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Structural Features Predict Sexual Trauma and Interpersonal Problems in Borderline Personality Disorder but Not in Controls: A Multi-Voxel Pattern Analysis

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Child trauma plays an important role in the etiology of Bordeline Personality Disorder (BPD). Of all traumas, sexual trauma is the most common, severe and most associated with receiving a BPD diagnosis when adult. Etiologic models posit sexual abuse as a prognostic factor in BPD. Here we apply machine learning using Multiple Kernel Regression to the Magnetic Resonance Structural Images of 20 BPD and 13 healthy control (HC) to see whether their brain predicts five sources of traumas: sex abuse, emotion neglect, emotional abuse, physical neglect, physical abuse (Child Trauma Questionnaire; CTQ). We also applied the same analysis to predict symptom severity in five domains: affective, cognitive, impulsivity, interpersonal (Zanarini Rating Scale for Borderline Personality Disorder; Zan-BPD) for BPD patients only. Results indicate that CTQ sexual trauma is predicted by a set of areas including the amygdala, the Heschl area, the Caudate, the Putamen, and portions of the Cerebellum in BPD patients only. Importantly, interpersonal problems only in BPD patients were predicted by a set of areas including temporal lobe and cerebellar regions. Notably, sexual trauma and interpersonal problems were not predicted by structural features in matched healthy controls. This finding may help elucidate the brain circuit affected by traumatic experiences and connected with interpersonal problems BPD suffer from.

Keywords: multi-voxel pattern analysis, borderline personality disorder, multiple kernel learning, machine learning, child trauma, biomarkers, brain imaging

INTRODUCTION

The Borderline Personality Disorder (BPD) is a complex mental disorder with a characteristic pervasive pattern of instability on affect regulation showing different dysphoric states shifting from one interpersonally reactive mood to another with great fluidity (Zanarini et al., 1998; Stiglmayr et al., 2001; Dadomo et al., 2016, 2018). Impulsiveness (Mortensen et al., 2010; Lapomarda et al., 2021a,b), strong feelings of very deep inadequacy, dissociative experiences (Zanarini et al., 1990;

Koenigsberg et al., 2002), interpersonal relationships and problem with self-image (Lieb et al., 2004; De Panfilis et al., 2019)are the main characteristics of BPD. This disorder affects approximately 1–3% of the general population (Lenzenweger et al., 2007; Trull et al., 2010) up to 10% of outpatient psychiatric patients (Zimmerman et al., 2005) 20% of hospitalized patients and 15–25% of the clinical population (McGlashan et al., 2000).

Various types of adverse life events in childhood, including experiences of neglect and abuse, would appear to be one of the most important factors (Zanarini et al., 1989; Lobbestael et al., 2010). The most frequent of these is childhood sexual abuse, reported by 40–71% of patients linked to the severity of the abuse itself (Shearer et al., 1990; Paris et al., 1994; Zanarini et al., 2002). Consistent evidence show as sexual abuse during childhood is a reliable predictor of chronic PTSD (Müller et al., 2018), is strongly linked to ultra-high risk of psychosis (UHR), first –episode psychosis (FEP; Ciocca et al., 2021). Sexual trauma is particularly relevant for the development of addiction (Poppa et al., 2019) and it is often associated with the ineffectiveness of pharmacological treatment of anxiety disorders (Kim et al., 2021).

Among several traumatic life events, childhood sexual abuse and emotional maltreatment seem to constitute a keys etiological risk factor for the BPD (Johnson et al., 1999; Zlotnick et al., 2003; Lobbestael and Arntz, 2010; Preißler et al., 2010; Dadomo et al., 2016, 2018; de Aquino Ferreira et al., 2018). These traumatic events have a specific effect on the subject's behavior and accurately predicts the symptom class observed in the borderline patients such as affective and interpersonal dysfunctionalities, which negatively impact on their relationships (Ball and Links, 2009). Indeed, BPD patients are characterized by impaired mental state attribution, impairment in cognitive empathy and in emotion recognition abilities (Preißler et al., 2010; De Panfilis et al., 2019).

