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BRIEF COMMUNICATION

Examining differences in brain metabolism associated with childhood maltreatment and suicidal attempts in euthymic patients with bipolar disorder: a PET and machine learning study

Dante **Duarte**,[1,2] Manuel **Schütze**,[3] Mazen **Elkhayat**,[4] Maila de Castro **Neves**,[5] Marco A. **Romano-Silva**,[3,5] Humberto **Correa**[5,6]

[1]*Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada.* [2]*Seniors Mental Health Program, St. Joseph's Healthcare Hamilton, ON, Canada.* [3]*Instituto Nacional de Ciência e Tecnologia de Medicina Molecular (INCT-MM), Universidade Federal de Minas Gerais (UFMG), MG, Brazil.* [4]*Department of Psychology, Neuroscience & Behaviour, McMaster University, Hamilton, ON, Canada.* [5]*Programa de Pós-Graduação em Medicina Molecular, UFMG, MG, Brazil.* [6]*Departamento de Saúde Mental, UFMG, MG, Brazil.*

Objective: Childhood maltreatment (CM) is a significant risk factor for the development and severity of bipolar disorder (BD) with increased risk of suicide attempts (SA). This study evaluated whether a machine learning algorithm could be trained to predict if a patient with BD has a history of CM or previous SA based on brain metabolism measured by positron emission tomography.
Methods: Thirty-six euthymic patients diagnosed with BD type I, with and without a history of CM were assessed using the Childhood Trauma Questionnaire. Suicide attempts were assessed through the Mini International Neuropsychiatric Interview (MINI-Plus) and a semi-structured interview. Resting-state positron emission tomography with 18F-fluorodeoxyglucose was conducted, electing only grey matter voxels through the Statistical Parametric Mapping toolbox. Imaging analysis was performed using a supervised machine learning approach following Gaussian Process Classification.
Results: Patients were divided into 18 participants with a history of CM and 18 participants without it, along with 18 individuals with previous SA and 18 individuals without such history. The predictions for CM and SA were not significant (accuracy = 41.67%; p = 0.879).
Conclusion: Further investigation is needed to improve the accuracy of machine learning, as its predictive qualities could potentially be highly useful in determining histories and possible outcomes of high-risk psychiatric patients.

Keywords: Bipolar disorder; childhood maltreatment; suicide attempt; 18F-FDG; positron emission tomography; machine learning

Introduction

Childhood maltreatment (CM) is a significant risk factor for the development and severity of bipolar disorder (BD) with increased risk of suicide attempts (SA).[1-4] Identifying risk of suicide in patients with BD is of critical importance because the SA rate in patients with BD is approximately 10-20 times higher than in the general population.[2] Patients with BD who experienced CM may be at an even higher risk of suicide. When compared to patients with BD who did not experience CM, those who were maltreated are 1.5 to 3.4 times as likely to attempt suicide, depending on the type of CM experienced.[5]

Despite the prevalence of SA in patients with a history of CM, evidence suggests that healthcare professionals often fail to identify cases of CM. A recent review found that less than one-third (28%) of CM cases had been documented in the patients' medical records.[6] Assessment forms, a common method for assessing patient history, are also not effective at identifying CM. The abuse/neglect sections of assessment forms are left blank in up to 54.9% of the cases.[7] These findings indicate a need for more accurate and objective assessments of patient histories, especially in the case of CM, which puts patients at a greater risk of suicide. Accurate assessments of CM and SA can then help inform treatment plans and improve patient outcomes.

Functional neuroimaging markers are promising candidates for the identification of CM and SA in patients with BD. The association between CM and SA in patients with BD suggests an underlying neurophysiological substrate. Prior research has shown that patients with BD and a

Correspondence: Dante Duarte, McMaster University, Department of Psychiatry and Behavioral Neurosciences, 100 West 5th Street, Suite H117, Hamilton, ON L8N 3K7, Canada.
E-mail: duartedante@mcmaster.ca
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history of CM present distinct structural and functional features in the frontal and limbic regions of the brain.[8,9] Frontolimbic networks have also been shown to be disrupted in patients with BD who have attempted suicide.[10,11]

Positron emission tomography with 18F-fluorodeoxyglucose (18F-FDG PET) is a functional tool that measures glucose metabolism, an indirect indicator of neuronal and synaptic activity.[12,13] Previous resting-state positron emission tomography (PET) studies in patients with depression and BD types I and II have shown increased amygdala and ventral-striatal-limbic activity compared to healthy controls.[14]

