2023

Opioid Use Disorder Prediction Using Machine Learning of fMRI Data

A. Temtam
Old Dominion University, atemt001@odu.edu

Liangsuo Ma
Virginia Commonwealth University

F. Gerard Moeller
Virginia Commonwealth University

M. S. Sadique
Old Dominion University, msadi002@odu.edu

K. M. Iftekharuddin
Old Dominion University, kiftekha@odu.edu

See next page for additional authors

Original Publication Citation

Temtam, A., Ma, L., Moeller, F. G., Sadique, M. S., & Iftekharuddin, K. M. (2023). Opioid use disorder prediction using machine learning of fMRI data. In K.M. Iftekharuddin & W. Chen (Eds.), *Medical Imaging 2023: Computer-Aided Diagnosis, Proceedings of SPIE 12465* (1-5). SPIE. https://doi.org/10.1117/12.2655568

Opioid Use Disorder Prediction Using Machine Learning of fMRI Data

A. Temtam*[a], Liangsuo Ma [b,c], F Gerard Moeller [b,c], M. S. Sadique[a], K. M. Iftekharuddin [a]
[a]Dept. of Electrical and Computer Engineering, Old Dominion University, Norfolk, VA, USA 23529; [b]Institute of Drug and Alcohol Studies, [c]Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA 23284-2520

ABSTRACT

According to the Centers for Disease Control and Prevention (CDC) more than 932,000 people in the US have died since 1999 from a drug overdose. Just about 75% of drug overdose deaths in 2020 involved Opioid, which suggests that the US is in an Opioid overdose epidemic. Identifying individuals likely to develop Opioid use disorder (OUD) can help public health in planning effective prevention, intervention, drug overdose and recovery policies. Further, a better understanding of prediction of overdose leading to the neurobiology of OUD may lead to new therapeutics. In recent years, very limited work has been done using statistical analysis of functional magnetic resonance imaging (fMRI) methods to analyze the neurobiology of Opioid addictions in humans. In this work, for the first time in the literature, we propose a machine learning (ML) framework to predict OUD users utilizing clinical fMRI-BOLD (Blood oxygen level dependent) signal from OUD users and healthy controls (HC). We first obtain the features and validate these with those extracted from selected brain subcortical areas identified in our previous statistical analysis of the fMRI-BOLD signal discriminating OUD subjects from that of the HC. The selected features from three representative brain areas such as default mode network (DMN), salience network (SN), and executive control network (ECN) for both OUD participants and HC subjects are then processed for OUD and HC subjects' prediction. Our leave one out cross validated results with sixty-nine OUD and HC cases show 88.40% prediction accuracies. These results suggest that the proposed techniques may be utilized to gain a greater understanding of the neurobiology of OUD leading to novel therapeutic development.

Keywords: Opioid use disorder, healthy controls, Machine learning, fMRI, fMRI-BOLD signal

1. DESCRIPTION OF PURPOSE

Opioid use disorder affects an estimated 2 million people in the United States at very high cost [1-2]. Many patients use opioids consistently as these are patients diagnosed with obsessive compulsive disorder. Several studies have developed automated algorithms to identify nonmedical opioid use and OUD using patient claims data or electronic health records [3–4]. These algorithms mainly use traditional statistical analysis methods.

One of our prior studies for the study the neurobiology of addictions in humans [5] has shown that selected brain subcortical areas including executive control network (ECN) functional connectivity may differ between OUD and HC. The study is based on a resting state functional magnetic resonance imaging (fMRI) statistical signal analysis. Recently, though machine learning (ML) methods have been used for analysis of OUD, these works do not consider fMRI signal analysis. The authors in [6] implement the Gradient Boosting trees algorithm using a commercial claims database for the analysis of patient overdose status. The work in [7] analyzes information from electronic health records to predict opioid substance dependence. Another work [8] uses a ML to Predict (OUD) using National Survey on Drug Use and Health data. Also, the work in [9] applies deep learning methods to predict OUD for patients on opioid medications using electronic health records. However, there is no prior work in the literature that uses fMRI ML analysis for predictive analysis of OUD cases from HC.

This work, for the first time in the literature, presents an ML approach to predict individuals with OUD from HC using fMRI-BOLD signals. We first obtain the features and validate these with those extracted from selected brain subcortical areas identified in our previous statistical analysis of the fMRI-BOLD signal discriminating OUD subjects from that of the HC [5]. This study is expected to offer greater understanding of the neurobiology of OUD.

