripheral vestibular deficiency was not found in children and adults 4–6 months post-concussion.⁶³

Although not observed on conventional neuroimaging, the rotational forces sustained at impact are believed to disrupt white matter integrity.^{64,65} The DTI is sensitive to the microstructural integrity of white matter fibers and axonal injury.^{66–68} In SRC, DTI has revealed reduced white matter integrity, not explained by structural damage or volume loss.^{64,69–71} In patients with mTBI examined 22 days post-injury, a decreased cerebellar FA and increased MD correlated with vestibular dysfunction.²⁶ Vestibular laboratory findings were not reported, and the patients with mTBI differed in many aspects from the athletes with SRC in our present study.

To date, only one previous study investigated both the peripheral and central vestibular systems, examining a cohort of patients with mixed-TBI who had imbalance or dizziness 2–77 days post-injury.³¹ A decreased FA and increased MD was observed, correlating with vestibular dysfunction.³¹ These results are in contrast to our present 7T DTI and volumetry findings, although these

studies differ concerning selected patients, time points, mechanism, and injury severity. Decreased MK and/or RK in the DKI metrics were apparent in two cerebellar tracts, not confirmed by DTI, volumetrics, or by central vestibular tests. The high signal-to-noise ratio (SNR) of 7T MRI scanners allows for high-resolution structural imaging in feasible scan times, and the high image contrast can aid detection of diffuse pathology.⁷²

Arguably, these subtle findings on 7T MRI suggest discrete white matter changes insufficient to explain the impairment of the vestibular tests. If central white matter changes were more substantial, widespread alterations in the cerebellar tracts on both DKI and DTI would be expected and confirmed with a central pattern on vestibular laboratory tests. The subtle DKI findings could explain why some athletes with SRC presented with a combined deficit on vestibular tests. Further, this study does not address supratentorial white matter alterations, which may also cause vestibular symptoms if pronounced.

Some previous reports have suggested a peripheral origin of vestibular dysfunction. A retrospective study found that 26% of children and adolescents with vestibular disturbance had a peripheral vestibular disorder four months post-SRC.²⁹ Not all patients underwent vestibular testing, however.²⁹ In patients with TBI who had vestibular symptoms, acute unilateral peripheral vestibular loss was found in 19%,³⁰ and postmortem studies revealed degeneration of the superior and inferior vestibular nerves.^{73,74}

We observed that many athletes with SRC differed from controls on vHIT, cVEMP, VNG, and posturography, with a specific pattern of dysfunction suggesting a peripheral vestibular pathology, in contrast to some earlier reports.^{27,28,63} Athletes with SRC had abnormal results in the posterior semicircular canal in vHIT and the ipsilateral side in cVEMP. The inferior branch of the vestibular nerve is tested directly by cVEMP and through the posterior semicircular canal and sacculus by vHIT. Both vHIT and cVEMP confirmed the location of injury to the inferior vestibular nerve, in a repeatable manner. While the caloric test, VNG, PEM, and posturography were inconclusive, they do not exclude an inferior vestibular nerve injury.

On 7T MRI, no difference in cerebellar volumes or DTI metrics was observed and only minor changes in DKI metrics, arguing against central structural pathology and supporting the hypothesis of a peripheral vestibular injury.

The mechanisms causing a lesion of the inferior posterior nerve have not been established. In vestibular neuritis, the superior branch of the vestibular nerve is more affected than the inferior one,^{75,76} attributed to the longer route through the temporal bone.⁷⁷ Reversely, a longer bony canal may protect the nerve better in case of acceleration-deacceleration relative to the skull base,

resulting in lesions to the inferior nerve. Although hypothetical, this might be a plausible pathophysiological mechanism for our findings.

Limitations

We evaluated a highly characterized cohort of athletes with SRC who had persistent post-concussive symptoms ≥ 6 months. Thus, our cohort may not be representative of all athletes with SRC. Because we had no control group of recovered athletes with SRC nor athletes evaluated at an earlier post-injury time, other results could have been achieved in such cohorts. The selected groups and relatively small sample size may compromise generalizability and correlation analyses.

