

Multiparameter cortical surface morphology in former amateur contact sport athletes

Grace Recht¹, Jiancheng Hou^{1,2}, Claire Buddenbaum¹, Hu Cheng^{3,4}, Sharlene D. Newman⁵, Andrew J. Saykin^{6,7}, Keisuke Kawata^{1,4,8,*}

¹Department of Kinesiology, Indiana University School of Public Health-Bloomington, 1025 E. 10th Street, Bloomington, IN 47405, United States

²Research Center for Cross-Straits Cultural Development, Fujian Normal University, Cangshan Campus, No. 8 Shangshan Road, Cangshan District, Fuzhou, Fujian 350007, China

³Department of Psychological and Brain Sciences, College of Arts and Sciences, Indiana University, 1101 E. 10th Street, Bloomington, IN 47405, United States

⁴Program in Neuroscience, The College of Arts and Sciences, Indiana University, 1101 East 10th Street, Bloomington, IN 47405, United States

⁵Alabama Life Research Institute, College of Arts & Sciences, University of Alabama, 211 Peter Bryce Blvd., Tuscaloosa, AL 35401, United States

⁶Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine, 355 West 16th Street, Indianapolis, IN 46202, United States

⁷Department of Radiology and Imaging Sciences, Indiana University School of Medicine, 550 University Blvd, Indianapolis, IN 46202, United States

⁸Department of Pediatrics, Indiana University School of Medicine, 1130 W Michigan St, Indianapolis, IN 46202, United States

*Corresponding author: Keisuke Kawata, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States.

Email: kkawata@indiana.edu

The lifetime effects of repetitive head impacts have captured considerable public and scientific interest over the past decade, yet a knowledge gap persists in our understanding of midlife neurological well-being, particularly in amateur level athletes. This study aimed to identify the effects of lifetime exposure to sports-related head impacts on brain morphology in retired, amateur athletes. This cross-sectional study comprised of 37 former amateur contact sports athletes and 21 age- and sex-matched noncontact athletes. High-resolution anatomical, T1 scans were analyzed for the cortical morphology, including cortical thickness, sulcal depth, and sulcal curvature, and cognitive function was assessed using the Dementia Rating Scale-2. Despite no group differences in cognitive functions, the contact group exhibited significant cortical thinning particularly in the bilateral frontotemporal regions and medial brain regions, such as the cingulate cortex and precuneus, compared to the noncontact group. Deepened sulcal depth and increased sulcal curvature across all four lobes of the brain were also notable in the contact group. These data suggest that brain morphology of middle-aged former amateur contact athletes differs from that of noncontact athletes and that lifetime exposure to repetitive head impacts may be associated with neuroanatomical changes.

Key words: traumatic brain injury; concussion; cortical thickness; chronic traumatic encephalopathy; cognition.

Introduction

The prevalence of neurodegenerative diseases, such as Alzheimer's disease (AD) and AD-related dementia, is anticipated to triple over the next three decades (Collaborators 2022). While well-established risk factors like age, genetics, obesity, and cardiovascular diseases are associated with AD (Xu et al. 2015), emerging research highlights traumatic brain injury (TBI) as a modifiable risk factor, particularly through repetitive concussive and nonconcussive head impacts in sports (Baumgart et al. 2015; Livingston et al. 2020; Echlin et al. 2021; Nowinski et al. 2024). This includes cases of chronic traumatic encephalopathy (CTE), where repeated mechanical forces disrupt structural elements of the brain and accelerate the aging process (McKee et al. 2016). Over the past two decades, significant effort has been invested in understanding the etiology and treatment of concussions, establishing limits for tolerance to repetitive head impacts (RHIs), and identifying risk factors and diagnostic criteria for CTE. However, these endeavors have predominantly focused on either active athletic population (e.g. professional, collegiate, adolescent) or the deceased, revealing a critical knowledge gap regarding the association between RHI and brain health in middle aged adults.

Owing to the structural vulnerability of axons to shear and strain forces, athletes experiencing RHI consistently show

damage at the axonal microstructural level (Schneider et al. 2019). Conversely, alterations in brain structure at a macro-level have been thought to require prolonged exposure to RHI. For example, active soccer and rugby players in their 20s and 30s demonstrate no sign of cortical morphological changes (Wojtowicz et al. 2018; Oliveira et al. 2020), yet reduced cortical thickness in frontotemporal regions and parietal lobes are notable years after retirement from professional American football and soccer (Goswami et al. 2016; Koerte et al. 2016). On the other hand, a more recent neuroimaging study by Zuidema et al. (2024), including 205 adolescent football players and 70 age-sex-race-matched noncontact control athletes, revealed significant cortical thinning in the frontooccipital regions of football players' brains. Similarly, active high school and college football players exhibited greater brain volume reduction and cortical thinning in frontotemporal regions after a single (Dudley et al. 2022) and multiple seasons (Mills et al. 2020), in comparison to control athletes such as volleyball. This observation supports the concept that alterations in brain morphology can occur without discernible clinical signs of neurodegenerative conditions (Meier et al. 2016; Zuidema et al. 2024), which is further underscored by a recent report highlighting cases of CTE among young adults with a history of RHI exposure (McKee et al. 2023). Thus, a rigorous characterization technique in premortem brain integrity is of paramount importance to public health.

Received: April 26, 2024. Revised: June 29, 2024. Accepted: July 8, 2024

© The Author(s) 2024. Published by Oxford University Press. All rights reserved. For permissions, please e-mail: journals.permission@oup.com.

Complementary to measuring cortical thickness, a geometric analysis provides insights into sulcal depth and sulcal curvature measures, offering indicators of the neurobiological aspects of brain aging (Zilles et al. 1988). Computational studies suggest that traumatic forces to the brain prompt the rapid clustering of cerebral spinal fluid in the base of sulci, causing shearing waves known as “water hammer” effects (Kochunov et al. 2005). Repetitive mechanical stress can accelerate tissue atrophy and deepen sulci (Zuidema et al. 2024). Gyrus formation occurs during prenatal and postnatal stages until age 2, but various stressors, including brain trauma, can alter gyrification and complexity of curvatures. For example, adults with recent concussions showed a significant increase in frontal lobe sulcal curvature compared to controls, coupled with reduced sulcal curvature in the temporal lobe (Gharehghazlou et al. 2022). Moreover, individuals who experienced brain trauma at an early age (1 to 8 yr) demonstrated altered cortical organization, as illustrated by increased sulcal curvature in widespread frontoparietal and posterior temporal regions (Wilde et al. 2021). These findings provide insights into the dynamic cortical changes in individuals with a history of RHI.

In this cohort study, we applied to these neuroimaging techniques to examine cortical morphological differences between a broad range of middle-aged adults (30 to 60 yr) with an extensive history (10+ years) of contact sports and age-/sex-matched control adults with a history of noncontact sports. We hypothesized that the contact group would exhibit cortical thinning, greater sulcal depth, and altered sulcal curvature patterns compared to those of the control group. Our exploratory analysis included potential relationships between cognitive performance and brain morphology.

Materials and methods

Participants

This cohort study included 60 participants, including 38 contact sport athletes (28 males, 10 females) and 22 age- and sex-matched noncontact athletes (14 males, 8 females). Potential participants were recruited by emails to community partners, social media posts, and Indiana CTSI's iCONNECT. Data were collected from February to September 2023. Potential participants were screened as either a retired contact sport or retired noncontact sport athlete. A contact sport was operationally defined as sports that have routine, body-to-body contact that is expected as part of the sport played. This includes, but is not limited to, sports such as football, rugby, soccer, wrestling, boxing, and ice hockey. Noncontact sports were operationally defined as sports where body-to-body contact is rare and unexpected. This includes, but is not limited to, baseball, cross-country/track, volleyball, and tennis (Katz et al. 2018). Inclusion criteria for the contact group included having at least 10 years of organized, amateur level contact sport participation experience and being between the ages of 30 and 60. For the noncontact group, participants needed to have at least 10 years of participation in organized, amateur level noncontact sports, no history of participation in contact sports, and be between the ages of 30 and 60. Amateur-level athlete was operationally defined as athletes who had participated in childhood, high school, and/or collegiate level sports. Exclusion criteria for both groups were any history of head, neck, or facial injuries, including concussions, in the 6 months prior to study participation, pregnancy, a history of any neurological disorders, impaired decisional capacity, metal implants in the head, and any implanted electro/magnetic devices. Please see Fig. 1 for a flow chart of the study. All participants provided informed consent

