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Appendix E1

Materials and Methods

Subjects

Fighters who participated in the study consisted of boxers, mixed martial arts fighters, martial arts fighters, and mixed fighters. There were 111 boxers (11 women), 147 mixed martial arts fighters (eight women), 22 martial arts fighters (three women), and 17 mixed fighters (two women). 20 boxers (four women), 36 mixed martial arts fighters (one woman), four martial arts fighters (one woman), and two mixed fighters (both men) returned for follow-up imaging. Only male fighters were included in the analysis for this study. Fighters licensed for martial arts were those fighters who were permitted to use fighting techniques such as judo, karate, kendo, and other forms of combat sports except boxing or wrestling. Mixed martial arts fighters were those fighters who were permitted to use the fighting techniques of boxing, wresting, kickboxing, judo, karate, and other forms of martial arts. "Mixed" fighters were those who had professional fighting records as boxers or martial arts fighters but not as mixed martial arts fighters. The distribution of these fighters at baseline and follow-up and their classification as impaired and nonimpaired fighters is shown in Figure E1.

T1-weighted and Diffusion-weighted Imaging Preprocessing

Surface and volume-based measurements.—

Volume and thickness measurements were computed for each subject by using the FreeSurfer pipeline (19,50–54). Each T1-weighted image was spatially and intensity normalized to the Talairach atlas, and volumetric segmentation and subcortical labeling was performed on the normalized images. The gray and WM boundaries were then identified and reconstructed into a mesh of more than 150 000 tessellated vertices for surface measures at each point that is consistent throughout all subjects. Gyral anatomy was further aligned to a standard spherical template by using surface convexity and curvature measures. Both volume and thickness measure maps were coregistered to a standard template (fsaverage). Anatomic labels in FreeSurfer from the Desikan-Killany atlas (55) were used to extract 34 thickness measures on each hemispheres (aparcstats2table) and 45 volumetric measures (asegstats2table), yielding 113 measurements for each subject (Table E1).

Volume and surface-based measurements from T1-weighted images of subjects imaged at baseline and follow-up were processed by using the longitudinal stream outlined in the study by Reuter et al (20,56,57). First, intensity-normalized and skull-stripped images from both the baseline and follow-up T1 sequence were obtained independently. A within-subject template image were then obtained from both time points by using a robust registration of each time point to an average image. The template image is then processed with FreeSurfer to obtain an estimate of the subject anatomy. Finally, a dataset from both time points was processed by initializing the results from the template, and 113 measurements for each subject at both baseline and follow-up were estimated.

Diffusion-derived measurements from diffusion-weighted images.—

Each of the diffusion-weighted images was manually inspected for signal intensity dropouts. Motion correction and eddy current distortion correction (58) was performed on all diffusion-weighted images by using software (FSL; Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, Oxford, England; *http://www.fmrib.ox.ac.uk/fsl/*) (59). A single tensor was fitted and various diffusion-derived metrics such as FA, axial diffusivity, radial diffusivity, and mean diffusivity were derived in all voxels of the corrected diffusion-weighted data (60). FA images of all subjects were normalized to the Montreal Neurologic Institute 152 space by using tbss_2_reg and tbss_3_postreg subroutines of tract-based spatial statistics in FSL (61). This transformation was applied to axial, radial and mean diffusivity images of all subjects. This step ensured that the scalar maps (FA and mean, axonal, and radial diffusivity) of each subject were in a common Montreal Neurological Institute 152 space. Only those voxels with FA greater than 0.2 were retained in each of the scalar maps to include only WM voxels (60).

Anterior thalamic radiation (left and right), corticospinal tract (left and right), cingulum (left and right), cingulum-hippocampal (left and right), inferior frontal-occipital fasciculus (left and right), inferior longitudinal fasciculus (left and right), superior longitudinal fasciculus (left and right), superior longitudinal fasciculus-temporal (left and right), uncinate fasciculus (left and right), forceps major and forceps minor from Johns Hopkins University (21) probabilistic WM RBFN tract atlas in Montreal Neurologic Institute 152 space was then used as a mask to extract FA and mean, axonal, and radial diffusivity in each tract for each subject.

An anatomic atlas labeling template in the Montreal Neurological Institute 152 template space (22) was used to extract mean diffusivity values in the 116 gray matter regions of the anatomic atlas labeling template. All regions of interest used to extract diffusion-derived metrics are shown in Table E2.

Classification analysis.—

Since the dataset in our cohort was significantly imbalanced for population among the two groups, sampling from a multivariate Gaussian distribution (23) was performed to generate 1000 samples in each group that best explain the variance in the original dataset. The covariance matrix for sampling was constructed after we verified that each of the features in each group followed a normal distribution. The Shapiro-Wilk normality test was conducted to test for significant differences in the normal distribution of the feature set. A classifier was designed by using Matlab scripts designed in house to find the features that were associated with cognitive impairment in our cohort of fighters. A two-step process was used for classification analysis: (a) The least absolute shrinkage and selection operator, or LASSO (25) algorithm was used to ensure that the retained features were the best features that explained the group differences, while a low variance was maintained by shrinking the coefficients of all other unexplainable features to 0. LASSO was applied to the sampled dataset (n = 1000 in both the groups) and all feature sets that were considered explanatory of the group differences were retained. (b) The radial basis functional network, or RBFN (26), a nonlinear neural network that includes radial basis functions as activation networks was used. The final output was chosen as a linear combination of radial basis functions of the inputs and the neuronal parameters. An optimum choice of neuronal parameter (σ) of the radial basis function, which was Gaussian in our algorithm, and the number of radial basis functions (K) that maximized the area under the curve

(AUC) were optimized by iterating through a range of σ (0.5–2 in 0.5-step increments) for every K in the range of 2–15 in steps of 1.

