Research Article

Machine Learning Classification of Mild Traumatic Brain Injury Using Whole-Brain Functional Activity: A Radiomics Analysis

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Objectives. To investigate the classification performance of support vector machine in mild traumatic brain injury (mTBI) from normal controls.

Methods. Twenty-four mTBI patients (15 males and 9 females; mean age, 38.88 ± 13.33 years) and 24 age and sex-matched normal controls (13 males and 11 females; mean age, 40.46 ± 11.4 years) underwent resting-state functional MRI examination. Seven imaging parameters, including amplitude of low-frequency fluctuation (ALFF), fractional amplitude of low-frequency fluctuation (fALFF), regional homogeneity (ReHo), degree centrality (DC), voxel-mirrored homotopic connectivity (VMHC), long-range functional connectivity density (FCD), and short-range FCD, were entered into the classification model to distinguish the mTBI from normal controls.

Results. The ability for any single imaging parameters to distinguish the two groups is lower than multiparameter combinations. The combination of ALFF, fALFF, DC, VMHC, and short-range FCD showed the best classification performance for distinguishing the two groups with optimal AUC value of 0.778, accuracy rate of 81.11%, sensitivity of 88%, and specificity of 75%. The brain regions with the highest contributions to this classification mainly include bilateral cerebellum, left orbitofrontal cortex, left cuneus, left temporal pole, right inferior occipital cortex, bilateral parietal lobe, and left supplementary motor area.

Conclusions. Multiparameter combinations could improve the classification performance of mTBI from normal controls by using the brain regions associated with emotion and cognition.

1. Introduction

Traumatic brain injury (TBI), a major public health problem and a leading cause of disability, affects half the world’s population [1]. Approximately 70%-90% of TBI patients are mild TBI (mTBI), and 30-40% of whom cannot fully recover even at 6 months postinjury [1, 2]. Patients with mild head injury often manifest as dizziness, headache, and memory and attention deficit, which was considered to be associated with abnormal changes of brain networks [3]. Recently, functional and structural neuroimaging methods have been widely used to address the functional and morphological changes of mTBI [4–11]. Zhou et al. found abnormal functional connectivity within the default mode network in mTBI patients, which was associated with cognitive neurological dysfunction and posttraumatic symptoms (i.e., depression, anxiety, fatigue, and postconcussion syndrome) [12]. Nakamura et al. found that mTBI was associated with changes in the “small world” networks [13]. Zhan et al. found decreased ReHo value in the left insula, left pre-/postcentral gyrus, and left supramarginal gyrus in mTBI patients [14]. However, the potential neurobiological mechanism of the mTBI left unclear.

Most current studies focus attentions on investigating group differences between two different labels (knowing the classes of all subject before statistics); however, group-based methods cannot classify different types for individual classification and are not sensitive for feature selection [15]. Support vector machine (SVM) classifier is an efficient and sensitive neuroimaging biological indicator for feature selection and classification. There is a growing application of the SVM algorithm into several diseases, such as insomnia [16, 17], epilepsy [15], and autistic spectrum disorder [18]. However, the mTBI has not been studied. Differences in
brain regions in mTBI were not the same when we analyzed the between-group differences by different neuroimaging methods, which may be associated with the sensitivity of different methods in searching features (brain areas). Therefore, we hypothesized that the combination of different neuroimaging methods may improve the sensitivity for feature selection. To address these hypotheses, the present study is the first to apply the SVM algorithm to perform the classification for mTBI.

2. Materials and Methods

2.1. Subjects. This case-control study comprised 170 subjects from our hospital between May 2014 and May 2021, among whom a total of 146 subjects were excluded, including 139 subjects unmatched diagnosis with mTBI, 4 mTBI with acute amnesia less than 24 hours. Exclusion criteria for patients with acute mTBI were as follows: (a) have a diagnosis of mTBI within two weeks, (b) age between 18 and 65 years, (c) time of lack of consciousness less than 30 min, and (d) time of posttraumatic amnesia less than 24 hours. Exclusion criteria for patients with acute mTBI were as follows: (a) involvement in litigation, (b) a history of psychiatric disorders, (c) a history of addiction, and (d) a history of traumatic brain injury. This study was approved by the Human Research Ethics Committee in accordance with the Declaration of Helsinki, and written informed consent was obtained.