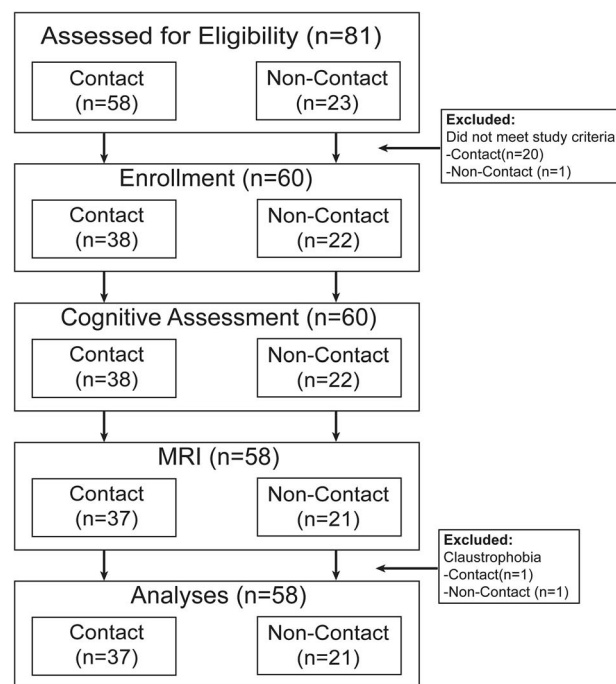


Fig. 1. Study flow chart.

prior to participation in any study procedures. The study protocol was approved by the Indiana University Institutional Review Board (#17763).

Cognitive assessment

Prior to MRI scan, participants in both groups underwent cognitive assessment using the Dementia Rating Scale-2 (DRS-2), which is designed to assess cognitive impairment related to neurodegenerative disorders (Jurica et al. 2001). The DRS-2 is administered by a trained mental health professional to the participant. The assessment consists of 36 tasks across 5 cognitive domains: attention, initiation/perseveration, construction, conceptualization, and memory. Briefly, the attention subscale, which tests both auditory-visual and verbal-nonverbal memory, is composed of 8 tasks with 37 possible points. The perseveration subscale, which measures the participants ability to switch, initiate, or terminate a specific activity, is comprised of 11 tasks with a maximum of 37 points. The construction section requires the participant to recreate stimulus designs with varying degrees of difficulty and includes six tasks with a maximum of six points. The conceptualization subscale, which measures the ability to induce and detect differences among verbal and visual stimuli, consists of six tasks with the potential of 39 points. The memory subscale includes verbal and nonverbal stimuli presented to examine immediate or delayed recall and consists of five tasks with a maximum of 25 points. The highest score of the DRS-2 is 144, derived from the sum of each subsection.

Mental health questionnaires

Participants also completed mental health scales that assessed symptoms of depression [Patient Health Questionnaire–Depression (PHQ-9)], PTSD [PTSD Checklist–Civilian Version (PCL-C)], and ADHD [DSM-5 Diagnostic Criteria for ADHD]. The PHQ-9 assesses depression-related symptoms: each of the nine items describes one symptom that corresponds to one of the diagnostic criteria for depression (Kroenke et al. 2001). The PCL-C assesses

symptoms that are key for a diagnosis of PTSD (Conybeare et al. 2012). The DSM-5 Diagnostic Criteria for ADHD is an 18-item screening tool developed to assess for key symptoms of an ADHD diagnosis in adults (Solanto et al. 2012). These three mental health questionnaires were selected for the following reasons. The PHQ-9 is a validated questionnaire for depressive symptomatology, which has been impacted by exposure to RHI (Buddenbaum et al. 2024; de Souza et al. 2024). Similarly, interactive effects of RHI and ADHD symptoms have been postulated, where ADHD symptoms may mimic persistent postconcussive symptoms (Cook et al. 2020), as well as ADHD increasing vulnerability to RHI (Nowak et al. 2022). Lastly, a correlation between RHI and PTSD symptoms has been well-established, including our recent research in adults with RHI history exhibiting heightened PTSD symptoms (Buddenbaum et al. 2024).

MRI data acquisition

The MRI data were acquired on a 3 T Siemens Prisma scanner (Siemens, Erlangen, Germany), equipped with a 64-channel head/neck coil. Cortical morphometry measurements were based on high-resolution T1-weighted, anatomical images, which were acquired using 3D MPAGE pulse sequence with the following parameters: TR/TE=2400/2.3 ms, TI=1060 ms, flip angle=8, matrix=320 × 320, bandwidth=210 Hz/pixel, and iPAT=2, which resulted in 0.8 mm isotropic resolution.

MRI quality control procedures

The quality control (QC) step was performed through the DPABI QC module in DPABI toolbox. During the preprocessing, T1 images were re-oriented to enhance the accuracy of coregistration and segmentation, especially if the initial orientation was inconsistent with a standard template. The DPABI QC module rates the quality of structural images on a scale from 0 to 5 (with 5 being very good and 0 being very poor) by screening for distortions, head motion, ghosting, or structural abnormalities (Yan et al. 2016). The QC process rated “5” for all our participants’ images. Additionally, one team member performed a visual screening of the T1 images, which yielded no visible abnormalities.

Cortical morphometry preprocessing and analyses

The Computational Anatomy Toolbox (CAT12; <https://neuro-jena.github.io/cat/>), which is a plug-in software that is based on Statistical Parametric Mapping (SPM12; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) was used for preprocessing of the T1-weighted MRI data. The preprocessing consisted of bias-field correction, skull stripping, and alignment of the Montreal Neurological Institute structural template to classify white matter (WM), gray matter (GM), and cerebrospinal fluid. Spatial normalization was conducted with Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) registration (1.5 mm) (Li et al. 2021).

Cortical thickness was analyzed based on the workflow that is specified in a previous study (Dahnke et al. 2013). To estimate the WM segment, a voxel-based distance method was used by calculating the distance from the inner GM boundary. The GM thickness was generated by using the values at the outer GM boundary in the WM distance map projected back to the inner GM boundary. A central surface was then created at the 50% level of the percentage position between the WM distance and the GM thickness. A topology correction based on spherical harmonics was used to account for any topological deficits for the resultant central surface (Li et al. 2021). The central surface was then reparametrized into a common coordinate system through

spherical mapping (Desikan et al. 2006). Cortical thickness data were then spherically smoothed with a Gaussian kernel with a 15 mm full-width at half-maximum (FWHM).

Sulcal curvature, as an indication for cortical folding, was calculated as absolute mean curvature based on spherical harmonics (Luders et al. 2006). Mean curvature is an extrinsic surface measure which provides information about the change from normal direction along the surface. Sulcal depth measures the depth of the sulci and is calculated as the Euclidean distance between the central surface and its convex hull based on spherical harmonics, then transformed with the sqrt function (Luders et al. 2006). For these analyses, a 25 mm FWHM Gaussian kernel was used during the spatial smoothing step for sulcal curvature and sulcal depth analyses.

Statistical analysis

Demographic differences between the contact and noncontact groups were assessed with two-tailed independent samples t-tests for continuous variables and chi-square tests for categorical variables. Group differences in the sum and five individual domains of scores were assessed using multivariable linear regressions with the following covariates: age, sex, and depression score via PHQ-9. There is a multicollinearity issue among mental health scores that showed significant group differences (PHQ-9, PCL-C, and ADHD: all $r < 0.65$, $P < 0.05$); thus, we selected PHQ-9 to be included in the models as a representative covariate. A level of significance was set to $P < 0.008$ to reflect six outcomes. These analyses were conducted using R, version 4.3.2 (R Project for Statistical Computing) with the package nlme. The analysis was summarized by providing a contrast estimate with its 95% CI and P-value in the following format: [estimate (CI low, CI high); P-value].

Group comparisons of cortical thickness, sulcal depth, and sulcal curvature were performed using CAT12 and analyzed with a nonparametric permutation technique (5000 permutations). Age, sex, PHQ-9, and intracranial volume were included as covariates. The threshold-free cluster enhancement was used in the permutation test, which gives a cluster-based threshold for familywise error correction, and the level of significance was set to $P < 0.017$ to reflect 3 morphological outcomes. Brain regions with a cluster size of at least 30 vertices (cluster size × percentage covered in the specific region produced by CAT12) were reported. The Desikan–Killiany atlas (DK40) (Potvin et al. 2017) was used to identify the cortical regions, and results were visualized using CAT12.

Lastly, a series of linear regression model was used to explore whether cognitive function was related to cortical structural morphology. A total DRS-2 score was regressed against cortical regions that showed significant group differences. The level of significance was set to $P < 0.017$ to reflect 3 morphological predictors. Regression analysis was conducted using CAT12.