Medical Imaging 2023: Computer-Aided Diagnosis, edited by Khan M. Iftekharuddin, Weijie Chen, Proc. of SPIE Vol. 12465, 124650Q · © 2023 SPIE
1605-7422 · doi: 10.1117/12.2655568

2. METHODS

2.1 Dataset

The clinical data and high-resolution resting state fMRI data for this study are obtained from a National Institute on Drug Abuse (NIDA) funded study (Phenotyping Assessments Battery [PhAB] Feasibility and Validation Study in Non-Intoxicated Drug Users). The human subjects OUD study is approved by the Virginia Commonwealth University Committee for the Protection of Human Subjects and is a joint collaboration between department of drug and alcohol studies, Virginia Commonwealth University and Vision Lab at Old Dominion University. The summary of the data is shown in Table 1.

Table 1. Dataset distribution summary.

Subjects	Male	Female	Total	Mean Age
HC	20	20	40	33.8
OUD	18	11	29	39.6
TOTAL	38	31	69	

For the fMRI data acquisition, T1-weighted MPRAGE and resting state fMRI data were acquired from a 3T MRI scanner (Philips Ingenia wide-bore, Best, the Netherlands) with a phased-array SENSE 32-channel receiver head coil. For the rsfMRI scan, during which subjects were instructed to relax, keep looking at a fixation cross, and remain awake, blood-oxygen-level-dependent (BOLD) signal was measured with a T2* gradient-echo EPI sequence (SENSE in-plane acceleration factor 1.5, multiband factor 3, repetition-time=1.625 seconds, echo-time=30 milliseconds, 45 axial slices, slice-thickness=2.5 mm, 0.3 mm gap, field-of-view=[240×240] mm, in-plane resolution=[2.5×2.5] mm, flip-angle=52°, 420 volumes after 12 dummy volumes, and total duration 11 minutes 22 seconds). The fMRI data have been preprocessed in order to remove signal artifacts (including artifacts due to head motion and cardiac and respiratory extraneous signals) using the procedure as described in [10]. The data is one modality with dimensions [91,109,91,420].

2.2 Methodology

In this work, we first apply standard preprocessing steps to the fMRI-BOLD signal and prepare the input signals for input to a pipeline for pattern estimation. We use data representation to represent the areas of the brain that are activated in order to recover the onsets of pseudo-events triggering a hemodynamic response from fMRI-BOLD voxel-wise signal [5]. The hemodynamic response function (rsHRF) [11,12] is used as the feature extraction mechanism. then, we treat the fMRI-BOLD signal as a linear time invariant system. The convolution function is applied to obtain an output signal, and to remove unwanted artifacts then transform the data into a standard format. The pipeline of the proposed method is shown in Figure 1.

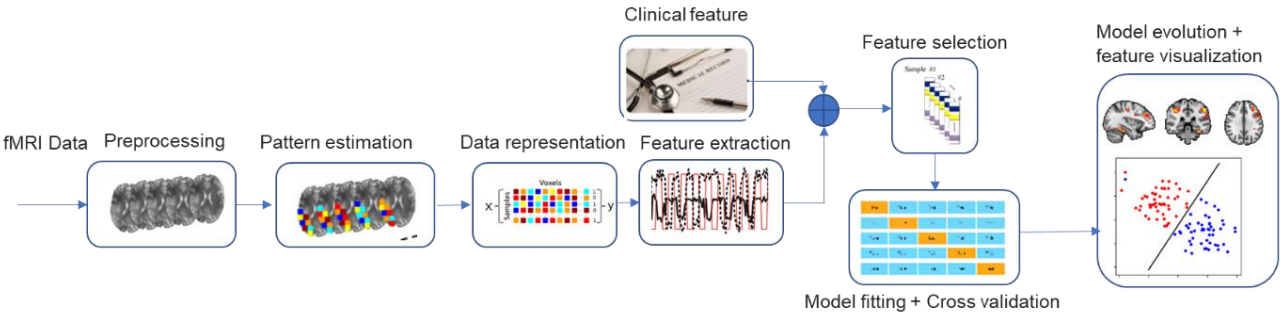


Figure 1. The pipeline for Opioid use disorder prediction.

3. RESULTS

In this study, the features are extracted from the fMRI-BOLD signals for OUD and HC subjects from ECN, SN and DMN areas of the brain as shown in Figure. 2 (1. (a), (b)). We evaluate the functional connectivity clusters for both OUD and HC classes using the AAL3 atlas. For OUD we use a threshold of 0.001, then we apply the functional connectivity clusters for different subcortical areas (DMN, SN and ECN), which is obtained after thresholding are overlapped on standard structural brain images, as shown in Figure. 2 (2. (a), (b)).

According to AAL3 atlas, the left superior frontal gyrus (centered at [x=-16, y=19, z=52] mm, MNI coordinates) has been observed in [5] and is also found in our analysis (i.e., left Superior frontal gyrus, dorsolateral, 185 voxels, centered at [x=-22, y=28, z=46] mm, MNI coordinates) as shown in Figure 3. For the HC we use a threshold of 0.00001 that yields the left Superior frontal gyrus, dorsolateral, 185 voxels, centered at [x=-22, y=42, z=30] mm as the area of interest for prediction. This step validates the representative features between this current and our prior statistical-based methods for OUD prediction.