2.2. MRI Parameters. MRI data were acquired with a clinical 3-Tesla MRI scanner (Trio Tim, SIEMENS, Erlangen, Germany), including T1WI, T2WI, T2-FLAIR, high-resolution T1WI, functional MRI, and SWI. A total of 176 three-dimensional high-resolution anatomical T1-weighted volumes were acquired in a sagittal orientation (rapid-gradient-echo sequence, repetition time = 1900 ms, echo time = 2.26 ms, thickness = 1.0 mm, matrix = 256 × 256, and field of view = 240 mm × 240 mm). For functional images, a total of 250 volumes (Echo-Planar Imaging pulse sequence, 30 transverse slices, repetition time = 2000 ms, echo time = 40 ms, thickness = 4.0 mm, matrix = 64 × 64, field of view = 240 mm × 240 mm, and flip angle 90°) were acquired.

2.3. Data Processing. All functional MRI data preprocessing were performed with DPABI (version 2.1, http://rfmri.org/DPABI) toolbox. First, the first ten volumes were deleted, and the remaining volumes were converted their data format. The following steps of slice timing, head motion correction, spatial normalization, smooth (Gaussian kernel of 8 × 8 × 8 mm³), linear regression of possible spurious covariates, linearly detrended, and temporally band-pass filtered (0.01-0.1 Hz) were performed for data preprocessing. After the step of head motion correction, a “head motion scrubbing regressors” procedure was implemented, and the subjects who had more than 1.5 degree of motion rotation and/or 1.5 mm maximum translation in x, y, or z directions were excluded. Furthermore, the head motion effect was regressed out with Friston 24 head motion parameter model. During the step of spatial normalization, all data were spatially normalized to Montreal Neurological Institute (MNI) space and resampled at a resolution of 3 × 3 × 3 mm³.

2.4. Feature Selection and Binary Classification. We calculated seven MRI parameters, including ALFF, fALFF, ReHo, degree centrality, long-term FCD, short-term FCD, and VMHC. The maps of MRI parameters were segmented into
116 regions of interest (ROIs) using the automated anatomical labeling (AAL) atlas. The total of 812 features was extracted in the following classification with multivariate pattern analysis (MVPA).

We used a LIBSVM toolbox (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) to perform the classification, and a 5-fold cross-validation was used to validate the classification performance of the classifier. Permutation test was used to evaluate the probability of the classification performance for 5000 times randomly. The clusters of brain regions with higher than 70% of classification accuracy were considered as accuracies. The area under curve (AUC), sensitivity, and specificity of the classifier were quantified.

2.5. Statistical Analyses. Comparisons of demographic factors were performed using two-sample \( t \)-tests. Chi-square \( (\chi^2) \) test was used for categorical data. Statistical analysis was performed using IBM SPSS 21.0 version. Data are presented as mean \( \pm \) standard deviation. All the quoted results are two-tailed values, and \( p < 0.05 \) was considered as statistically significant.

3. Results

3.1. Sample Characteristics. There were no significant differences in mean age \( (t = -0.442, p = 0.66) \), sex \( (\chi^2 = 0.343, p = 0.558) \), and educational level \( (t = 0.33, p = 0.743) \) between the healthy controls and patients with mTBI. Compared with healthy controls, patients with mTBI had higher HAMA score \( (t = 5.077, p < 0.001) \), ADL score \( (t = 4.654, p < 0.001) \), and BDI score \( (t = 3.808, p = 0.001) \), and a lower MMSE score \( (t = -2.284, p = 0.03) \). The mean time between injury and MRI examination of patients with mTBI was 3.58 \( \pm \) 3.28 days. The mean GCS score, DRS score,
Table 2: Weight ranking of the 116 brain regions to the classification of the combination with ALFF, fALFF, DC, VMHC, and short-term FCD.