Results

Demographics and mental health variables

A total of 60 participants were included in this study (contact $n = 38$, noncontact = 22). Of the 38 contact athletes, 28 (73.7%) were male. Of the 22 noncontact athletes, 14 (63.6%) were male. The sample was predominately White (92.1%–95.5%) and were not Latino/Hispanic (90.9%–100%). Of the 60 participants, 2 (contact $n = 1$, noncontact $n = 1$) were not included in MRI analysis due to claustrophobia in scanner. As a result, a total of 58 participants (contact $n = 37$, noncontact $n = 21$) contributed to cortical morphometry analysis. There were no differences of demographics or mental health variables between the two groups. All

Table 1. Group demographics.

Group	Contact sport	Noncontact sport	P-value
n	37	21	–
Sex (%)	28 M (75.6%)	13 M (61.9%)	0.42
Age, years (SD)	41.6 (9.1)	45.0 (8.2)	0.15
No. of previous concussion			0.06
0, n (%)	24 (64.9)	18 (85.7)	–
1, n (%)	5 (13.5)	1 (4.8)	–
2, n (%)	2 (5.4)	1 (4.8)	–
3+, n (%)	6 (16.2)	1 (4.8)	–
Level of play up to, n (%) ^a			
High school	9 (24.3)	11 (52.4)	
College	28 (75.7)	10 (47.6)	
Postcollege	3 (8.1)	6 (28.6)	
Organized sport experience, n (%) ^{b,c}	15.6 (6.0)	17.0 (6.1)	0.40
Football	24 (63.2)	0	–
Soccer	16 (42.1)	0	–
Wrestling	9 (23.7)	0	–
Hockey	7 (18.4)	0	–
Baseball	0	15 (68.2)	–
Cross country/track	0	8 (36.4)	–
Volleyball	0	6 (27.3)	–
Tennis	0	4 (18.2)	–
Race, n (%)			0.74
White	34 (91.9)	20 (95.2)	–
Black/African American	0 (0)	0 (0)	–
Asian	2 (5.4)	1 (4.8)	–
Multiracial	1 (2.7)	0 (0)	–
Ethnicity, n (%)			0.24
Not Latino/Hispanic	37 (100)	19 (90.5)	–
Latino/Hispanic	0 (0)	2 (9.5)	–
Mental Health Symptoms			
PHQ-9, mean (SD)	4.4 (5.2)	2 (3.4)	0.03
PCL-C, mean (SD)	25.3 (10.4)	20.7 (4.6)	0.02
ADHD, mean (SD)	9.8 (10.7)	5.3 (7.6)	0.05

SD, standard deviation; PHQ-9, Patient Health Questionnaire – 9 assesses depressive symptoms; PCL-C, PTSD Checklist—Civilian Version assesses key symptoms of posttraumatic stress disorder; ADHD, DSM-5 diagnostic criteria for ADHD, measures key symptoms of attention deficit/hyperactivity disorder.

^aN and percentages are equal to more than 100% due to individuals participating in amateur level sports postcollege. ^bThe four most participated in sports.

^cN and percentages are equal to more than 100% due to individuals participating in multiple sports.

demographics and mental health outcomes are summarized in Table 1.

Cognition

There was no difference in total DRS-2 scores, as well as all 5 cognitive domains, between the contact and noncontact groups [total DRS-2 score: -0.07 (-2.70 , 2.54), $P=0.9$]. See Fig. 2 and Supplemental Table 2 for group differences in all comparisons and Supplemental Table 1 for all statistical output.

Group differences in cortical structure

Cortical thickness

Compared to the noncontact group, the contact athletes showed significant cortical thinning in various brain regions of both hemispheres. These areas include the rostral middle frontal gyrus, the precuneus, the posterior cingulate gyrus, and the isthmus cingulate gyrus (Fig. 3A). Cortical thinning in the contact group was particularly pronounced in the occipitotemporal regions, such as superior/middle/inferior temporal gyri, lingual gyrus, and lateral occipital gyrus, as well as medial cortical regions, including cingulum, precuneus, and insula. Detailed information for each brain region is listed in Table 2.

Sulcal depth

Significantly greater (deeper) sulcal depth was observed in the contact group as compared to the noncontact group in both

hemispheres. Greater sulcal depth was pronounced in the lateral side of the cortex, where the frontal, temporal, and parietal lobes merge, such as the postcentral, superior temporal, pars opercularis, lateral orbitofrontal, and pars triangularis. In addition, identical to cortical thickness, a significant group difference was observed in the left precuneus, whereby the contact group showing greater depth of sulci (Fig. 3B). Detailed information for each brain region is listed in Table 2.

Sulcal curvature

Relative to noncontact athletes, contact athletes showed greater sulcal curvature across four lobes, with the precuneus and precentral gyrus being impacted bilaterally. Additionally, large clusters of group differences were observed in the right lateral orbitofrontal gyrus, lateral occipital gyrus, and middle temporal gyrus. The contact group had three regions that showed lesser sulcal curvature than those of the noncontact group, including the left postcentral and superior parietal gyri and right superior frontal gyrus. (Fig. 3C). Detailed information for each brain region is listed in Table 2.

Associations between cognition and cortical morphology

An exploratory analysis was conducted to evaluate whether cognitive function was related to cortical structural morphology. A series of regression analyses yielded no cortical region achieving

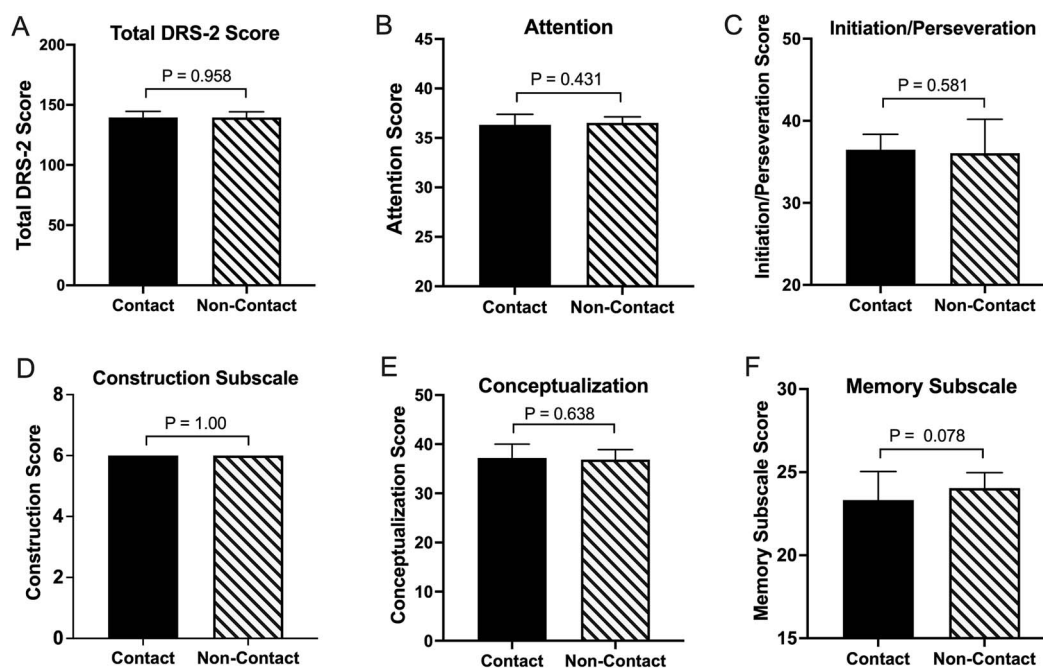


Fig. 2. Group differences in cognitive function as assessed by the DRS-2. There were no significant differences in total DRS-2 scores between groups (A) as well as no observed significant group differences in any of the five subscales [attention (B), initiation/perseveration (C), construction (D), conceptualization (E), and memory (F)].