Despite recent advances in the field, there is an unmet need on the understanding of 18F-FDG PET changes related to suicidality and CM in patients with BD. In terms of functional neuroimaging studies on CM and/or SA in patients with BD, the literature using 18F-FDG PET is scant and primarily based on functional magnetic resonance imaging (MRI) in patients with depression.[10,14-17] 18F-FDG PET has been shown to detect different regional patterns of glucose metabolic rates in the prefrontal and ventromedial regions of the brain of suicide attempters and non-attempters diagnosed with major depressive disorder, suggesting that similar success could be achieved in patients with BD.[17]

Machine learning (ML) algorithms have shown previous success in neuroimaging studies of psychiatric populations. A recent review found that various ML models used to identify patients with BD, as opposed to other disorders such as major depressive disorder, had accuracy levels between 64% and 98%.[18] However, most of the included studies used MRI data. Another study used ML along with MRI data to identify 13 gray matter regions that could be associated with childhood trauma.[19] It is unknown whether this success will be reproduced when using 18F-FDG PET images.

The current study aimed to evaluate whether a ML algorithm based on Gaussian processes could be trained to predict if a patient with BD had a history of CM or previous SA. Our hypothesis was that distinctive patterns of brain metabolism identified by the algorithm could predict previous CM and SA.

Materials and methods

Participants

This study included 36 right-handed patients aged between 18 and 65 years and diagnosed with BD type I (BD-I) (14 men and 22 women). Mean age was 41.6 years (SD = 12.0). Participants were recruited at Núcleo de Transtornos Afetivos (a tertiary service specialized in affective disorders) of Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil. None of the participants received any financial incentives. All enrolled individuals gave informed consent, and all procedures were approved by the local ethics committee (COEP-UFMG). The exclusion criteria were: [1] presence of active tobacco, alcohol, and drug use disorders in the past 12 months, [2] serious medical conditions that adversely affected the central nervous system, [3] current neurological disorders, and [4] lifetime history of head injuries.

Psychiatric evaluation

The assessment protocol has been fully detailed in previous studies.[9,11] Briefly, diagnosis was established using a structured diagnostic interview (Mini International Neuropsychiatric Interview [MINI-Plus]) based on DSM-IV-TR. The sample only included patients with BD-I in euthymia, defined by scores under 8 in the Young Mania Rating Scale and the 21-item version of the Hamilton Depression Rating Scale. CM was categorically assessed using the Childhood Trauma Questionnaire (CTQ)[20]; lifetime suicide history was verified using a semi-structured interview, the MINI-Plus section for suicide, and by reviewing medical records. All participants were under psychiatric treatment and on medication.

Image acquisition

Resting-state brain 18F-FDG PET/computed tomography (CT) images of patients were acquired in a GE Discovery 690 (GE Healthcare, Milwaukee, United States) PET/CT scanner. The participants had fasted for at least six hours before the assessment. After an intravenous bolus injection of 5.18 MBq/kg of 18F-FDG, the participants rested for 50 minutes in a quiet and dark room with minimum stimuli. PET brain images were subsequently acquired, with an acquisition time of 10 minutes, and were reconstructed in a 192x192x47 matrix using the Ordered Subsets Expectation Maximization (OSEM) algorithm with two iterations and 20 subsets. Attenuation correction was performed on the CT images.

Image processing

Before analysis, each PET image was spatially processed using the Statistical Parametric Mapping toolbox (SPM8, Wellcome Trust Centre for Neuroimaging, 2008), implemented within Matlab 7.12.0 (MathWorks, Natick, MA, United States). Images were manually reoriented, spatially normalized onto a custom 18F-FDG PET template in MNI space, smoothed with a 12 mm FWHM Gaussian kernel, and each voxel value was scaled by the global mean to account for differences in global signal between participants.[21] To investigate neuronal and synaptic activity, a custom mask was used to select only grey matter voxels from the image, resulting in a sample of 158,899 voxels. The information extracted from each 18F-FDG PET scan was thus a single 158,899 $\times$ 1 data vector that represented each patients' grey matter metabolism.