The original unbalanced dataset was divided into training (60%; 110 of 182 nonimpaired and 55 of 91 impaired fighters), validation (20%; 36 of 182 nonimpaired and 18 of 91 impaired fighters) and testing (20%; 36 of 182 nonimpaired and 18 of 91 impaired fighters) dataset and a 10-fold cross-validation between training and validation dataset was used to select the optimized σ and K of RBFN. 10-fold cross-validation was repeated 10 times by randomly shuffling the training and validation samples to ensure that any bias due to chance selection of σ and K was minimized. Inverse probability weighting (24) was applied to offset class imbalances in both of the groups. The testing dataset was always independent of the training and validation dataset.

Various established state-of-the-art algorithms such as random forest (62), LASSO (25), support vector machines with an RBFN kernel (63), and a gradient-boosting classifier (64) were compared with our classifier. The following formulae were used to compute classification accuracy, sensitivity, and specificity for each classifier (65). The AUC, which was a combined marker for sensitivity and specificity, was also obtained for each classifier.

$$\mathrm{FR} = \frac{100 \cdot \mathrm{FR}}{\mathrm{TF}},$$

where *FR* indicates the features retained and TF indicates total number of features.

$$\mathrm{CA} = \frac{(\mathrm{TPC} + \mathrm{TNC})}{(\mathrm{TPC} + \mathrm{TNC} + \mathrm{FPC} + \mathrm{FNC})},$$

where *CA* is classification accuracy, *FNC* is false-negative class, *FPC* is false-positive class, *TPC* is true-positive class, and *TNC* is true-negative class.

$$\mathrm{Se} = \frac{(100 \cdot \mathrm{TPC})}{(\mathrm{TPC} + \mathrm{FNC})}, \text{ where Se is sensitivity.}$$

$$\mathrm{Sp} = \frac{(100 \cdot \mathrm{TNC})}{(\mathrm{TNC} + \mathrm{FPC})}, \text{ where Sp is specificity.}$$

Impaired and nonimpaired fighters were chosen to be in the positive and negative class, respectively.

Results

Comparison of Various State-of-the-Art Classification Algorithms with Our Algorithm

In comparison with our algorithm, classification accuracy and AUCs obtained with various state-of-the-art machine-learning algorithms, namely LASSO, support vector machines and RBFN, random forest, and gradient-boosting algorithms were 68.52% (37 of 54 subjects; AUC, 0.53), 74.07% (40 of 54; AUC, 0.63), 70.37% (38 of 54; AUC, 0.6), and 59.26% (32 of 54; AUC, 0.47), respectively (Table E3, Fig E2).

Performance of the Classifier on Female Fighters

To investigate the influence of sex on our imaging biomarkers, we applied our classifier to all female fighters at baseline to classify impaired and nonimpaired groups. We found a low classification accuracy of 37.5% (nine of 24 subjects) with AUC of 0.53, which supports the hypothesis that there is a strong dependence of sex on the structural organization of human brain.

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Table E1: Regions of Interest in Desikan-Killany Atlas in FreeSurfer That Were Used to Calculate Volume and Cortical Thickness

Regions for Volume Measurements	Regions for Thickness Measurements
Lateral ventricle (L,R)	Banks of the superior temporal sulcus (L,R)
Inferior lateral ventricle (L,R)	Caudal anterior cingulate (L,R)
Cerebellum WM (L,R)	Caudal middle frontal (L,R)
Cerebellum cortex (L,R)	Cuneus (L,R)
Thalamus proper (L,R)	Entorhinal (L,R)
Caudate (L,R)	Fusiform (L,R)
Putamen (L,R)	Inferior parietal (L,R)
Pallidum (L,R)	Inferior temporal (L,R)
Brain stem	Isthmus cingulate (L,R)
Hippocampus (L,R)	Lateral occipital (L,R)
Amygdala (L,R)	Lateral orbitofronal (L,R)
Corticospinal fluid	Lingual (L,R)
Accumbens area (L,R)	Medial orbitofrontal (L,R)
Ventral DC (L,R)	Middle temporal (L,R)
Vessel (L,R)	Parahippocampal (L,R)
Choroid plexus (L,R)	Paracentral (L,R)
Optic chiasm	Pars opercularis (L,R)
Posterior corpus callosum	Pars orbitalis (L,R)
Middle posterior corpus callosum	Pars triangularis (L,R)
Central corpus callosum	pericalcarine (L,R)
Middle anterior corpus callosum	Postcentral (L,R)
Anterior corpus callosum	Posterior vingulate (L,R)
Cortex volume (L,R)	Precentral (L,R)
Cortex volume	Precuneus (L,R)
Cortical WM volume (L,R)	Rostral anterior cingulate (L,R)
Cortical WM volume	Rostral middle frontal (L,R)
Subcortical gray matter Volume	Superior frontal (L,R)
Total gray volume	Superior parietal (L,R)
Supratentorial volume	Superior temporal (L,R)
Cortical WM volume	Supramarginal (L,R)
	Frontal pole (L,R)
	Temporal pole (L,R)