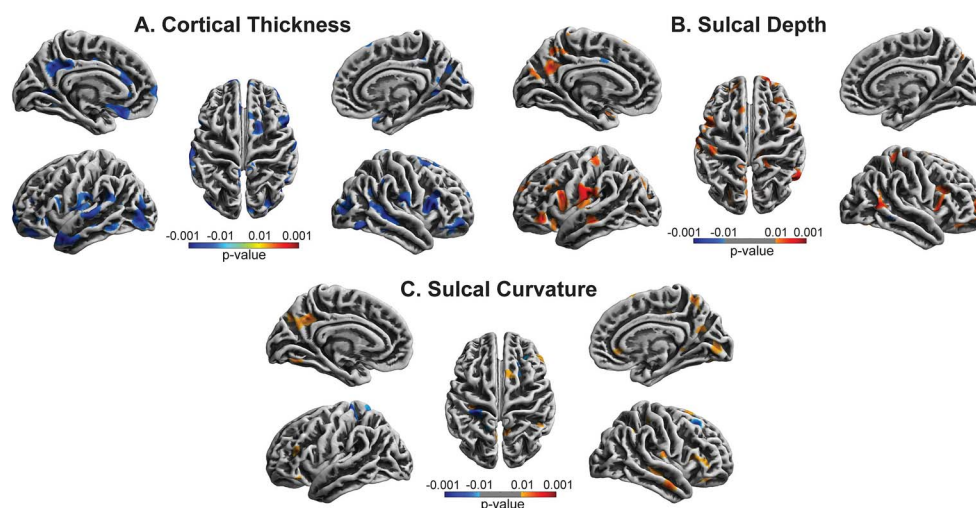


Fig. 3. Cortical morphometric panel. Significant group differences were observed in (A) cortical thickness, (B) sulcal depth, and (C) sulcal curvature in various parts of the brain. The multiple comparison was accounted for by nonparametric permutations ($n = 5000$) and the threshold-free cluster enhancement (TFCE) correction after 5000 permutations. Red: the contact group is higher compared to the noncontact group. Blue: the contact group is lower compared to the noncontact group.

the adjusted statistical significance. Of note, there were a few marginal associations, including overall DRS-2 score and lower sulcal curvature in the left superior parietal lobule in the contact group ($F = 4.437$, $y = 34.700 - 0.071x$, $P = 0.042$). Also in the noncontact group, overall DRS-2 score was marginally associated with lower cortical thickness in the right precentral gyrus ($F = 4.771$, $y = 5.193 - 0.019x$, $P = 0.043$) and left superior temporal gyrus ($F = 4.488$, $y = 4.716 - 0.012x$, $P = 0.049$), as well as increased sulcal depth in the right inferior parietal lobule ($F = 4.786$, $y = 0.936 + 0.011x$, $P = 0.043$).

Discussion

Our study revealed distinct neuroanatomical differences between former amateur athletes with at least 10 years of contact sport

experience as compared to age- and sex-matched noncontact control athletes. The data confirmed some previous findings and also generated critical knowledge about effects of decades of contact sport participation on brain morphology. The study yielded four notable findings. Relative to the noncontact group, (i) the contact group showed greater cortical thinning in widespread regions of the cortex, particularly in the right frontotemporal regions; (ii) deepening of sulcal depth was pronounced in the contact group, especially in the left hemisphere; (iii) group differences in the sulcal curvature were region-dependent. Increased sulcal curvature was notable in the right hemisphere, such as the precuneus and precentral gyrus, whereas localized decrease in sulcal curvature was observed in both hemispheres, including the left post-central and superior parietal gyri and right superior frontal gyrus; and lastly, (iv) despite profound differences in cortical morphology

Table 2. Differences in cortical morphology between the contact and noncontact groups.

Measures	Brain regions	BA	Coordinates			Cluster size	Peak t value	P value
			x	y	z			
Cortical thickness								
Contact > noncontact	Left isthmus cingulate cortex	23	−2	−10	25	50	−2.43	0.036
	Left posterior cingulate cortex	23	−20	−32	62	50	−2.60	0.016
	Right precuneus	7	12	−73	48	624	−2.49	0.012
	Right lateral occipital gyrus	17	33	−85	12	104	−2.61	0.012
	Right cuneus	17	14	−73	29	203	−2.46	0.012
	Right isthmus cingulate cortex	23	12	17	40	95	−2.62	0.012
	Right posterior cingulate cortex	23	10	20	−40	149	−2.95	0.012
	Right rostral middle frontal gyrus	45	6	56	29	224	−2.57	0.012
	Right lateral orbitofrontal gyrus	47	2	66	17	149	−2.69	0.015
	Right parsopercularis gyrus	44	57	36	6	184	−2.40	0.015
	Right postcentral gyrus	1	28	−26	58	150	−2.48	0.015
	Right supramarginal gyrus	40	50	−23	3	124	−2.58	0.027
	Right insula	47	36	19	5	104	−2.60	0.015
Sulcal depth								
Contact > noncontact	Left insula	13	−45	10	3	993	2.80	0.014
	Left parsopercularis gyrus	44	−10	29	59	397	2.72	0.014
	Left lateral orbitofrontal gyrus	11	−22	72	40	57	2.51	0.014
	Left supramarginal gyrus	40	−50	−33	2	318	2.86	0.014
	Left parstriangularis gyrus	44	−32	74	15	124	2.46	0.014
	Left rostral middle frontal gyrus	11	−48	45	7	33	3.03	0.014
	Left caudal middle-frontal gyrus	45	−51	−2	13	119	2.91	0.014
	Left transverse temporal gyrus	41	−59	−1	−12	119	3.90	0.014
Sulcal curvature								
Contact > noncontact	Left precuneus	7	−6	−58	27	228	3.27	0.015
	Left lateral orbitofrontal gyrus	11	−43	52	−1	186	2.73	0.023
	Left insula	13	−36	13	9	105	2.72	0.023
	Left posterior cingulate cortex	23	−8	−43	23	68	3.16	0.015
	Right superior temporal gyrus	6	48	4	−12	81	2.70	0.000
	Right insula	47	36	13	12	641	3.77	0.000
	Right lateral orbitofrontal gyrus	47	32	47	−23	595	2.99	0.000
	Right middle temporal gyrus	21	47	−34	21	458	2.36	0.000
	Right partriangularis gyrus	44	47	56	21	320	2.24	0.000
	Right parsopercularis gyrus	44	30	54	−1	275	3.26	0.000
	Right precuneus	7	10	−46	8	256	2.70	0.023
	Right precentral gyrus	1	8	233	69	229	2.49	0.000
	Right postcentral gyrus	1	26	−46	43	183	2.97	0.000
Contact < noncontact	Left postcentral gyrus	1	−29	−12	45	164	−2.80	0.029

The statistical analysis to cortical thickness, sulcal depth, and sulcal curvature was used through the nonparametric permutations ($n = 5000$) and threshold-free cluster enhancement (TFCE) $P < 0.017$ after 5000 permutations.

between groups, there was no discernable group difference in all domains of cognitive function. These data suggest that there are structural differences in the brains of retired contact athletes as compared to noncontact control athletes.

Evidence of macrolevel, morphological changes in the brain during typical aging in healthy individuals have been well documented such that when a person ages there is significant cortical thinning particularly in the central sulcal region of the left and right hemispheres (Rettmann et al. 2006), and these brain structural alterations may accelerate in neurodegenerative diseases, including mild cognitive impairment (MCI) (Singh et al. 2006), AD (Wee et al. 2013), and CTE (Mackay et al. 2019). Our data revealed that even in the absence of apparent cognitive impairments, former amateur contact athletes exhibit significant cortical thinning across broader cortical areas. For example, notable clusters of reduced cortical thickness manifest in the bilateral temporal regions (e.g. middle/superior/inferior temporal gyri) and regions associated with default mode network (DMN) (e.g. precuneus, posterior cingulate cortex, middle frontal cortex). These regions play a crucial role in maintaining

mental stability and supporting higher cognitive functions. While brain structural integrity and neural function generally correlate (Segall et al. 2012), functional MRI is an ideal tool for detecting the functional integrity of neural networks. However, existing literature strongly aligns with our findings, demonstrating that even a single TBI or RHI can induce cortical thinning of the frontal, parietal, and temporal lobes (Wilde et al. 2012; Goswami et al. 2016; Govindarajan et al. 2016; Koerte et al. 2016). Moreover, these brain injuries are associated with declines in mental health wellbeing and impaired functional connectivity related to the DMN across a diverse spectrum of patients, spanning from pediatric to adult populations, including retired professional athletes.