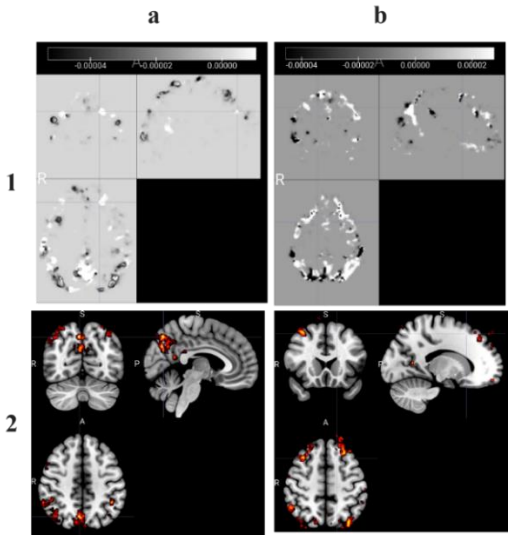


Figure 2. Analysis results: (1a) Display of fMRI-BOLD signals for HC, (2a) overlay of fMRI-BOLD for HC over standard structural brain images, displayed in 'red' are the significant clusters. (1b) Display of fMRI-BOLD signals for OUD, (2b) overlay of fMRI-BOLD for OUD over standard structural brain images, displayed in 'red' are the significant clusters in specific subcortical areas: DMN, SN and ECN.

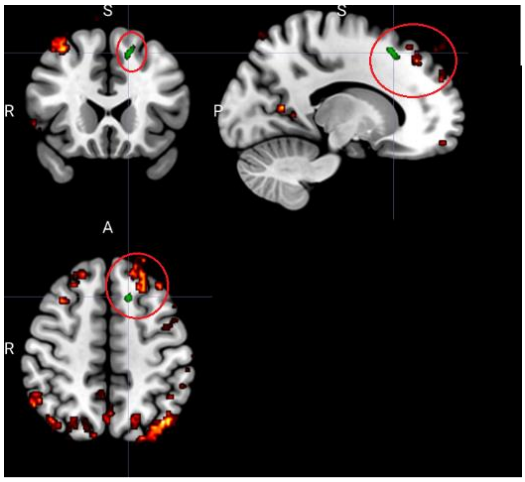
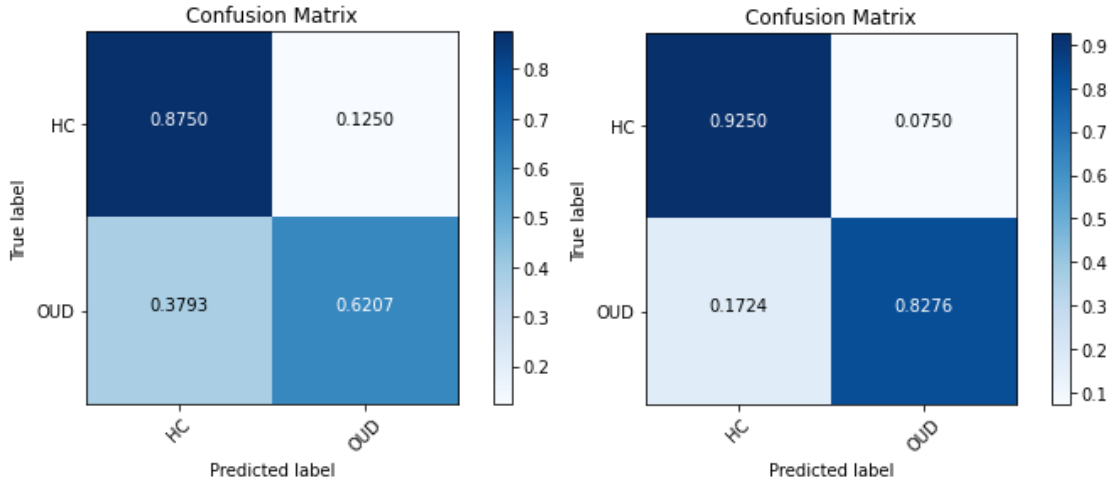


Figure .3. Displayed in 'red' are the functional connectivity clusters found in our study and in 'green' are the significant cluster found in [5] for OUD cases in specific subcortical areas: DMN, SN and ECN.

For prediction, we input the extracted feature data into the model. To evaluate the performance of our model, we employ a 5-fold cross-validation technique. We implement an automated model selection process to identify the top-performing classifier among multiple options. (e.g., XGB Classifier, Decision Tree, linear SVM Classifier, Random Forest Classifier) based on accuracy metric. The results show the Decision Tree and linear SVM Classifier offer the best accuracy performance. Additionally, for the best classifier, we compute the area under the curve (AUC). The results are shown in Table .2. We further perform Leave-one-out cross-validation LOO-CV for the best classifiers to mitigate the risk of over-fitting. The LOO-CV yields competitive prediction accuracies of 73.91 ± 0.42% for Linear SVM classifier and 88.40 ± 0.32% for Decision tree classifier, respectively.

