Detection of mild traumatic brain injury utilizing multifeature analysis of MRI

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PURPOSE: A major challenge in understanding and treating mild traumatic brain injury (MTBI) is the lack of an accurate and objective means of establishing the diagnosis. Several notable national and international organizations, namely the World Health Organization, American Congress of Rehabilitation Medicine, the Centers for Disease Control and Prevention and the Department of Defense all differ in their respective definitions of MTBI. We have shown group differences between MTBI patients and controls using several novel noninvasive brain imaging techniques including non-Gaussian diffusion-weighted imaging (NGDWI), magnetic field correlation (MFC), resting state functional MRI (RS-fMRI), and MR volumetry. While this has been helpful to elucidate the neurobiology of disease, none of these metrics alone has been found to be useful as an independent biomarker of MTBI. Integrating findings using multiple metrics may bring these results into useful clinical practice. The purpose of this study is to assess the correlation between the aforementioned multiple imaging features and neuropsychological testing; and to further combine all features for predicting patient long-term outcome including post-concussive syndrome (PCS).

MATERIALS AND METHODS: 24 patients (mean age of 34.08 ±std 11.16 years; 6 female and 18 males) and 26 demographically similar healthy controls (mean age of 37.89 ±std 11.66 years; 11 female and 15 males) were studied. The mean interval between MRI and trauma for patients was 23 days (3-56 days). The clinical assessment including six categories of neurocognitive testing and four clinical scores was performed within 12 hours of MR imaging for all subjects. 17 patients were assessed following one-year with both MRI and clinical measures.

All MRI experiments were performed using the 3T Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany). MR images were acquired using a body coil for transmission and a 12-element SENSE coil for reception. In addition to the diffusion and functional MRI data, a set of co-planar T2-weighted Turbo spin echo images, a whole-brain 3D T1-weighted volume images, and susceptibility weighted imaging were also acquired to exclude non-traumatic lesions. The 3D MPRAGE (TR/TE/TI=2300/2.98/900ms, flip angle=9^o, resolution=1x1x1mm^3) was used for cortical and subcortical gray matter and white matter parcellation. The MPRAGE data were also used as reference images for overlaying RS-fMRI activation and connectivity maps as well as for delineation of thalamus using ROI-based analysis. MFC Imaging was performed with an asymmetric spin echo (ASE) pulse sequence using a segmented echo planar imaging (EPI) sequence with 33 lines of phase space being obtained for each excitation (i.e., EPI factor=33) with echo time (TE) of 40 ms, and 180° (sinc) refocusing pulse time shifts were t_s=0, −4ms, and −16 ms, (negative signs indicating a reduction in the interval between the refocusing pulse and the initial 90° excitation pulse). The field of view was 220×220 mm^2, matrix size=128x128, slice thickness = 1.7mm; yielding an isotropic resolution of 1.72mm, and TR=3420 ms to obtain a total of 48 axial slices, was repeated four times to facilitate error estimation of the MFC values. Diffusion kurtosis imaging (DKI) was performed with NGDWI acquired along 30 gradient directions and 3 b-values (b=0, 1000, 2000 s/mm^2) based on a twice-refocused spin-echo sequence. Scan parameters include TR/TE=3700/96 ms, voxel size =2.7x2.7x2.7mm^3 and acquisition time of ~8 minutes. For RS-fMRI, a standard gradient-echo EPI (TR/TE=2sec/30msec, number of volumes=153, flip angle = 75^o, FOV= 220x220 mm^2, matrix=128x128, 153 volumes) was performed in axial plane parallel to the AC-PC line with 5 mm slice thickness and 1mm gap and positioned to cover nearly the entire cerebrum, with resultant spatial resolution of 1.72x1.72x6 mm^3 and acquisition time of 5 minutes and 6 seconds. All patients and healthy subjects were instructed to close their eyes but stay awake during the resting-state fMRI imaging examination.

3D MPRAGE data were analyzed using FreeSurfer v.5.1.0 (www.freesurfer.net) for parcellation of regional brain structures using validated, well-established reproducible techniques. Specifically, thalamic and frontal white matter (WM) volumes were analyzed, namely thalamus, frontal pole, anterior cingulate, middle frontal, lateral and medial orbitofrontal and precentral regions bilaterally. Thalamic thickness was computed using software from (https://www.ia.unc.edu/dev/tutorials/CorticalThickness). After co-registration and averaging, images from the ASE pulse sequence were used to generate parametric maps of the MFC [1]: total, macroscopic and microscopic component MFC maps. Two regions of interest (thalamus and frontal white matter) were placed on three central continuous slices for regional average MFC (total and component) evaluation using the MRIcro software. The DKI data were processed with in-house MATLAB scripts [2]. The average of apparent kurtosis coefficient (Kmean) was evaluated in the thalamic ROI. The fMRI data was processed to derive the thalamic resting state network (RSN) by calculating the number of thalamic connected voxels (N) with a correlation threshold of P<0.01.

Fourteen imaging features were analyzed based on preliminary data showing statistical differences between groups. Clinical features (total of 19) and 2 demographic features (age and gender) were also included. To select features most helpful for classifying subjects and controls as well as to identify redundant features, we applied the following feature selection methods: primary component analysis, minimum Redundancy Maximum Relevance (mRMR, http://penglab.janelia.org/proj/mRMR) and correlation-feature based subset evaluator. Several widely-used classification methods were employed including Bayes network (BayesNet), radial basis function (RBF), multi-layer perceptron and sequential minimal optimization using WEKA software (www.weka.org). For testing and training, 10-fold cross validation method and the entire training set were used. For statistical correlation analysis between imaging features and clinical features (both at initial visit and 1-year follow-up), regressors such as ZeroR rule-based, decision stump trees and Gaussian process classifier with 10-fold cross validation methods were evaluated.

RESULTS: We found almost all features contribute significantly to the original feature matrix data (most features remain with 95% selection criteria) using primary component analysis. Based on mRMR criteria, 6 imaging features were selected including thalamic mean kurtosis (MK), thalamic RSN, thalamic microscopic MFC, thalamic thickness, frontal WM MFC and anterior cingulate WM volume. Among the classifiers, BayesNet classifier gave the best results with 86% accuracy for 10-fold cross-validation and 92% accuracy for the whole training dataset (improved from 74% with single best feature). Combining multiple features also improved prediction of subject performance on neuropsychological tests: we found the correlation significance increased from P=0.049 (between single thalamic micro MFC and California verbal learning test-CVLT) to P=0.015 after combining all six imaging features using a linear regression model. Including subject age was found to improve multi-feature imaging fitting to CVLT score with P=0.007. Furthermore combining the imaging features and neuropsychological features, RBF neuron-network classifier can achieve 97% of accuracy (94% sensitivity and 100% specificity); while the multi-layer perceptron classifier can achieve 100% accuracy. In terms of long-term prediction, we found that with the ZeroR rule-based regressors, the clinical symptom at follow-up visit could be predicted with high accuracy from baseline imaging features with r=-0.82, P<0.001 for depression; r=-0.65, P=0.01 for anxiety; r=-0.71, P=0.005 for fatigue; and r=-0.67, P=0.008 for PCS.

CONCLUSIONS: Our pilot study demonstrates that an automatic classification based on objective metrics can achieve a high accuracy and a robust prediction for the long-term outcome (P≤0.01).

References [1] Jensen et al. Magn Reson Med 2009; 61:481-5. [2] Jensen et al. Magn Reson Med 2005; 53(6):1432-40.