| ROI weight | Voxel size |
|------------|------------|
| Vermis_10  | 1.948      | 34         |
| Cerebellum_9_R | 1.470   | 156        |
| Cerebellum_10_L | 1.465   | 40         |
| Cerebellum_9_L | 1.455    | 158        |
| Frontal_Mid_Orb_L | 1.417   | 224        |
| Frontal_Sup_Orb_L | 1.398   | 280        |
| Cuneus_L | 1.353      | 472        |
| Cerebellum_Crus2_R | 1.329   | 539        |
| Cerebellum_7b_L | 1.265    | 98         |
| Cerebellum_Crus2_L | 1.257   | 543        |
| Frontal_Mid_Orb_L | 1.256    | 273        |
| Temporal_pole_Mid_L | 1.222   | 177        |
| Occipital_Inf_R | 1.220     | 316        |
| Parietal_Sup_L | 1.136      | 575        |
| Paracentral_lobule_R | 1.134   | 221        |
| Frontal_Sup_R | 1.118      | 1120       |
| Cuneus_R | 1.117      | 416        |
| Cerebellum_Crus1_R | 1.103    | 723        |
| Occipital_Inf_L | 1.103      | 263        |
| Vermis_7 | 1.102      | 54         |
| Calcarine_L | 1.076      | 649        |
| Occipital_Sup_R | 1.074      | 407        |
| Rectus_L | 1.070      | 258        |
| Postcentral_R | 1.055     | 1050       |
| Paracentral_lobule_L | 1.053    | 340        |
| Precentral_R | 1.009      | 941        |
| Parietal_Inf_R | 1.008      | 397        |
| Occipital_Sup_L | 0.998      | 373        |
| Cerebellum_10_R | 0.997     | 37         |
| Cerebellum_7b_R | 0.975     | 78         |
| Cerebellum_8_L | 0.961      | 303        |
| Cerebellum_6_L | 0.960      | 524        |
| Vermis_9 | 0.959      | 50         |
| Temporal_Inf_R | 0.959     | 1076       |
| Occipital_Mid_L | 0.954     | 947        |
| Cerebellum_Crus1_L | 0.950   | 725        |
| Lingual_L | 0.945      | 662        |
| Supp_motor_area_L | 0.937     | 630        |
| Frontal_Mid_R | 0.931      | 1448       |
| Calcarine_R | 0.925      | 528        |
| Temporal_Mid_L | 0.922      | 1437       |
| Parietal_Sup_R | 0.921      | 569        |
| Cerebellum_4_5_L | 0.919     | 352        |
| Frontal_Sup_medial_L | 0.918   | 847        |
| Lingual_R | 0.916      | 683        |
| Angular_R | 0.916      | 511        |
| Temporal_pole_Sup_R | 0.918   | 325        |

Table 2: Continued.

| ROI weight | Voxel size |
|------------|------------|
| Cerebellum_6_R | 0.908     | 532        |
| Precuneus_R | 0.908      | 927        |
| Temporal_Sup_R | 0.907    | 942        |
| Frontal_Sup_L | 0.890      | 987        |
| Angular_L | 0.860      | 341        |
| Precuneus_L | 0.851      | 1008       |
| Cingulum_post_L | 0.850    | 111        |
| Frontal_Inf_Tri_L | 0.848   | 675        |
| Frontal_Mid_L | 0.847      | 1323       |
| Temporal_pole_Sup_L | 0.828    | 329        |
| Temporal_Sup_L | 0.825      | 694        |
| Temporal_pole_Mid_R | 0.822   | 246        |
| Cerebellum_8_R | 0.810      | 298        |
| Cerebellum_3_R | 0.801      | 65         |
| Occipital_Mid_R | 0.796     | 578        |
| Supp_motor_area_R | 0.790    | 695        |
| Vermis_4_5 | 0.788      | 176        |
| Frontal_Sup_medial_R | 0.787    | 589        |
| Frontal_Inf_Tri_R | 0.783      | 560        |
| Supramarginal_R | 0.779     | 562        |
| Precentral_L | 0.764      | 931        |
| Heschl_R | 0.763      | 60         |
| Frontal_Mid_Orb_R | 0.762    | 296        |
| Frontal_Sup_Orb_R | 0.752      | 296        |
| Frontal_Inf_Orb_L | 0.752     | 504        |
| Cerebellum_3_L | 0.750      | 42         |
| Supramarginal_L | 0.750      | 357        |
| Fusiform_L | 0.747      | 665        |
| Temporal_Inf_L | 0.745      | 948        |
| Vermis_1_2 | 0.738      | 9          |
| Rectus_R | 0.728      | 208        |
| Parietal_Inf_L | 0.723     | 687        |
| Cerebellum_4_5_R | 0.719     | 239        |
| Frontal_Inf_Oper_R | 0.715    | 396        |
| Caudate_L | 0.703      | 270        |
| Postcentral_L | 0.702      | 1069       |
| Fusiform_R | 0.688      | 759        |
| Pallidum_L | 0.685      | 76         |
| Vermis_6 | 0.675      | 87         |
| Amygdala_L | 0.672      | 63         |
| Putamen_L | 0.660      | 280        |
| Frontal_Inf_Orb_R | 0.660    | 498        |
| Frontal_Mid_Orb_R | 0.657     | 271        |
| Vermis_8 | 0.652      | 60         |
| Insula_R | 0.646      | 497        |
| Rolandic_Oper_L | 0.645     | 301        |
| Cingulum_Mid_L | 0.635     | 579        |
| Olfactory_L | 0.632      | 80         |
In this case-control study, we documented two novel findings. First, we developed an SVM classifier that was a useful neuro-imaging biomarker for mTBI classification. We found that the combination with ALFF, fALFF, DC, VMHC, and short-term FCD received the highest classification performances among all combination (accuracy = 81.1%, sensitivity = 88.0%, and specificity = 75.0%). Second, the consensus brain regions with the highest contributions to classification were located in the bilateral cerebellum, left orbitofrontal cortex, left cuneus, left temporal pole, right inferior occipital gyrus, bilateral parietal lobe, and left supplementary motor area (Table 2).