	Transverse temporal (L,R)
	Insula (L,R)

Note.—L and R = left and right hemisphere, respectively.

Table E2: Regions of Interest for Anatomic Atlas Labeling and Johns Hopkins University WM Probabilistic Atlas

Gray Matter Regions in Anatomic Atlas Labling Atlas (Montreal Neurological Institute 152 space)	Johns Hopkins University Probabilistic WM Tract Atlas (Montreal Neurological Institute152 space)
Precentral (L,R)	Anterior thalamic radiation (L,R)
Frontal superior (L,R)	Corticospinal tract (L,R)
Frontal superior orbital (L,R)	Cingulum (L,R)
Frontal middle (L,R)	Cingulum-hippocampal tract (L,R)
Frontal middle orbital (L,R)	Inferior frontal-occipital fasciculus (L,R)
Frontal Inferior operculum (L,R)	Inferior longitudinal fasciculus (L,R)
Frontal inferior triangularis (L,R)	Superior longitudinal fasciculus (L,R)
Frontal inferior orbital (L,R)	Superior lonitudinal fasciculus-temporal (L,R)
Rolandic operculum (L,R)	Uncinate fasciculus (L,R)
Supplementary motor area (L,R)	Forceps Major
Olfactory (L,R)	Forceps Minor
Frontal superior medial (L,R)	
Frontal medial orbital (L,R)	
Rectus (L,R)	
Insula (L,R)	
Cingulum anterior (L,R)	
Cingulum middle (L,R)	
Cingulum posterior (L,R)	
Hippocampus (L,R)	
Parahippocampal (L,R)	
Amygdala (L,R)	
Calcarine (L,R)	
Cuneus (L,R)	
Lingual (L,R)	
Occipital superior (L,R)	
Occipital middle (L,R)	
Occipital inferior (L,R)	

Fusiform (L,R)	
Postcentral (L,R)	
Parietal superior (L,R)	
Parietal inferior (L,R)	
Supramarginal (L,R)	
Angular (L,R)	
Precuneus (L,R)	
Paracentral lobule (L,R)	
Caudate (L,R)	
Putamen (L,R)	
Pallidum (L,R)	
Thalamus (L,R)	
Heschl (L,R)	
Temporal superior (L,R)	
Temporal pole superior (L,R)	
Temporal Middle (L,R)	
Temporal pole middle (L,R)	
Temporal Inferior (L,R)	
Cerebellum Crus1 (L,R)	
Cerebellum Crus2 (L,R)	
Cerebellum 3 (L,R)	
Cerebellum 4 and 5 (L,R)	
Cerebellum 6 (L,R)	
Cerebellum 7b (L,R)	
Cerebellum 8 (L,R)	
Cerebellum 9 (L,R)	
Cerebellum 10 (L,R)	
Vermis 1 and 2	
Vermis 3	
Vermis 4 and 5	
Vermis 6	
Vermis 7	
Vermis 8	
Vermis 9	

Vermis 10

Table E3: Comparison of Classifiers

Variable	Our Algorithm (LASSO and RBFN)	LASSO	SVM and RBFN	Random Forest	Gradient-Boosting Method
Baseline					
Features retained (%)	2.22 (7/315)	3.17 (10/315)	100 (315/315)	100 (315/315)	100 (315/315)
Classification accuracy (%)	75.93 (41/54)	68.52 (37/54)	74.07 (40/54)	70.37 (38/54)	59.26 (32/54)
Sensitivity (%)	72.22 (13/18)	5.56 (1/18)	27.78 (5/18)	27.78 (5/18)	11.11 (2/18)
Specificity (%)	77.78 (28/36)	100 (36/36)	97.22 (35/36)	91.67 (33/36)	83.33 (30/36)
AUC	0.75	0.53	0.63	0.6	0.47
Follow-up		NA	NA	NA	NA
Classification accuracy (%)	73.21 (41/56)				
Sensitivity (%)	70.59 (12/17)				
Specificity (%)	74.36 (29/39)				
AUC	0.72				

Note.—Data in parentheses are numerators and denominators. Our classifier was only compared at baseline with the other classifiers. Several metrics such as percentage of features retained, classification accuracy, sensitivity, specificity, and area under the curve (AUC) are reported for every classifier at baseline and at both time points for the classifier. The values inside the bracket represents the numerator and denominator. LASSO = least absolute shrinkage and selection operator, NA = not applicable, RBFN = radial basis functional networks, SVM = support vector machines.