The potential mechanisms underlying the observed cortical thinning may be relevant to the neurobiological correlates of RHI. The cortical thinning process is often linked with the loss of neurons, dendrite, and synaptic density (Morrison and Hof 1997). In 2010, Fleischman et al. conducted a study including older individuals (average 81.2 years old) without dementia and revealed that cortical thinning in 13 brain regions exhibited robust

correlations ($P < 0.00007$) with circulating inflammatory markers (e.g. IL-6, TNF- α , C-reactive protein) (Fleischman et al. 2010). Remarkably, our data align with these findings, indicating cortical thinning in 10 out of those 13 regions, including the lateral orbitofrontal, inferior temporal, and lingual gyri (Fleischman et al. 2010). Neuroinflammation, especially associated with astrogliosis, stands out as a hallmark response to RHI. Biomarkers linked to astrogliosis, such as S100B and glial fibrillary acidic protein (GFAP), not only acutely elevate after a single concussion (Schulte et al. 2014; Jones et al. 2020) but also respond to nonconcussive RHI (Kawata et al. 2017; Kawata et al. 2018; Zonner et al. 2019; Zuidema et al. 2023). These data suggest that athletes engaged in contact sports with frequent RHI exposure are predisposed to chronic astrogliosis. Furthermore, as individuals age, the progression of cortical thinning has been associated with the extent of astrocyte and microglial activations (Vidal-Pineiro et al. 2020). Studies have begun establishing the link between astrogliosis and cortical thinning in former athletes, whereby both astrogliosis and astrocytic degeneration, characterized by beaded, broken astrocytic processes, emerge as common phenotypes in deceased individuals with extensive contact sport experience (Hsu et al. 2018; Arena et al. 2020). In addition to astrogliosis, cortical thinning has also been linked to decreased neurogenesis (Sowell et al. 2003). Studies have demonstrated that a reduction of neurogenesis, particularly in the hippocampus, have been correlated with mood disorders and cognitive decline (Lucassen et al. 2010). This is of importance as both CTE (McKee et al. 2023) and Alzheimer's Disease (Ihara et al. 2018) are associated with hippocampal sclerosis. A future longitudinal study incorporating astrocyte-related blood biomarkers and cortical morphometry is imperative to elucidate biological mechanisms behind the cortical thinning in former contact sports athletes.

This study introduces an innovative approach by integrating geometric features, specifically sulcal depth and sulcal curvature, to gain a comprehensive understanding of cortical morphology among former amateur athletes. While cortical folding primarily occurs during the prenatal period, the ongoing evolution of gyri and sulci responds to various stressors, including mechanical impact (e.g. TBI) (Wilde et al. 2021), internal factors like depression and anxiety (Schmaal et al. 2017), and environmental influences such as nutrition and socioeconomic status (Brito and Noble 2014; Bernardoni et al. 2018), and the natural aging process (de Moraes et al. 2024). Our findings indicate that individuals with a history of contact sports exhibit greater sulcal depth in the frontal, temporal, and parietal lobes, with notable clusters observed in the postcentral gyrus, precuneus, and middle/superior temporal gyri. These results challenge the prevailing consensus regarding neurodegenerative disorders, where individuals with MCI and AD often present shallower sulcal depths compared to their healthy counterparts (Im et al. 2008) due to gray matter atrophy on the cortical surface (Thompson et al. 2003). However, trauma-induced neurodegenerative conditions, such as CTE, display a distinct biological signature, including aggregations of phosphorylated tau (p-tau) around small vessels at the depths of cortical sulci (Bieniek et al. 2021; Katz et al. 2021). Specifically, individuals with a history of repeated mild TBI had a preferential concentration of thorn-shaped astrocytes, a unique phenotype resulting from p-tau tangling within astrocytes, in the depths of sulci. This pattern is not observed in the brains of AD patients (Arena et al. 2020). Furthermore, our recent data in high school football players align with this current study's finding, such that greater sulcal depths were observed throughout the cortex in areas such as the superior/middle temporal gyri, the postcentral gyrus, and the pars opercularis, compared to noncontact control athletes

(Zuidema et al. 2024). These data may offer insights into the increased sulcal depth observed in our sample and shed light on the cortical alterations that can occur after decades of contact sports participations.

The alteration of sulcal curvature, specifically after trauma to the brain, can lead to significant functional consequences. Studies have demonstrated that divergence from typical cortical folding patterns can be linked to cognitive deficits, such as impaired executive dysfunction, memory, and attention (Im et al. 2006; Lamballais et al. 2020). Moreover, alterations in sulcal curvature have been shown to associate with disorders in sensory processing, including impairments in visual and auditory perception (Cachia et al. 2008; Schultz et al. 2013). Additional studies have shown that psychiatric conditions such as generalized anxiety disorder (Molent et al. 2018), depression (Depping et al. 2018), and schizophrenia (Palaniyappan et al. 2011) have been associated with abnormal cortical folding patterns, which highlights the role that sulcal curvature plays in emotional regulation.

As for the impact of trauma in cortical folding, Gharehgzlou et al. conducted a study involving adults in the subacute phase of concussion (2 wk to 3 mo postconcussion) and discovered significant increase in sulcal curvature in the frontal and medial regions of the brain compared to healthy controls (Gharehgzlou et al. 2022). Similarly, Wilde et al. (2021) reported increased sulcal curvature in the frontal and temporal regions among adolescents with a history of TBI, suggesting a compensatory mechanism to reinforce impaired brain regions. These findings may help elucidate why the contact group from this study exhibited greater sulcal curvature in frontotemporal and medial brain regions.

Normal, healthy cognitive changes is expected and well documented as a person advances in their years. As someone ages, there are some cognitive domains, such as vocabulary, that are resilient to aging or even gradually improve. While other domains, such as memory, processing speed, and conceptualization, gradually decline over time starting around the age of 30 (Harada et al. 2013). However, there is growing evidence that exposure to RHI is associated with impaired cognition in athletes at all levels (Koerte et al. 2017; Alosco et al. 2020). Specifically in areas such as working memory (Alosco et al. 2020) and response time (Koerte et al. 2017). However, in this study, we found no significant differences in cognition between the contact and noncontact sport athletes. Regrettably, this nonsignificance may be due to the selection of the DRS-2 as a cognitive measure. The DRS-2 was created to assess cognition in those aged 56 and older who were already experiencing some sort of cognitive impairment (Jurica et al. 2001) and therefore may not have been the most appropriate assessment for the present sample. There are various other cognitive scales that would have been more appropriate for this sample. For example, the Behavior Rating Inventory of Executive Function—Adult Version (BRIEF-A) Metacognition Index may be more suitable. The BRIEF-A is a standardized assessment tool that was designed to evaluate everyday behaviors related to various executive function domains in adults aged 18 to 90 years old (Gioia et al. 2002). This broader age range would better encapsulate the sample in this study. Another cognition scale could be the Montreal Cognitive Assessment (MoCA). The MoCA is an assessment that is widely used to its sensitivity in detecting early cognitive changes in neurodegenerative dementias (Nasreddine et al. 2005). While the typical age of the MoCA is 55 to 85 years old, it has been shown to be a useful screening device in samples similar to the one in this study (Alosco et al. 2021). Future iterations of this study would benefit from a more sensitive and well-suited cognitive screening tool.

Limitations

The results of this study should be interpreted within the context of several limitations. The sample size was limited with 37 contact and 21 noncontact retired amateur athletes. A longitudinal study with a larger sample size is needed to decipher the clinical significance of the observed changes in cortical morphology. While a novel study sample of male and female retired amateur athletes, more racial and ethnic diversity would increase the generalizability of this sample. It would be beneficial to broaden the recruitment area, potentially to multiple sites. It is also recognized that this study has a large age range of 30 to 60 years old. A more limited age range would encapsulate the “middle-aged” population. It should be noted that concussion history was self-reported by participants. With the rapidly changing guidelines for concussions diagnosis, it is likely that there were many undiagnosed concussions in this sample. Therefore, the secondary analysis on the role of concussion history on brain morphology was invalid. Further, the use of the DRS-2 was designed to screen individuals who are already exhibiting signs of cognitive decline. It may be less sensitive to subtle changes in middle-aged adults. More sensitive cognitive assessments may detect subtle changes that are not seen the present study, such as the BRIEF-A Metacognition Index and the MoCA. Additionally, an exploration of sex effects would be an interest to the research community; however, our skewed sample sizes between males and females in each group hindered our ability to conduct factorial ANOVA to examine the potential interaction effects between sex and RHI-induced morphological changes.

Conclusion

In summary, our data resulting from advanced neuroimaging techniques suggest that mid-life, retired amateur contact sport athletes have reduced cortical thickness, increased sulcal depth, and both increased and decreased sulcal curvature in widespread regions of the brain as compared to noncontact control athletes. Many of the affected brain regions were observed in areas that are important for executive function, emotional regulation, and memory processing and retrieval. No group differences in cognition were found between contact and noncontact athletes. These data illustrate the importance of continued research into cortical morphology in retired, amateur athletes.