4. Discussion

In this case-control study, we documented two novel findings. First, we developed an SVM classifier that was a useful neuro-imaging biomarker for mTBI classification. We found that the combination with ALFF, fALFF, DC, VMHC, and short-term FCD received the highest classification performances among all combination (accuracy = 81.1%, sensitivity = 88.0%, and specificity = 75.0%). Second, the consensus brain regions with the highest contributions to classification were located in the bilateral cerebellum, left orbitofrontal cortex, left cuneus, left temporal pole, right inferior occipital gyrus, bilateral parietal lobe, and left supplementary motor area (Table 2).

Our study is the first to apply the SVM classifier to find a promising model for mTBI classification. Although several previous studies have offered insights into brain functional and structural abnormalities of mTBI using traditional group-level statistical differences based on one single imaging method, they could not be translated into predictive or diagnostic neurobiological biomarkers for mTBI. The emergence of radiomics has broadened the scope of routine medical imaging, which carried multimodality medical information to reflect the development and progression of diseases [19, 20]. Machine learning classification based on the radiomics strategy allows detecting subtle, nonstrictly localized effects that may remain invisible to the conventional analysis with univariate statistics [21, 22], which are being increasingly used in functional MRI data [15, 16]. These findings could explain the high classification performance of the SVM classifier.

Cerebellum is associated with emotion, motor, and advanced cognitive function [23]. The cerebellum anterior lobe is associated with sensorimotor function, and the cerebellum posterior lobe is associated with the regulation of coordinating movement, balance and sleep, and emotional changes [24–28]. Brain volume atrophy and reduction of metabolism functional activity can be found in subjects after TBI [29–31]. Peskind et al. found that soldiers with mTBI showed reduction of glucose metabolism in the cerebellar vermis, cerebellar hemisphere, and pons and functional deficits in attention, language, and working memory [31]. In addition, cerebellar activation was also significantly reduced during auditory-related task stimulation [30]. These studies suggest that the cerebellum plays an important role in the neuropathological basis of mTBI, which supports our findings of high contributions of the cerebellum to the SVM classifier.

The prefrontal lobe is one of the brain areas that are most vulnerable to the mTBI. Even minor brain damage can easily cause a damage of the frontal lobe. Studies have found that abnormal functional changes in the frontal lobe are one of the neural mechanisms of emotional numbness, attention, planning, high alertness, and psychological avoidance in patients with posttraumatic injury [32–34]. Keightley et al.

### Table 2: Continued.

| ROI weight | Voxel size |
|------------|------------|
| Thalamus_R | 0.631      | 296        |
| Frontal_Inf_Oper_L | 0.628      | 309        |
| Parahippocampal_L | 0.624      | 298        |
| Pallidum_R | 0.621      | 67         |
| Cingulum_Ant_R | 0.621      | 385        |
| Temporal_Mid_R | 0.619      | 1311       |
| Cingulum_Ant_L | 0.598      | 425        |
| Thalamus_L | 0.596      | 280        |
| Cingulum_Mid_R | 0.574      | 612        |
| Vermis_3 | 0.549      | 62         |
| Rolandic_Oper_R | 0.548      | 404        |
| Heschl_L | 0.548      | 72         |
| Olfactory_R | 0.538      | 88         |
| Cingulum_post_R | 0.522      | 69         |
| Caudate_R | 0.511      | 287        |
| Parahippocampal_R | 0.506      | 318        |
| Hippocampus_L | 0.493      | 279        |
| Amygdala_R | 0.474      | 73         |
| Insula_L | 0.465      | 545        |
| Putamen_R | 0.436      | 309        |
| Hippocampus_R | 0.411      | 282        |

MAS score, and ABS score in patients with mTBI were $14.42 \pm 0.88$, $2.58 \pm 2.36$, $44.38 \pm 5.86$, and $14.42 \pm 0.78$, respectively. The details are shown in Table 1.