Data analysis

Imaging analysis was performed using a supervised ML approach. In general terms, supervised ML works by creating a model using matched input-output pairs (i.e., ''learning'' from data) and then applying this model to predict the output for new ''unseen'' inputs. By iteratively training and testing the model on different data subsets

(cross-validation), it is possible to measure how well the model generalizes to new data (the primary outcome measure of ML). Cross-validation also reduces overfitting, which occurs when the algorithm starts "memorizing" training data instead of "learning" how to generalize from a trend.[22] ML is a multivariate approach at the single-subject level and therefore differs from Statistical Parametric Mapping, which is a mass univariate approach.[23] ML is especially useful when dealing with a high number of predictor variables, such as the tens of thousands of voxels in a PET image, in association with a much lower number of samples. Furthermore, it considers the distributed pattern of effects across the whole brain, accounting for correlations and complex interactions between metabolic activities at different brain regions.[24]

Gaussian Process Classification (GPC)[25] was chosen as the ML method in this study because the output variable of interest was a group label. It then provided a principled, practical, and probabilistic approach in kernel machines, which are a class of algorithms for pattern analysis whose best-known member is the support vector machine (SVM). This approach has the advantage of creating maps of the most relevant features for prediction and has a few methods for feature selection based on Gaussian process regression.[25] This study used the GPC implementation available within the kernlab R library.[26-28] The kernel function was set to polynomial, and the initial noise variance and tolerance of termination criteria were both set to 0.001.

Two analyses were performed: whether GPC could classify patients with BD and a history of childhood trauma from patients with BD who did not have such a history; and whether GPC could classify patients with a history of SA from those who did not have such a history. Leave-one-out cross-validation (LOOCV) was performed to measure the methods of prediction accuracy because it is reliable (less biased), validated, and less computationally heavy.[29] This process involved removing one participant from each group and training the GPC algorithm on the remaining data. The obtained model was then used to predict the class of the removed participant. The process was repeated n times, where n is the number of individuals in each group. The results were arranged in a contingency table, and accuracy was calculated. If the GPC algorithm was able to accurately classify individuals into groups, this would suggest a distinct pattern of metabolic activity in the grey matter of patients with BD that differentiated the groups.

Additionally, descriptive statistics for sex and age were used to depict the characteristics of the sample. A Student's *t*-test was carried out to assess age differences and a chi-square test was used to assess sex differences.

Results

A total of 36 patients with BD-I were examined in this study. Nine of them presented a history of CM and nine presented a history of SA. Nine participants presented both features, and nine participants had no history of CM or previous SA. Patients were divided in such a way that we were able to compare 18 individuals with a history of CM to 18 individuals without it, and 18 individuals with previous SA to 18 individuals without it.

Table 1 shows that there were no significant differences between groups regarding age, sex, years of study, comorbidities, total years of disease, and medication intake.

During the LOOCV, the ML algorithm was trained with the images of 36 individuals and their corresponding group labels and then predicted the labels of the removed pair based on their images. This was repeated 18 times so that all individuals had their labels predicted and predictions were compared to their actual labels in order to establish prediction accuracy. Regarding the prediction of childhood trauma history, the sensitivity and specificity of group trauma were 38.89% and 44.44%, respectively, and the accuracy was 41.67% (p = 0.879). Considering the prediction of previous SA, the sensitivity and specificity of the group with no SA were 44.44% and 38.89%, respectively; the accuracy was also 41.67% (p = 0.879). The classification of participants is shown in Figure 1.

Discussion

This study aimed to investigate whether functional changes in the rate of resting-state grey matter glucose metabolism could be linked to a previous history of CM and SA. An ML approach based on GPC was used due to its higher sensibility and its ability to detect small but consistent changes in glucose metabolism. Both analyses showed a low accuracy in differentiating groups. This finding infers that neither a history of CM nor previous SA seem to be related to consistent changes in the pattern of grey matter glucose metabolism in a magnitude that could be captured by the ML algorithm. Given that there was no statistical difference in the amount of medication taken by

Table 1 Differences between groups with and without CM and SA

Group name	CM (n = 18)	No CM (n = 18)	χ^2 or *t*	p-value	SA (n = 18)	No SA (n = 18)	χ^2 or *t*	p-value
Male	8	6	0.46	0.494	7	8	0.11	0.735
Female	10	12			11	10		
Age, mean	43.4	39.1	1.07	0.291	42.9	39.2	0.93	0.357
Years of study, mean	11	12.2	0.78	0.316	11.9	11.26	0.46	0.874
Psychiatric comorbidities	7	9	0.62	0.433	7	9	0.27	0.605
Total years of disease	15.1	16.2	0.34	0.734	16.65	14.48	0.64	0.524
Lithium, dose (mg)	855.0	870.0	1.74	0.864	878.5	853.8	0.27	0.787
Anticonvulsants, dose (mg)	785.7	916.6	1.39	0.183	928.5	775.0	1.83	0.102

No significant differences in sex and age were observed between groups.
CM = childhood maltreatment; SA = suicide attempt; *t* = Student's-*t* test; χ^2 = chi-square test.