Acknowledgments

The authors would like to extend their gratitude to the study participants for their time and engagement in the study. Recht, Buddenbaum, Hou, Cheng, and Newman report no conflict of interest relevant to the manuscript. Dr Kawata receives support from NIH grants (R01NS137276, R01NS113950). Dr Saykin receives support from multiple NIH grants (P30, AG010133, P30 AG072976, R01 AG019771, R01 AG057739, U19 AG024904, R01 LM013463, R01 AG068193, T32 AG071444, U01 AG068057, U01 AG072177, and U19 AG074879). He has also received support from Avid Radio-pharmaceuticals, and subsidiary of Eli Lilly (in kind contribution of PET tracer precursor) and participated in Scientific Advisory Boards (Bayer Oncology, Eisai, Novo Nordisk, and Siemens Medical Solutions USA, Inc) and on Observational Study Monitoring Board (MESA, NIH NHLBI), as well as several other NIA External Advisory Committees. He also serves as Editor-in-Chief of Brain Imaging and Behavior, a Springer-Nature Journal.

Author contributions

Dr Kawata had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kawata, Recht, Saykin.

Acquisition of data: Recht, Buddenbaum, Cheng,

Analysis and interpretation of data: Recht, Kawata, Saykin, Cheng, Hou, Newman.

Drafting of the manuscript: Recht, Hou, Kawata.

Critical revision of the manuscript for important intellectual content: Recht, Hou, Kawata, Buddenbaum, Cheng, Saykin, Newman.

Obtained funding: Kawata.

Administrative, technical, or material support: Kawata, Cheng.

Study supervision: Kawata, Cheng.

Grace Recht (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing—original draft, Writing—review & editing), Jiancheng Hou (Formal analysis, Writing—original draft, Writing—review & editing), Claire Buddenbaum (Investigation, Project administration, Writing—review & editing), Hu Cheng (Data curation, Formal analysis, Investigation, Resources, Software, Supervision, Writing—review & editing), Sharlene D Newman (Formal analysis, Writing—review & editing), Andrew Saykin (Conceptualization, Formal analysis, Writing—review & editing), Keisuke Kawata (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Visualization, Writing—original draft, Writing—review & editing).

Funding

This study was partly supported by National Institutes of Health—National Institute of Neurological Disorders and Stroke (to K Kawata: R01NS113950) and the Indiana Spinal Cord and Brain Injury Research Fund from the Indiana State Department of Health (to K. Kawata: SCTBIRF 00055049).

Conflict of interest statement: None declared.

References

- Alosco ML, Tripodis Y, Baucom ZH, Mez J, Stein TD, Martin B, Haller O, Conneely S, McClean M, Nosheny R, et al. Late contributions of repetitive head impacts and TBI to depression symptoms and cognition. *Neurology*. 2020;95(7):e793–e804. <https://doi.org/10.1212/WNL.00000000000010040>.
- Alosco ML, Mariani ML, Adler CH, Balcer LJ, Bernick C, Au R, Banks SJ, Barr WB, Bouix S, Cantu RC, et al. Developing methods to detect and diagnose chronic traumatic encephalopathy during life: rationale, design, and methodology for the DIAGNOSE CTE research project. *Alzheimers Res Ther*. 2021;13(1):136. <https://doi.org/10.1186/s13195-021-00872-x>.
- Arena JD, Johnson VE, Lee EB, Gibbons GS, Smith DH, Trojanowski JQ, Stewart W. Astroglial tau pathology alone preferentially concentrates at sulcal depths in chronic traumatic encephalopathy neuropathologic change. *Brain Commun*. 2020;2(2):fcaa210. <https://doi.org/10.1093/braincomms/fcaa210>.
- Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement*. 2015;11(6):718–726. <https://doi.org/10.1016/j.jalz.2015.05.016>.
- Bernardoni F, King JA, Geisler D, Birkenstock J, Tam FI, Weidner K, Roessner V, White T, Ehrlich S. Nutritional status affects

- cortical folding: lessons learned from anorexia nervosa. *Biol Psychiatry*. 2018;84(9):692–701. <https://doi.org/10.1016/j.biopsych.2018.05.008>.
- Bieniek KF, Cairns NJ, Crary JF, Dickson DW, Folkerth RD, Keene CD, Litvan I, Perl DP, Stein TD, Vonsattel JP, et al. The second NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *J Neuropathol Exp Neurol*. 2021;80(3):210–219. <https://doi.org/10.1093/jnen/nlab001>.
- Brito NH, Noble KG. Socioeconomic status and structural brain development. *Front Neurosci*. 2014;8:276. <https://doi.org/10.3389/fnins.2014.00276>.
- Buddenbaum CV, Recht GO, Rodriguez AK, Newman SD, Kawata K. Associations between repetitive head impact exposure and midlife mental health wellbeing in former amateur athletes. *Front Psychiatry*. 2024;15:1383614. <https://doi.org/10.3389/fpsyt.2024.1383614>.
- Cachia A, Paillere-Martinot ML, Galinowski A, Januel D, de Beaupaire R, Bellivier F, Artiges E, Andoh J, Bartres-Faz D, Duchesnay E, et al. Cortical folding abnormalities in schizophrenia patients with resistant auditory hallucinations. *NeuroImage*. 2008;39(3):927–935. <https://doi.org/10.1016/j.neuroimage.2007.08.049>.
- Collaborators GBDDF. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the global burden of disease study 2019. *Lancet Public Health*. 2022;7:e105–e125.
- Conybeare D, Behar E, Solomon A, Newman MG, Borkovec TD. The PTSD checklist-civilian version: reliability, validity, and factor structure in a nonclinical sample. *J Clin Psychol*. 2012;68(6):699–713. <https://doi.org/10.1002/jclp.21845>.
- Cook NE, Sapigao RG, Silverberg ND, Maxwell BA, Zafonte R, Berkner PD, Iverson GL. Attention-deficit/hyperactivity disorder mimics the post-concussion syndrome in adolescents. *Front Pediatr*. 2020;8:2. <https://doi.org/10.3389/fped.2020.00002>.
- Dahnke R, Yotter RA, Gaser C. Cortical thickness and central surface estimation. *NeuroImage*. 2013;65:336–348. <https://doi.org/10.1016/j.neuroimage.2012.09.050>.
- de Moraes FHP, Sudo F, Carneiro Monteiro M, de Melo BRP, Mattos P, Mota B, Tovar-Moll F. Cortical folding correlates to aging and Alzheimer's disease's cognitive and CSF biomarkers. *Sci Rep*. 2024;14(1):3222. <https://doi.org/10.1038/s41598-023-50780-3>.
- de Souza NL, Bogner J, Corrigan JD, Rabinowitz AR, Walker WC, Kumar RG, Dams-O'Connor K. The effects of repetitive head impact exposure on mental health symptoms following traumatic brain injury. *J Head Trauma Rehabil*. 2024;1–12. <https://doi.org/10.1097/HTR.0000000000000936>.
- Depping MS, Thomann PA, Wolf ND, Vasic N, Sosic-Vasic Z, Schmitgen MM, Sambataro F, Wolf RC. Common and distinct patterns of abnormal cortical gyrification in major depression and borderline personality disorder. *Eur Neuropsychopharmacol*. 2018;28(10):1115–1125. <https://doi.org/10.1016/j.euroneuro.2018.07.100>.
- Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. 2006;31(3):968–980. <https://doi.org/10.1016/j.neuroimage.2006.01.021>.
- Dudley JA, Slutsky-Ganesh AB, Diekfuss JA, Avedesian JM, Yuan W, DiCesare CA, Williams B, Meehan WP 3rd, Hill D, Panzer MB, et al. Helmet technology, head impact exposure, and cortical thinning following a season of high school football. *Ann Biomed Eng*. 2022;50(11):1608–1619. <https://doi.org/10.1007/s10439-022-03023-x>.
- Echlin HV, Rahimi A, Wojtowicz M. Systematic review of the long-term neuroimaging correlates of mild traumatic brain injury and repetitive head injuries. *Front Neurol*. 2021;12:726425. <https://doi.org/10.3389/fneur.2021.726425>.
- Fleischman DA, Arfanakis K, Kelly JF, Rajendran N, Buchman AS, Morris MC, Barnes LL, Bennett DA. Regional brain cortical thinning and systemic inflammation in older persons without dementia. *J Am Geriatr Soc*. 2010;58(9):1823–1825. <https://doi.org/10.1111/j.1532-5415.2010.03049.x>.
- Gharehagzlou A, Jetly R, Rhind SG, Reichelt AC, Da Costa L, Dunkley BT. Cortical gyrification morphology in adult males with mild traumatic brain injury. *Neurotrauma Rep*. 2022;3(1):299–307. <https://doi.org/10.1089/neur.2021.0032>.
- Gioia GA, Isquith PK, Retzlaff PD, Espy KA. Confirmatory factor analysis of the behavior rating inventory of executive function (BRIEF) in a clinical sample. *Child Neuropsychol*. 2002;8(4):249–257. <https://doi.org/10.1076/chin.8.4.249.13513>.
- Goswami R, Dufort P, Tartaglia MC, Green RE, Crawley A, Tator CH, Wennberg R, Mikulis DJ, Keightley M, Davis KD. Frontotemporal correlates of impulsivity and machine learning in retired professional athletes with a history of multiple concussions. *Brain Struct Funct*. 2016;221(4):1911–1925. <https://doi.org/10.1007/s00429-015-1012-0>.
- Govindarajan KA, Narayana PA, Hasan KM, Wilde EA, Levin HS, Hunter JV, Miller ER, Patel VK, Robertson CS, McCarthy JJ. Cortical thickness in mild traumatic brain injury. *J Neurotrauma*. 2016;33(20):1809–1817. <https://doi.org/10.1089/neu.2015.4253>.
- Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med*. 2013;29(4):737–752. <https://doi.org/10.1016/j.cger.2013.07.002>.
- Hsu ET, Gangolli M, Su S, Holleran L, Stein TD, Alvarez VE, McKee AC, Schmidt RE, Brody DL. Astrocytic degeneration in chronic traumatic encephalopathy. *Acta Neuropathol*. 2018;136(6):955–972. <https://doi.org/10.1007/s00401-018-1902-3>.
- Ihara R, Vincent BD, Baxter MR, Franklin EE, Hassenstab JJ, Xiong C, Morris JC, Cairns NJ. Relative neuron loss in hippocampal sclerosis of aging and Alzheimer's disease. *Ann Neurol*. 2018;84(5):741–753. <https://doi.org/10.1002/ana.25344>.
- Im K, Lee JM, Yoon U, Shin YW, Hong SB, Kim IY, Kwon JS, Kim SI. Fractal dimension in human cortical surface: multiple regression analysis with cortical thickness, sulcal depth, and folding area. *Hum Brain Mapp*. 2006;27(12):994–1003. <https://doi.org/10.1002/hbm.20238>.
- Im K, Lee JM, Seo SW, Hyung Kim S, Kim SI, Na DL. Sulcal morphology changes and their relationship with cortical thickness and gyral white matter volume in mild cognitive impairment and Alzheimer's disease. *NeuroImage*. 2008;43(1):103–113. <https://doi.org/10.1016/j.neuroimage.2008.07.016>.
- Jones CMC, Harmon C, McCann M, Gunyan H, Bazarian JJ. S100B outperforms clinical decision rules for the identification of intracranial injury on head CT scan after mild traumatic brain injury. *Brain Inj*. 2020;34(3):407–414. <https://doi.org/10.1080/02699052.2020.1725123>.
- Jurica PJ, Leitten CL, Mattis S. DRS-2 : Dementia Rating Scale-2: Professional Manual: Psychological Assessment Resources. California, 2001.
- Katz DI, Bernick C, Dodick DW, Mez J, Mariani ML, Adler CH, Alosco ML, Balcer LJ, Banks SJ, Barr WB, et al. National Institute of Neurological Disorders and Stroke consensus diagnostic criteria for traumatic encephalopathy syndrome. *Am Acad Neurol*. 2021;96(18):848–863.