3.2. Classification Performance. First, we compared the classification performances of the seven MRI parameters and found they could not differentiate well between healthy controls and patients with mTBI (AUC: 0.66 ± 0.03, range, 0.61–0.69; accuracy rate: 66.4% ± 3.4%, range, 60.2%–70.9%; sensitivity: 64.1% ± 7.9%, range, 49.0%–75.0%; and specificity: 68.4% ± 5.6%, range, 61.0%–75.0%). Second, we combined these MRI parameters and found the features with the highest contributions to the classification to discriminate between mTBI and healthy controls. We found that the combination with ALFF, fALFF, DC, VMHC, and short-term FCD significantly reached up the classification accuracy, sensitivity, and specificity and received the highest classification performances among all combination with classification accuracy of 81.1% ($p < 0.001$), sensitivity of 88.0% ($p < 0.001$), and specificity of 75.0% ($p < 0.001$) (Figure 1).

3.3. Consensus Features and Region Weight. In this study, all consensus features were mapped to AAL116 template (116 brain regions), and each of the 116 brain regions was given a weight value which indicates the contribution to classification model. For the combination with ALFF, fALFF, DC, VMHC, and short-term FCD, Table 2 shows the weight ranking of the 116 brain regions from highest to lowest.

Among the 116 brain regions, a total of 51 brain regions showed higher contributions to the classification than the average weight value (contribution), including the bilateral cerebellum, left orbitofrontal cortex, left cuneus, left temporal pole, right inferior occipital gyrus, bilateral parietal lobe, and left supplementary motor area (Table 2).
found that adolescents with mTBI showed weaker working memory and language function and reduced brain activity in supplementary motor areas, dorsolateral prefrontal lobe, and superior parietal lobe than that of healthy adolescents [35]. Pardini et al. and Jantzen et al. found that parietal lobe and orbitofrontal cortex are associated with severity of mTBI and postconcussion symptoms [36, 37]. Our findings support these studies. Therefore, the abnormal functional changes in the frontal-parietal lobe may be associated with the posttraumatic injury severity and symptoms, which contribute to the high contributions to the SVM classifier.

Abnormal functional connectivity between temporal pole and parietal lobe and decreased glucose metabolism in these two areas were found in mTBI patients relative to normal controls [31, 38, 39]. The temporal pole is closely related to the functions such as social interaction, face recognition, semantic memory, mental speculation, and emotion and is responsible for the synthesis of complex and finely processed perceptual input of internal emotions [40]. The abnormal function of the temporal pole in mTBI patients will help us understand the biological mechanism of daily life disorders of mTBI.

5. Conclusions

In this study, we developed an SVM classifier that can be severed as a promising sensitive neuroimaging biomarker for mTBI classification based on a combination of multiple imaging indicators. Our analysis using the model showed that the bilateral cerebellum, left orbitofrontal cortex, left cuneus, left temporal pole, right inferior occipital gyrus, bilateral parietal lobe, and left supplementary motor areas exhibited the highest contributions to the classification model. These findings may expand our understanding of the neurobiological mechanism of mTBI. However, there are several limitations that should be addressed. First, the sample size of our study was relatively small. A larger number of sample sizes and multiple center studies are necessary to corroborate our findings. Second, the data of subacute mTBI and follow-up were scarce. Third, this study only used SVM to perform the classification, and other classification methods should be introduced to compare their performances. Fourth, location and size of the lesion, disease of severity, and subtype of mild traumatic brain injury were not considered in the classification.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Authors’ Contributions

X.L., D.L., S.X., and D.W. conceived and designed the whole experiment; X.W., W.H., and H.Y. collected the data; X.L., D.L., and H.Y. take responsibility for the integrity of the data, the accuracy of the data analysis, and the statistical data analysis; X.L. wrote the main manuscript text and undertook the critical interpretation of the data. All authors contributed to the final version of the paper and have read, as well as, approved the final manuscript.

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