Although 7T MRI enables the acquisition of T1w images at a submillimeter resolution, subcortical image artefacts caused by B1+ inhomogeneity⁷⁸ appeared in some subjects. The motivation for using 7T MRI is its higher SNR compared with 3T MRI.⁷⁹ The 7T MRI, however, suffers from greater susceptibility-related artefacts,^{80,81} which explains the artifactual foreshortening of the brainstem in the anteroposterior direction seen in Fig. 1b. Moreover, the shorter T2 relaxation times compared with 3T partially cancels the relative SNR-benefit of 7T, especially for diffusion MRI, which necessitates longer echo times.⁸² Combining ultra-high field strengths with ultra-strong gradients could mitigate that problem.^{83,84} Slightly higher effect sizes, however, have been found at 7T compared to 3T.⁸⁵

The size of a tract is known to affect the performance of TractSeg, but merely in small tracts such as the fornix and the anterior commissure. The cerebellar tracts, however, are sufficiently large and should not be affected.⁴⁶

Vestibular laboratory tests are sensitive and can be influenced by tiredness and previous MRI.⁸⁶ To avoid these sources of error, the athletes with SRC and controls did their examinations well-rested during the midmorning and before the MRI. Several of the vestibular tests are challenging to interpret, because the results may both indicate a peripheral or central deficit, may be influenced by side differences, or body positioning and movement during the examinations. Therefore, we chose not to compare the specific numbers between the groups but instead compare pathological from normal responses. This classification was done by a neurotology specialist (MM), who was blinded to injury status, MRI findings, and questionnaire results.

Future use of 7T MRI

Ultrahigh field 7T diffusion MRI has the potentials to characterize human morphology and neuronal substructure, providing exquisite anatomical details and delineation of fiber substructures. Findings in substructures have been reported in the cochlear nucleus,⁸⁷

pedunculopontine nucleus, and surrounding white matter tracts⁸² and brainstem tracts.⁸⁸ Moreover, promising methods have been developed for improving image quality in 7T diffusion weighted MRI, which could subsequently increase the effectiveness of ultrahigh field diffusion MRI,^{79,89} summarized in the article by Gallichan.⁹⁰ Interestingly, one direction could be the fusion of 3T and 7T, exploiting the perks of both worlds, with high angular and spatial resolution, respectively.⁹¹

Conclusion

An SRC may induce a multitude of pathologies in the peripheral and/or central parts of the vestibular system. Establishing an etiology of the impairment is crucial because it may guide intervention and clinical management. Our study, investigating both central and peripheral dysfunction, strongly implies a peripheral nerve dysfunction associated with vestibular dysfunction in athletes with SRC who have persistent post-concussive symptoms.

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NM and YT are scientific advisors for PolarCool[®] Inc. For the remaining authors, no competing financial interests exist.