- Katz BP, Kudela M, Harezlak J, McCrea M, McAllister T, Broglio SP, Investigators CC. Baseline performance of NCAA athletes on a concussion assessment battery: a report from the CARE consortium. *Sports Med.* 2018;48(8):1971–1985. <https://doi.org/10.1007/s40279-018-0875-7>.
- Kawata K, Rubin LH, Takahagi M, Lee JH, Sim T, Szwanki V, Bellamy A, Tierney R, Langford D. Subconcussive impact-dependent increase in plasma S100beta levels in collegiate football players. *J Neurotrauma.* 2017;34(14):2254–2260. <https://doi.org/10.1089/neu.2016.4786>.
- Kawata K, Tierney R, Langford D. Blood and cerebrospinal fluid biomarkers. *Handb Clin Neurol.* 2018;158:217–233. <https://doi.org/10.1016/B978-0-444-63954-7.00022-7>.
- Kochunov P, Mangin JF, Coyle T, Lancaster J, Thompson P, Riviere D, Cointepas Y, Regis J, Schlosser A, Royall DR, et al. Age-related morphology trends of cortical sulci. *Hum Brain Mapp.* 2005;26(3):210–220. <https://doi.org/10.1002/hbm.20198>.
- Koerte IK, Mayinger M, Muehlmann M, Kaufmann D, Lin AP, Steffinger D, Fisch B, Rauchmann BS, Immler S, Karch S, et al. Cortical thinning in former professional soccer players. *Brain Imaging Behav.* 2016;10(3):792–798. <https://doi.org/10.1007/s11682-015-9442-0>.
- Koerte IK, Nichols E, Tripodis Y, Schultz V, Lehner S, Igbino R, Chuang AZ, Mayinger M, Klier EM, Muehlmann M, et al. Impaired cognitive performance in youth athletes exposed to repetitive head impacts. *J Neurotrauma.* 2017;34(16):2389–2395. <https://doi.org/10.1089/neu.2016.4960>.
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–613. <https://doi.org/10.1046/j.1525-1497.2001.016009606.x>.
- Lamballais S, Vinke EJ, Vernooij MW, Ikram MA, Muetzel RL. Cortical gyrification in relation to age and cognition in older adults. *NeuroImage.* 2020;212:116637. <https://doi.org/10.1016/j.neuroimage.2020.116637>.
- Li Y, Wang N, Wang H, Lv Y, Zou Q, Wang J. Surface-based single-subject morphological brain networks: effects of morphological index, brain parcellation and similarity measure, sample size-varying stability and test-retest reliability. *NeuroImage.* 2021;235:118018. <https://doi.org/10.1016/j.neuroimage.2021.118018>.
- Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. *Lancet.* 2020;396(10248):413–446. [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6).
- Lucassen PJ, Stumpel MW, Wang Q, Aronica E. Decreased numbers of progenitor cells but no response to antidepressant drugs in the hippocampus of elderly depressed patients. *Neuropharmacology.* 2010;58(6):940–949. <https://doi.org/10.1016/j.neuropharm.2010.01.012>.
- Luders E, Thompson PM, Narr KL, Toga AW, Jancke L, Gaser C. A curvature-based approach to estimate local gyrification on the cortical surface. *NeuroImage.* 2006;29(4):1224–1230. <https://doi.org/10.1016/j.neuroimage.2005.08.049>.
- Mackay DF, Russell ER, Stewart K, MacLean JA, Pell JP, Stewart W. Neurodegenerative disease mortality among former professional soccer players. *N Engl J Med.* 2019;381(19):1801–1808. <https://doi.org/10.1056/NEJMoa1908483>.
- McKee AC, Abdolmohammadi B, Butler M, Huber BR, Uretsky M, Babcock K, Cherry JD, Alvarez VE, Martin B, Tripodis Y, et al. Neuropathologic and clinical findings in young contact sport athletes exposed to repetitive head impacts. *JAMA Neurol.* 2023;80(10):1037–1050. <https://doi.org/10.1001/jamaneurol.2023.2907>.
- McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Keene CD, Litvan I, Perl DP, Stein TD, Vonsattel JP, Stewart W, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol.* 2016;131(1):75–86. <https://doi.org/10.1007/s00401-015-1515-z>.
- Meier TB, Bellgowan PS, Bergamino M, Ling JM, Mayer AR. Thinner cortex in collegiate football players with, but not without, a self-reported history of concussion. *J Neurotrauma.* 2016;33(4):330–338. <https://doi.org/10.1089/neu.2015.3919>.
- Mills BD, Goubran M, Parivash SN, Dennis EL, Rezaii P, Akers C, Bian W, Mitchell LA, Boldt B, Douglas D, et al. Longitudinal alteration of cortical thickness and volume in high-impact sports. *NeuroImage.* 2020;217:116864. <https://doi.org/10.1016/j.neuroimage.2020.116864>.
- Molent C, Maggioni E, Cecchetto F, Garzitto M, Piccin S, Bonivento C, Maieron M, D'Agostini S, Balestrieri M, Perna G, et al. Reduced cortical thickness and increased gyrification in generalized anxiety disorder: a 3 T MRI study. *Psychol Med.* 2018;48(12):2001–2010. <https://doi.org/10.1017/S003329171700352X>.
- Morrison JH, Hof PR. Life and death of neurons in the aging brain. *Science.* 1997;278(5337):412–419. <https://doi.org/10.1126/science.278.5337.412>.
- Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695–699. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>.
- Nowak MK, Ejima K, Quinn PD, Bazarian JJ, Mickleborough TD, Harezlak J, Newman SD, Kawata K. ADHD may associate with reduced tolerance to acute subconcussive head impacts: a pilot case-control intervention study. *J Atten Disord.* 2022;26(1):125–139. <https://doi.org/10.1177/1087054720969977>.
- Nowinski CJ, Rhim HC, McKee AC, Zafonte RD, Dodick DW, Cantu RC, Daneshvar DH. 'Subconcussive' is a dangerous misnomer: hits of greater magnitude than concussive impacts may not cause symptoms. *Br J Sports Med.* 2024;58(14):754–756. <https://doi.org/10.1136/bjsports-2023-107413>.
- Oliveira TG, Ifrah C, Fleysher R, Stockman M, Lipton ML. Soccer heading and concussion are not associated with reduced brain volume or cortical thickness. *PLoS One.* 2020;15(8):e0235609. <https://doi.org/10.1371/journal.pone.0235609>.
- Palaniyappan L, Mallikarjun P, Joseph V, White TP, Liddle PF. Folding of the prefrontal cortex in schizophrenia: regional differences in gyrification. *Biol Psychiatry.* 2011;69(10):974–979. <https://doi.org/10.1016/j.biopsych.2010.12.012>.
- Potvin O, Dieumegarde L, Duchesne S, Alzheimer's Disease Neuroimaging I. Freesurfer cortical normative data for adults using Desikan-Killiany-Tourville and ex vivo protocols. *NeuroImage.* 2017;156:43–64. <https://doi.org/10.1016/j.neuroimage.2017.04.035>.
- Rettmann ME, Kraut MA, Prince JL, Resnick SM. Cross-sectional and longitudinal analyses of anatomical sulcal changes associated with aging. *Cereb Cortex.* 2006;16(11):1584–1594. <https://doi.org/10.1093/cercor/bhj095>.
- Schmaal L, Hibar DP, Samann PG, Hall GB, Baune BT, Jahanshad N, Cheung JW, van Erp TGM, Bos D, Ikram MA, et al. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA major depressive disorder working group. *Mol Psychiatry.* 2017;22(6):900–909. <https://doi.org/10.1038/mp.2016.60>.
- Schneider DK, Galloway R, Bazarian JJ, Diekfuss JA, Dudley J, Leach JL, Mannix R, Talavage TM, Yuan W, Myer GD. Diffusion tensor