Numerous neuroimaging studies have explored BPD features in recent years, leading to the identification of some cerebral structural and functional alterations associated with the pathogenesis of BPD. Up to 2013, the majority of studies indicated that structural differences in the amygdala hub, hippocampus and cingulate cortex are involved in affective deficits (Minzenberg et al., 2008; Nunes et al., 2009; Ruocco et al., 2012; Piretti et al., 2020). More recently, alterations in frontal (e.g., orbifrontal cortex, medial prefrontal cortex; Aguilar-Ortiz et al., 2018), cortical and subcortical regions (Ruocco et al., 2016; Stanley et al., 2018; Davies et al., 2020; Lapomarda et al., 2021a,b) have also been identified. Yet, if a meta-analysis confirmed this constellation of brain regions (Yu et al., 2019), other extended abnormality in temporal cortex and cerebellum (Schulze et al., 2016) will complete the puzzling picture. Therefore, a potential circuit involved in BPD seems still far from been exhaustive.

One of the main limitations of the previous neuroimaging studies on BPD concerns the use of mass univariate methods to compare groups (e.g., Minzenberg et al., 2008; Grecucci et al., 2015; Aguilar-Ortiz et al., 2018; Sorella et al., 2019; Pappaianni et al., 2020; Lapomarda et al., 2021a). Typically, comparisons of mean imaging indices between patients and healthy controls, across different brain regions using region of interest (ROI) or voxel-based techniques have been performed. This approach clearly has pro et contra: morphometric approaches, such as Voxel-based Morphometry (VBM), allow evaluating between-groups differences in certain brain structures, as a univariate technique it directly compares different voxels in different individuals' brains, neglecting their interrelationships. Furthermore, VBM sensitivity from large cortical areas to smaller subcortical structures is dramatically reduced (Aguilar-Ortiz et al., 2018). Therefore, it is clear that the high variability of the previous results is probably related to methodological differences and limitations, which in turn influenced the results of the various meta-analyzes. In this background, the use of multivariate methods would instead provide detailed information on how the regions are correlated, identifying naturally grouped circuits (Grecucci et al., 2016; Sorella et al., 2019; Saviola et al., 2020; Lapomarda et al., 2021a,b).

Pattern recognition methods, such as multi-voxel pattern analysis (MVPA), are inherently multivariate and use information distributed over multiple voxels as well as being sensitive to spatially distributed effects (Norman et al., 2006). Of note, MVPA can be used to predict ongoing psychological variables such as symptom severity or psychological variables (Davies et al., 2020). Multiple Kernel Regression (MKR), is a pattern recognition algorithm used in MVPA, a sparse machine learning method that can be used for the identification of the most relevant sources, such as psychological variables based on anatomical location (Mourao-Miranda et al., 2012). It can also help determine which regions of the brain contribute most to explaining psychological variables. In this regard, MVPA has recently been applied to patients with various psychiatric disorders (Orrù et al., 2012) or to investigate brain changes associated with clinical improvement (Whitfield-Gabrieli et al., 2016; Takamiya et al., 2020).

In this study, we aim at applying multivariate methods, using MVPA based on MKR, to explore brain circuits that predict trauma and symptoms severity. To do this we will use two tools: the Child Trauma Questionnaire (CTQ) and the Zanarini Rating Scale for Borderline Personality Disorder (Zan-BPD). The CTQ is a self-assessment tool used to evaluate the traumatic experiences experienced during childhood. On the other hand, the Zan-BPD measures the severity of symptoms of an affective nature such as anger, feelings of emptiness and mood instability; cognitive such as identity disturbance disassociation and paranoia; symptoms related to impulsivity such as self-mutilative/suicidal efforts and finally interpersonal symptoms such as intense, unstable relationships and frantic efforts to avoid abandonment of the borderline patient.