Supplementary Material

Supplementary Method 1
Supplementary Method 2

References

- Prien, A., Grafe, A., Rossler, R., Junge, A., and Verhagen, E. (2018). Epidemiology of head injuries focusing on concussions in team contact sports: a systematic review. *Sports Med.* 48, 953–969.
- Pierpoint, L.A., and Collins, C. (2021). Epidemiology of sport-related concussion. *Clin. Sports Med.* 40, 1–18.
- Ramkumar, P.N., Navarro, S.M., Haeberle, H.S., Luu, B.C., Jang, A., Frangiamore, S.J., Farrow, L.D., Schickendantz, M.S., and Williams, R.J. 3rd. (2019). Concussion in American versus European professional soccer: a decade-long comparative analysis of incidence, return to play, performance, and longevity. *Am. J. Sports Med.* 47, 2287–2293.
- Patel, B.H., Okoroha, K.R., Jildeh, T.R., Lu, Y., Idarraga, A.J., Nwachukwu, B.U., Shen, S.A., and Forsythe, B. (2019). Concussions in the National Basketball Association: analysis of incidence, return to play, and performance from 1999 to 2018. *Orthop. J. Sports Med.* 7, 2325967119854199.
- Pauelsen, M., Nyberg, G., Tegner, C., and Tegner, Y. (2017). Concussion in ice hockey - a cohort study across 29 seasons. *Clin. J. Sport Med.* 27, 283–287.
- Zuckerman, S.L., Kerr, Z.Y., Yengo-Kahn, A., Wasserman, E., Covassin, T., and Solomon, G.S. (2015). Epidemiology of sports-related concussion in NCAA athletes from 2009-2010 to 2013-2014: incidence, recurrence, and mechanisms. *Am. J. Sports Med.* 43, 2654–2662.
- McCrea, M., Guskiewicz, K.M., Marshall, S.W., Barr, W., Randolph, C., Cantu, R.C., Onate, J.A., Yang, J., and Kelly, J.P. (2003). Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA* 290, 2556–2563.
- McCrea, M., Guskiewicz, K., Randolph, C., Barr, W.B., Hammeke, T.A., Marshall, S.W., Powell, M.R., Woo Ahn, K., Wang, Y., and Kelly, J.P. (2013). Incidence, clinical course, and predictors of prolonged recovery time following sport-related concussion in high school and college athletes. *J. Int. Neuropsychol. Soc.* 19, 22–33.
- McCrorry, P., Feddermann-Demont, N., Dvorak, J., Cassidy, J.D., McIntosh, A., Vos, P.E., Echemendia, R.J., Meeuwisse, W., and Tarnutzer, A.A. (2017). What is the definition of sports-related concussion: a systematic review. *Br. J. Sports Med.* 51, 877–887.
- Emery, C.A., and Meeuwisse, W.H. (2006). Injury rates, risk factors, and mechanisms of injury in minor hockey. *Am. J. Sports Med.* 34, 1960–1969.
- Hiploylee, C., Dufort, P.A., Davis, H.S., Wennberg, R.A., Tartaglia, M.C., Mikulis, D., Hazrati, L.N., and Tator, C.H. (2017). Longitudinal study of postconcussion syndrome: not everyone recovers. *J. Neurotrauma* 34, 1511–1523.
- Tator, C.H., Davis, H.S., Dufort, P.A., Tartaglia, M.C., Davis, K.D., Ebraheem, A., and Hiploylee, C. (2016). Postconcussion syndrome: demographics and predictors in 221 patients. *J. Neurosurg.* 125, 1206–1216.
- American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition. Appendix B. American Psychiatric Association: Washington, D.C., pps. 704–706.
- World Health Organization. (1993). *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. World Health Organization: Geneva, pps. 63–64.
- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. American Psychiatric Association: Washington, D.C.
- Herdman, S.J. (2013). Vestibular rehabilitation. *Curr. Opin. Neurol.* 26, 96–101.
- Bisdorff, A., Von Brevern, M., Lempert, T., and Newman-Toker, D.E. (2009). Classification of vestibular symptoms: towards an international classification of vestibular disorders. *J. Vestib. Res.* 19, 1–13.
- Corwin, D.J., Wiebe, D.J., Zonfrillo, M.R., Grady, M.F., Robinson, R.L., Goodman, A.M., and Master, C.L. (2015). Vestibular deficits following youth concussion. *J. Pediatr.* 166, 1221–1225.
- Chorney, S.R., Suryadevara, A.C., and Nicholas, B.D. (2017). Audiovestibular symptoms as predictors of prolonged sports-related concussion among NCAA athletes. *Laryngoscope* 127, 2850–2853.
- Lau, B.C., Kontos, A.P., Collins, M.W., Mucha, A., and Lovell, M.R. (2011). Which on-field signs/symptoms predict protracted recovery from sport-related concussion among high school football players? *Am. J. Sports Med.* 39, 2311–2318.
- Anzalone, A.J., Blueitt, D., Case, T., McGuffin, T., Pollard, K., Garrison, J.C., Jones, M.T., Pavur, R., Turner, S., and Oliver, J.M. (2017). A positive vestibular/ocular motor screening (VOMS) is associated with increased recovery time after sports-related concussion in youth and adolescent athletes. *Am. J. Sports Med.* 45, 474–479.
- Sinnott, A.M., Elbin, R.J., Collins, M.W., Reeves, V.L., Holland, C.L., and Kontos, A.P. (2019). Persistent vestibular-ocular impairment following concussion in adolescents. *J. Sci. Med. Sport.* 22, 1292–1297.
- Dieterich, M., and Brandt, T. (2015). The bilateral central vestibular system: its pathways, functions, and disorders. *Ann. N. Y. Acad. Sci.* 1343, 10–26.
- Casale, J., Browne, T., Murray, I., and Gupta, G. (2021). *Physiology, Vestibular System*. StatPearls. StatPearls Publishing: Treasure Island, FL.
- Brandt, T., and Dieterich, M. (2017). The dizzy patient: don't forget disorders of the central vestibular system. *Nat. Rev. Neurol.* 13, 352–362.
- Alhilali, L.M., Yaeger, K., Collins, M., and Fakhran, S. (2014). Detection of central white matter injury underlying vestibulopathy after mild traumatic brain injury. *Radiology* 272, 224–32.
- Christy, J.B., Cochrane, G.D., Almutairi, A., Bussetini, C., Swanson, M.W., and Weise, K.K. (2019). Peripheral vestibular and balance function in athletes with and without concussion. *J. Neurol. Phys. Ther.* 43, 153–159.