- imaging in athletes sustaining repetitive head impacts: a systematic review of prospective studies. *J Neurotrauma*. 2019;36(20):2831–2849. <https://doi.org/10.1089/neu.2019.6398>.
- Schulte S, Podlog LW, Hamson-Utley JJ, Strathmann FG, Struder HK. A systematic review of the biomarker S100B: implications for sport-related concussion management. *J Athl Train*. 2014;49(6):830–850. <https://doi.org/10.4085/1062-6050-49.3.33>.
- Schultz CC, Wagner G, Koch K, Gaser C, Roebel M, Schachtzabel C, Nenadic I, Reichenbach JR, Sauer H, Schlosser RG. The visual cortex in schizophrenia: alterations of gyrification rather than cortical thickness—a combined cortical shape analysis. *Brain Struct Funct*. 2013;218(1):51–58. <https://doi.org/10.1007/s00429-011-0374-1>.
- Segall JM, Allen EA, Jung RE, Erhardt EB, Arja SK, Kiehl K, Calhoun VD. Correspondence between structure and function in the human brain at rest. *Front Neuroinform*. 2012;6:10. <https://doi.org/10.3389/fninf.2012.00010>.
- Singh V, Chertkow H, Lerch JP, Evans AC, Dorr AE, Kabani NJ. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. *Brain*. 2006;129(11):2885–2893. <https://doi.org/10.1093/brain/awl256>.
- Solanto MV, Wasserstein J, Marks DJ, Mitchell KJ. Diagnosis of ADHD in adults: what is the appropriate DSM-5 symptom threshold for hyperactivity-impulsivity? *J Atten Disord*. 2012;16(8):631–634. <https://doi.org/10.1177/1087054711416910>.
- Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci*. 2003;6(3):309–315. <https://doi.org/10.1038/nn1008>.
- Thompson PM, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, Semple J, Herman D, Hong MS, Dittmer SS, Dordrell DM, et al. Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci*. 2003;23(3):994–1005. <https://doi.org/10.1523/JNEUROSCI.23-03-00994.2003>.
- Vidal-Pineiro D, Parker N, Shin J, French L, Grydeland H, Jackowski AP, Mowinckel AM, Patel Y, Pausova Z, Salum G, et al. Cellular correlates of cortical thinning throughout the lifespan. *Sci Rep*. 2020;10(1):21803. <https://doi.org/10.1038/s41598-020-78471-3>.
- Wee CY, Yap PT, Shen D. Prediction of Alzheimer's disease and mild cognitive impairment using cortical morphological patterns. *Hum Brain Mapp*. 2013;34(12):3411–3425. <https://doi.org/10.1002/hbm.22156>.
- Wilde EA, Merkley TL, Bigler ED, Max JE, Schmidt AT, Ayoub KW, McCauley SR, Hunter JV, Hanten G, Li X, et al. Longitudinal changes in cortical thickness in children after traumatic brain injury and their relation to behavioral regulation and emotional control. *Int J Dev Neurosci*. 2012;30(3):267–276. <https://doi.org/10.1016/j.ijdevneu.2012.01.003>.
- Wilde EA, Merkley TL, Lindsey HM, Bigler ED, Hunter JV, Ewing-Cobbs L, Aitken ME, MacLeod MC, Hanten G, Chu ZD, et al. Developmental alterations in cortical organization and socialization in adolescents who sustained a traumatic brain injury in early childhood. *J Neurotrauma*. 2021;38(1):133–143. <https://doi.org/10.1089/neu.2019.6698>.
- Wojtowicz M, Gardner AJ, Stanwell P, Zafonte R, Dickerson BC, Iverson GL. Cortical thickness and subcortical brain volumes in professional rugby league players. *Neuroimage Clin*. 2018;18:377–381. <https://doi.org/10.1016/j.nicl.2018.01.005>.
- Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Zhao QF, Li JQ, Wang J, Yu JT. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2015;86(12):1299–1306. <https://doi.org/10.1136/jnnp-2015-310548>.
- Yan CG, Wang XD, Zuo XN, Zang YF. DPABI: data processing & analysis for (resting-state) brain imaging. *Neuroinformatics*. 2016;14(3):339–351. <https://doi.org/10.1007/s12021-016-9299-4>.
- Zilles K, Armstrong E, Schleicher A, Kretschmann HJ. The human pattern of gyrification in the cerebral cortex. *Anat Embryol (Berl)*. 1988;179(2):173–179. <https://doi.org/10.1007/BF00304699>.
- Zonner S, Ejima K, Bevilacqua ZW, Huibregtse ME, Charleston C, Fulgar CC, Kawata K. Association of increased serum S100B levels with high school football subconcussive head impacts. *Front Neurol*. 2019;10:327. <https://doi.org/10.3389/fneur.2019.00327>.
- Zuidema TR, Bazarian JJ, Kercher KA, Mannix R, Kraft RK, Newman SD, Ejima K, Rettke DJ, Macy JT, Steinfeldt JA, et al. Longitudinal associations of clinical and biochemical head injury biomarkers with head impact exposure in adolescent football players. *JAMA Netw Open*. 2023;6(5):e2316601. <https://doi.org/10.1001/jamanetworkopen.2023.16601>.
- Zuidema TR, Hou J, Kercher KA, Recht GO, Sweeney SH, Chenchiah N, Cheng H, Steinfeldt JA, Kawata K. Cerebral cortical surface structure and neural activation pattern among adolescent football players. *JAMA Netw Open*. 2024;7(2):e2354235. <https://doi.org/10.1001/jamanetworkopen.2023.54235>.