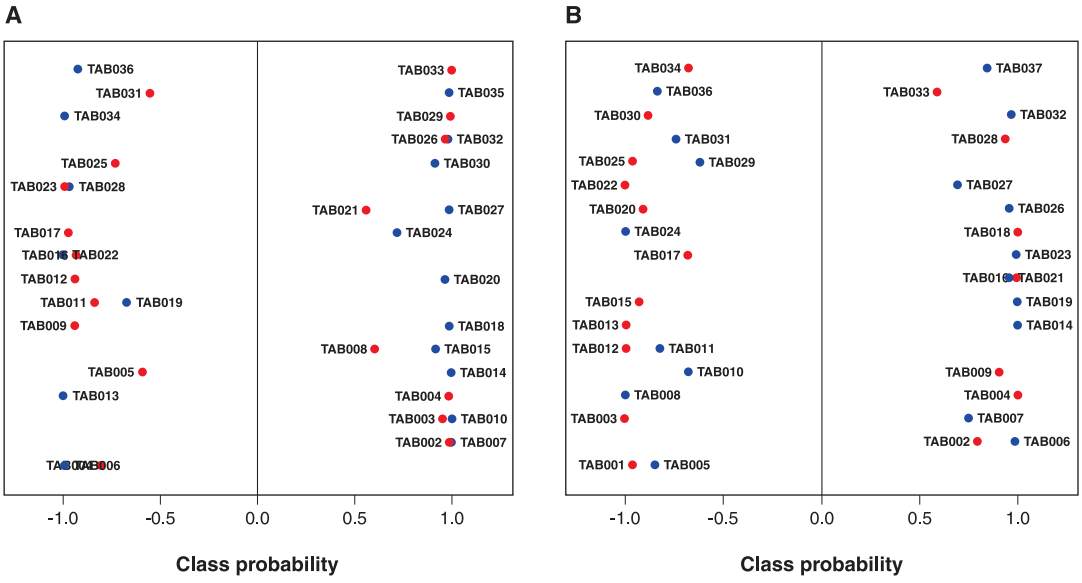

Figure 1 Gaussian process classification between groups. A) CM vs. no CM; B) Previous SA vs. no previous SA. Classification into groups based on brain metabolism: A) classification among patients with BD and CM (blue) and those without CM (red); B) classification among patients with BD and SA (blue) and those without SA (red). CM = childhood maltreatment; SA = suicide attempts; BD = bipolar disorder.

each group, psychiatric treatment does not seem to have influenced the results.

Some evidence explains the link between CM and suicidality mediated by epigenetic mechanisms,[30] ultimately influencing phenotypes and generating disruptive ecophenotypes.[31] The major challenge is to better understand the mechanisms behind the interaction between exposure to chronic maltreatment and gene expression, consequently affecting brain structure and functioning.[32,33] Some mechanisms involve the impairment of stress-response systems during early stages of child development, such as the hypothalamic-pituitary-adrenal axis, serotonin and catecholamine systems, and neurotrophic factors increasing the cellular allostatic load[34] and ultimately affecting neurodevelopment.[35] It is uncertain whether these mechanisms have a neural signature in BD or are transdiagnostic, that is, have a common signature across psychiatric diagnoses.

Prior studies have found a structural alteration in the prefrontal cortex and thalamus related to CM and in the anterior cingulate cortex related to SA in patients with BD.[11,36] A recent systematic review on neuroimaging studies of suicide behaviour[37] and a study about CM[9] also detailed similar findings.

The main limitations of the present study and explanations for our negative results rely on the small sample size and the dichotomous way of considering CM. The former reduces the power of the study; ML algorithms need a more substantial number of variables and sample size to better predict an outcome. The latter is based on current evidence suggesting that the total CTQ score should be evaluated as a continuous outcome rather than a dichotomous one. Five subscales can be used to delineate different impacts of specific forms of CM (emotional and physical neglect; sexual, physical, and emotional abuse); however, the total composite score has also shown a consistent effect on brain function in patients with BD and SA.

Given these results, it can be concluded that ML algorithms are currently unable to predict previous CM and SA using 18F-FDG PET images in small- to moderately sized samples. However, considering their success in other studies, ML algorithms have the potential to offer an alternative to clinician assessment and self-report forms, which have been shown to ignore many cases of CM. Future studies should focus on improving the accuracy of ML, as its application in patients with BD can help identify those at high risk of suicide and inform treatment plans. Approaches to this issue could include developing newer algorithms or identifying the optimal parameters for current models to maximize their effectiveness while being mindful of practical considerations.

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Disclosure

The authors report no conflicts of interest.

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