28. Alkathiry, A.A., Kontos, A.P., Furman, J.M., Whitney, S.L., Anson, E.R., and Sparto, P.J. (2019). Vestibulo-ocular reflex function in adolescents with sport-related concussion: preliminary results. *Sports Health* 11, 479–485.
29. Brodsky, J.R., Shoshany, T.N., Lipson, S., and Zhou, G. (2018). Peripheral vestibular disorders in children and adolescents with concussion. *Otolaryngol. Head Neck Surg.* 159, 365–370.
30. Marcus, H.J., Paine, H., Sargeant, M., Wolstenholme, S., Collins, K., Marroney, N., Arshad, Q., Tsang, K., Jones, B., Smith, R., Wilson, M.H., Rust, H.M., and Seemungal, B.M. (2019). Vestibular dysfunction in acute traumatic brain injury. *J. Neurol.* 266, 2430–2433.
31. Calzolari, E., Chepishcheva, M., Smith, R.M., Mahmud, M., Hellyer, P.J., Tahtis, V., Arshad, Q., Jolly, A., Wilson, M., Rust, H., Sharp, D.J., and Seemungal, B.M. (2021). Vestibular agnosia in traumatic brain injury and its link to imbalance. *Brain* 144, 128–143.
32. (2017). Sport concussion assessment tool - 5th edition. *Br. J. Sports Med.* 51, 851–858.
33. Jacobson, G.P., and Newman, C.W. (1990). The development of the Dizziness Handicap Inventory. *Arch. Otolaryngol. Head Neck Surg.* 116, 424–427.
34. Mutlu, B., and Serbetcioglu, B. (2013). Discussion of the dizziness handicap inventory. *J. Vestib. Res.* 23, 271–277.
35. Zigmond, A.S., and Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 67, 361–370.
36. Snaith, R.P. (2003). The Hospital Anxiety And Depression Scale. *Health Qual. Life Outcomes* 1, 29.
37. Fischl, B. (2012). *FreeSurfer*. *Neuroimage* 62, 774–781.
38. Ross, M.C., Dvorak, D., Sartini-Tarm, A., Botsford, C., Cogswell, I., Hoffstetter, A., Putnam, O., Schomaker, C., Smith, P., Stalsberg, A., Wang, Y., Xiong, M., and Cisler, J.M. (2021). Gray matter volume correlates of adolescent posttraumatic stress disorder: a comparison of manual intervention and automated segmentation in *FreeSurfer*. *Psychiatry Res. Neuroimaging* 313, 111297.
39. Veraart, J., Novikov, D.S., Christiaens, D., Ades-Aron, B., Sijbers, J., and Fieremans, E. (2016). Denoising of diffusion MRI using random matrix theory. *Neuroimage* 142, 394–406.
40. Kellner, E., Dhital, B., Kiselev, V.G., and Reiser, M. (2016). Gibbs-ringing artifact removal based on local subvoxel-shifts. *Magn. Reson. Med.* 76, 1574–1581.
41. Anderson, E.C., and Thompson, E.A. (2002). A model-based method for identifying species hybrids using multilocus genetic data. *Genetics* 160, 1217–1229.
42. Andersson, J.L., and Sotiropoulos, S.N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage* 125, 1063–1078.
43. Basser, P.J., Mattiello, J., and LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophys. J.* 66, 259–267.
44. Jensen, J.H., Helpert, J.A., Ramani, A., Lu, H., and Kaczynski, K. (2005). Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. *Magn. Reson. Med.* 53, 1432–1440.
45. Wasserthal, J., Neher, P.F., Hirjak, D., and Maier-Hein, K.H. (2019). Combined tract segmentation and orientation mapping for bundle-specific tractography. *Med. Image Anal.* 58, 101559.