Table 2. Analytical Performance of the Models using 5-fold CV.

Classifier	Accuracy Mean ± Std	Area Under Curve mean	Recall mean	f1_score mean	Support mean
Linear SVM	79.67 ± 0.07 %	78± 0.26 %	75 %	75 ± 0.17 %	34.50 %
Decision Tree Classifier	88.24 ± 0.08 %	87 ± 0.13 %	88 %	88 ± 0.12 %	34.50 %



Linear SVM Decidion Tree

Figuer.4. The HC and OUD prediction confusion matrix of linear SVM and decision tree models using 5-fold CV.

4. NOVEL CONTRIBUTION

In this paper, for the first time in the literature, ML model is developed that accurately predicts OUD cases when compared to HCs. The method combines clinical features and extracted features of fMRI-BOLD dataset. The extracted features are validated with those obtained in a prior functional connectivity discovered for these patients in default mode network (DMN), salience network (SN), and executive control network (ECN) in [5] respectively. The results further suggest altered executive function in OUD and supports further examination of functional connectivity in association with treatment response in OUD.

5. CONCLUSIONS

The results show that the Decision Tree Classifier model achieves the best predictive performance of OUD in terms of accuracy and AUC. In addition, our proposed framework extracts fMRI-Bold features, which are predictive of OUD. These preliminary results suggest that our functional connectivity clusters results in selected brain subcortical areas such as ECN, DMN and CN may offer discriminative features that are predictive of OUD and HC patients. Specifically, this finding on the left superior frontal gyrus is consistent with [5] showing altered executive function in OUD and supports further examination of functional connectivity in association with treatment response in OUD.

6. ACKNOWLEDGEMENTS

This research was partially supported by UG1DA050207 and by the National Institutes of Health through the NIH HEAL Initiative under award number: U54DA038999. We also acknowledge partial funding of this work by a NIBIB/NIH grant # R01 EB020683.

REFERENCES

[1] Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2021. Available at http://wonder.cdc.gov.
[2] Hedegaard H, Miniño AM, Spencer MR, Warner M. Drug Overdose Deaths in the United States, 1999–2020. National Center for Health Statistics, December 2021.
[3] Webster, Lynn R., and Rebecca M. Webster. "Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool." Pain medicine 6.6 (2005): 432-442.
[4] Ives, Timothy J., et al. "Predictors of opioid misuse in patients with chronic pain: a prospective cohort study." BMC health services research 6.1 (2006): 1-10.
[5] Kyle Woisard,Joel L Steinberg, Liangsuo Ma, Edward Zuniga, Tatiana Ramey, Michael Lennon, Lori Keyser-Marcus and F Gerard Moeller J Addict,Preliminary Findings of Weaker Executive Control Network Resting State fMRI Functional Connectivity in Opioid Use Disorder compared to Healthy Controls. J Addict Res Therapy, Vol 12(10), 2021.
[6] Segal, Zvi, et al. "Development of a machine learning algorithm for early detection of opioid use disorder." Pharmacology Research & Perspectives 8.6 (2020): e00669.
[7] Ellis, Randall J., et al. "Predicting opioid dependence from electronic health records with machine learning." BioData mining 12.1 (2019): 1-19.
[8] Wadekar, Adway. "Predicting Opioid Use Disorder (OUD) Using A Random Forest." 2019 IEEE 43rd Annual Computer Software and Applications Conference (COMPSAC). Vol. 1. IEEE, 2019.
[9] Dong, Xinyu, et al. "Identifying risk of opioid use disorder for patients taking opioid medications with deep learning." Journal of the American Medical Informatics Association 28.8 (2021): 1683-1693.
[10] Ma L, Hettema JM, Cousijn J, et al. Resting-State Directional Connectivity and Anxiety and Depression Symptoms in Adult Cannabis Users. Biological psychiatry. Cognitive neuroscience and neuroimaging. May 2021;6(5):545-555.
[11] W. D. Penny, K. J. Friston, J. T. Ashburner, S. J. Kiebel, and T. E. Nichols, Statistical parametric mapping: the analysis of functional brain images. Elsevier, 2011.
[12] Guo-Rong Wu, Nigel Colenbier, Sofie Van Den Bossche, Kenzo Clauw, Amogh Johri, Madhur Tandon, Daniele Marinazzo, rsHRF: A toolbox for resting-state HRF estimation and deconvolution, NeuroImage, Volume 244, 2021, 118591, ISSN 1053-8119.