46. Wasserthal, J., Neher, P., and Maier-Hein, K.H. (2018). TractSeg - Fast and accurate white matter tract segmentation. *Neuroimage* 183, 239–253.
47. Sotiropoulos, S.N., Jbabdi, S., Xu, J., Andersson, J.L., Moeller, S., Auerbach, E.J., Glasser, M.F., Hernandez, M., Sapiro, G., Jenkinson, M., Feinberg, D.A., Yacoub, E., Lenglet, C., Van Essen, D.C., Ugurbil, K., Behrens, T.E., and WU-Minn HCP Consortium. (2013). Advances in diffusion MRI acquisition and processing in the Human Connectome Project. *Neuroimage* 80, 125–143.
48. Ulmer, E., and Chays, A. (2005). [Curthoys and Halmagyi Head Impulse test: an analytical device]. *Ann. Otolaryngol. Chir. Cervicofac.* 122, 84–90.
49. Ulmer, E., Bernard-Demanze, L., and Lacour, M. (2011). Statistical study of normal canal deficit variation range. Measurement using the Head Impulse Test video system. *Eur. Ann. Otorhinolaryngol. Head Neck Dis.* 128, 278–282.
50. McGarvie, L.A., Martinez-Lopez, M., Burgess, A.M., MacDougall, H.G., and Curthoys, I.S. (2015). Horizontal eye position affects measured vertical VOR gain on the Video Head Impulse Test. *Front. Neurol.* 6, 58.
51. Wittmeyer Cedervall, L., Magnusson, M., Karlberg, M., Fransson, P.A., Nystrom, A., and Tjernstrom, F. (2021). vHIT testing of vertical semicircular canals with goggles yield different results depending on which canal plane being tested. *Front. Neurol.* 12, 692196.
52. Shepard, N.T., and Jacobson, G.P. (2016). The caloric irrigation test. *Handb. Clin. Neurol.* 137, 119–31.
53. Murphy, K.A., and Anilkumar, A.C. (2021). *Caloric Testing*. StatPearls Publishing: Treasure Island, FL.
54. Bárány, R. (1906). Untersuchungen ueber den vom Vestibularapparat des Ohres reflektorisch ausgelosten rhythmischen Nystagmus und seine Begleiterscheinungen. *Monatsschrift Ohrenheilkunde* 193–297.
55. Rosengren, S.M., Welgampola, M.S., and Colebatch, J.G. (2010). Vestibular evoked myogenic potentials: past, present and future. *Clin. Neurophysiol.* 121, 636–651.
56. Thompson, T.L., and Amedee, R. (2009). Vertigo: a review of common peripheral and central vestibular disorders. *Ochsner J.* 9, 20–26.
57. Johansson, R., Magnusson, M., Fransson, P.A., and Karlberg, M. (2001). Multi-stimulus multi-response posturography. *Math. Biosci.* 174, 41–59.
58. Lisberger, S.G. (2015). Visual guidance of smooth pursuit eye movements. *Annu. Rev. Vis. Sci.* 1, 447–468.
59. Andica, C., Kamagata, K., Hatano, T., Saito, Y., Ogaki, K., Hattori, N., and Aoki, S. (2020). MR Biomarkers of degenerative brain disorders derived from diffusion imaging. *J. Magn. Reson. Imaging* 52, 1620–1636.
60. Manley, G., Gardner, A.J., Schneider, K.J., Guskiewicz, K.M., Bailes, J., Cantu, R.C., Castellani, R.J., Turner, M., Jordan, B.D., Randolph, C., Dvorak, J., Hayden, K.A., Tator, C.H., McCrory, P., and Iverson, G.L. (2017). A systematic review of potential long-term effects of sport-related concussion. *Br. J. Sports Med.* 51, 969–977.
61. Gard, A., Lehto, N., Engstrom, A., Shahim, P., Zetterberg, H., Blennow, K., Marklund, N., and Tegner, Y. (2020). Quality of life of ice hockey players after retirement due to concussions. *Concussion* 5, CNC78.
62. McKee, A.C., Daneshvar, D.H., Alvarez, V.E., and Stein, T.D. (2014). The neuropathology of sport. *Acta Neuropathol.* 127, 29–51.
63. Alshehri, M.M., Sparto, P.J., Furman, J.M., Fedor, S., Mucha, A., Henry, L.C., and Whitney, S.L. (2016). The usefulness of the video head impulse test in children and adults post-concussion. *J. Vestib. Res.* 26, 439–446.
64. Gardner, A., Kay-Lambkin, F., Stanwell, P., Donnelly, J., Williams, W.H., Hiles, A., Schofield, P., Levi, C., and Jones, D.K. (2012). A systematic review of diffusion tensor imaging findings in sports-related concussion. *J. Neurotrauma* 29, 2521–2538.
65. Chamard, E., and Lichtenstein, J.D. (2018). A systematic review of neuroimaging findings in children and adolescents with sports-related concussion. *Brain Inj.* 32, 816–831.
66. Soares, J.M., Marques, P., Alves, V., and Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Front. Neurosci.* 7, 31.
67. Tae, W.S., Ham, B.J., Pyun, S.B., Kang, S.H., and Kim, B.J. (2018). Current clinical applications of diffusion-tensor imaging in neurological disorders. *J. Clin. Neurol.* 14, 129–140.
68. Richter, S., Winzeck, S., Kornaropoulos, E.N., Das, T., Vande Vyvere, T., Verheyden, J., Williams, G.B., Correia, M.M., Menon, D.K., Newcombe, V.F., Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Magnetic Resonance Imaging Substudy Participants and Investigators. (2021). Neuroanatomical substrates and symptoms associated with magnetic resonance imaging of patients with mild traumatic brain injury. *JAMA Netw Open* 4, e210994.
69. Oehr, L., and Anderson, J. (2017). Diffusion-tensor imaging findings and cognitive function following hospitalized mixed-mechanism mild traumatic brain injury: a systematic review and meta-analysis. *Arch. Phys. Med. Rehabil.* 98, 2308–2319.
70. Aoki, Y., Inokuchi, R., Gunshin, M., Yahagi, N., and Suwa, H. (2012). Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis. *J. Neurol. Neurosurg. Psychiatry* 83, 870–876.
71. Coughlin, J.M., Yuchuanwang, Y., Minn, I., Bienko, N., Ambinder, E.B., Xu, X., Peters, M.E., Dougherty, J.W., Vranesic, M., Koo, S.M., Ahn, H.H., Lee, M., Cottrell, C., Sair, H.I., Sawa, A., Munro, C.A., Nowinski, C.J., Dannals, R.F., Lyketos, C.G., Kassiou, M., Smith, G., Caffo, B., Mori, S., Guilarte, T.R., and Pomper, M.G. (2017). Imaging of glial cell activation and white matter integrity in brains of active and recently retired national football league players. *JAMA Neurol.* 74, 67–74.
72. Obusez, E.C., Lowe, M., Oh, S.H., Wang, I., Jennifer, B., Ruggieri, P., Hill, V., Lockwood, D., Emch, T., Moon, D., Loy, G., Lee, J., Kiczek, M., Manoj, M., Staszewych, V., Stultz, T., and Jones, S.E. (2018). 7T MR of intracranial pathology: preliminary observations and comparisons to 3T and 1.5T. *Neuroimage* 168, 459–476.
73. Knoll, R.M., Ishai, R., Lubner, R.J., Trakimas, D.R., Brodsky, J.R., Jung, D.H., Rauch, S.D., Nadol, J.B., Jr., Remenschneider, A.K., and Kozin, E.D. (2020).

- Peripheral vestibular organ degeneration after temporal bone fracture: a human otopathology study. *Laryngoscope* 130, 752–760.
74. Knoll, R.M., Ishai, R., Trakimas, D.R., Chen, J.X., Nadol, J.B., Jr., Rauch, S.D., Remenschneider, A.K., Jung, D.H., and Kozin, E.D. (2019). Peripheral vestibular system histopathologic changes following head injury without temporal bone fracture. *Otolaryngol. Head Neck Surg.* 160, 122–130.
 75. Aw, S.T., Fetter, M., Cremer, P.D., Karlberg, M., and Halmagyi, G.M. (2001). Individual semicircular canal function in superior and inferior vestibular neuritis. *Neurology* 57, 768–774.
 76. Fetter, M., and Dichgans, J. (1996). Vestibular neuritis spares the inferior division of the vestibular nerve. *Brain* 119, 755–763.
 77. Goebel, J.A., O'Mara, W., and Gianoli, G. (2001). Anatomic considerations in vestibular neuritis. *Otol. Neurotol.* 22, 512–518.
 78. O'Brien, K.R., Kober, T., Hagmann, P., Maeder, P., Marques, J., Lazeyras, F., Krueger, G., and Roche, A. (2014). Robust T1-weighted structural brain imaging and morphometry at 7T using MP2RAGE. *PLoS One* 9, e99676.
 79. Setsompop, K., Kimmlingen, R., Eberlein, E., Witzel, T., Cohen-Adad, J., McNab, J.A., Keil, B., Tisdall, M.D., Hoecht, P., Dietz, P., Cauley, S.F., Tountcheva, V., Matschl, V., Lenz, V.H., Heberlein, K., Potthast, A., Thein, H., Van Horn, J., Toga, A., Schmitt, F., Lehne, D., Rosen, B.R., Wedeen, V., and Wald, L.L. (2013). Pushing the limits of in vivo diffusion MRI for the Human Connectome Project. *Neuroimage* 80, 220–233.
 80. Choi, S., Cunningham, D.T., Aguila, F., Corrigan, J.D., Bogner, J., Mysiw, W.J., Knopp, M.V., and Schmalbrock, P. (2011). DTI at 7 and 3 T: systematic comparison of SNR and its influence on quantitative metrics. *Magn. Reson. Imaging* 29, 739–751.
 81. Cunningham, D.C., S. Corrigan, J. Bogner, J. Mysiw, W. Zachariah, C.R. Knopp, M.V. Schmalbrock, P. (2010). 7T DTI in mild chronic traumatic brain injury: assessment of the superior longitudinal fasciculus and cingulum bundle. Presented at the ISMRM Meeting, Stockholm.
 82. Henssen, D., Kuppens, D., Meijer, F.J.A., van Cappellen van Walsum, A.M., Temel, Y., and Kurt, E. (2019). Identification of the pedunculopontine nucleus and surrounding white matter tracts on 7T diffusion tensor imaging, combined with histological validation. *Surg. Radiol. Anat.* 41, 187–196.
 83. Vachha, B., and Huang, S.Y. (2021). MRI with ultrahigh field strength and high-performance gradients: challenges and opportunities for clinical neuroimaging at 7 T and beyond. *Eur. Radiol. Exp.* 5, 35.
 84. Jones, D.K., Alexander, D.C., Bowtell, R., Cercignani, M., Dell'Acqua, F., McHugh, D.J., Miller, K.L., Palombo, M., Parker, G.J.M., Rudrapatna, U.S., and Tax, C.M.W. (2018). Microstructural imaging of the human brain with a 'super-scanner': 10 key advantages of ultra-strong gradients for diffusion MRI. *Neuroimage* 182, 8–38.
 85. Polders, D.L., Leemans, A., Hendrikse, J., Donahue, M.J., Luijten, P.R., and Hoogduin, J.M. (2011). Signal to noise ratio and uncertainty in diffusion tensor imaging at 1.5, 3.0, and 7.0 Tesla. *J. Magn. Reson. Imaging* 33, 1456–1463.
 86. Roberts, D.C., Marcelli, V., Gillen, J.S., Carey, J.P., Della Santina, C.C., and Zee, D.S. (2011). MRI magnetic field stimulates rotational sensors of the brain. *Curr. Biol.* 21, 1635–1640.
 87. Epprecht, L., Qureshi, A., Kozin, E.D., Vachicouras, N., Huber, A.M., Kikinis, R., Makris, N., Brown, M.C., Reinshagen, K.L., and Lee, D.J. (2020). Human cochlear nucleus on 7 tesla diffusion tensor imaging: insights into micro-anatomy and function for auditory brainstem implant surgery. *Otol. Neurotol.* 41, e484–e93.
 88. Zitella, L.M., Xiao, Y., Teplitzky, B.A., Kastl, D.J., Duchin, Y., Baker, K.B., Vitek, J.L., Adriany, G., Yacoub, E., Harel, N., and Johnson, M.D. (2015). In vivo 7T MRI of the Nnn-human primate brainstem. *PLoS One* 10, e0127049.
 89. Wu, W., Poser, B.A., Douaud, G., Frost, R., In, M.H., Speck, O., Koopmans, P.J., and Miller, K.L. (2016). High-resolution diffusion MRI at 7T using a three-dimensional multi-slab acquisition. *Neuroimage* 143, 1–14.
 90. Gallichan, D. (2018). Diffusion MRI of the human brain at ultra-high field (UHF): a review. *Neuroimage* 168, 172–180.
 91. Sotiropoulos, S.N., Hernandez-Fernandez, M., Vu, A.T., Andersson, J.L., Moeller, S., Yacoub, E., Lenglet, C., Ugurbil, K., Behrens, T.E.J., and Jbabdi, S. (2016). Fusion in diffusion MRI for improved fibre orientation estimation: an application to the 3T and 7T data of the Human Connectome Project. *Neuroimage* 134, 396–409.