Combining the clinical scales and the application of whole-brain MVPA based on MKR in BPD patients, we sought to test two hypotheses. The first hypothesis is that sexual trauma and more specifically sexual abuse being the main etiologic factor in BPD can be successfully predicted by brain features. *Inter alia* we expect that basal ganglia and Heschl's gyrus is part of this circuit predicting both Child trauma (Zhang et al., 2015; Quidé et al., 2017) and symptomatology of borderline patients. The second hypothesis is that brain features also predict interpersonal problems, one of the main features of BPD patients.

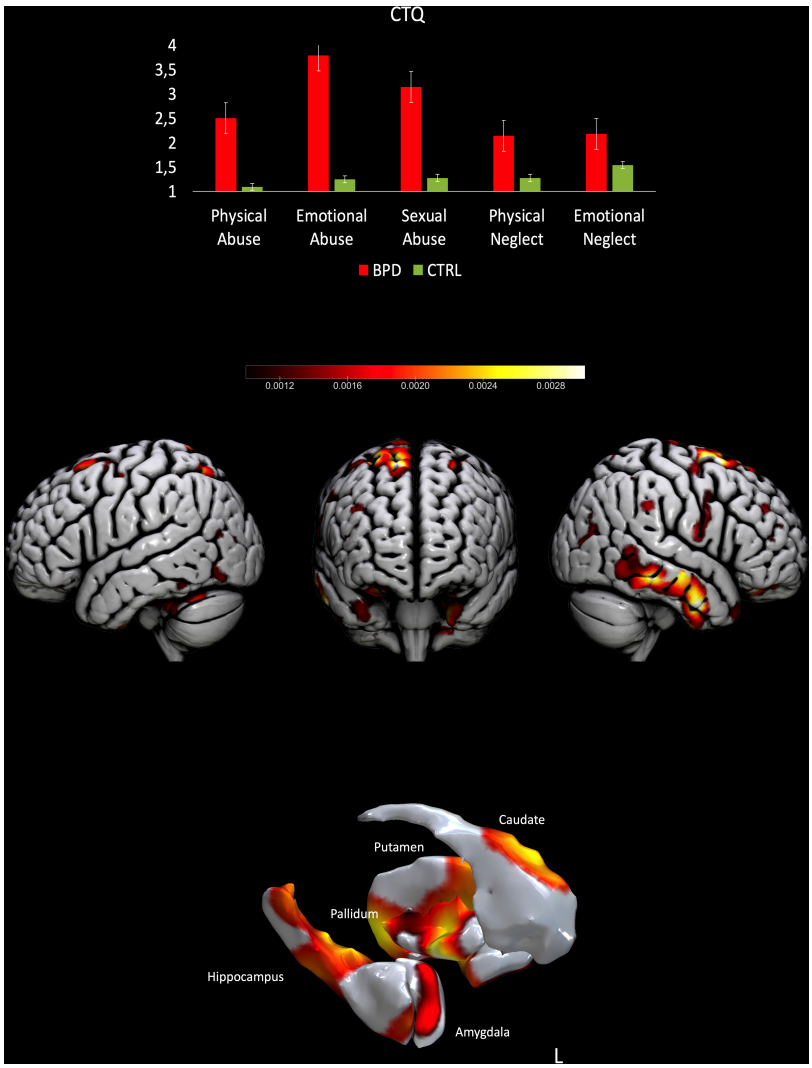

FIGURE 1 | Results from the prediction of sexual trauma for BPD patients. Upper part, results from the CTQ-subscales scores for both BPD patients and controls. Lower part, surface plots, including subcortical reconstruction of the significant regions predicting Sexual trauma in BPD patients.

We predict that structural alterations in temporal cortex will be predictive of interpersonal problems in BPD measured by the Zan-BPD questionnaire.

MATERIALS AND METHODS

Participants

Twenty patients with borderline personality disorder (BPD, M_{age} = 35.75, SD_{age} = 8.61), and 13 healthy participants as controls (HC, M_{age} = 32.53, SD_{age} = 8.3), matched for age (p = 0.63) and sex (p = 0.48) were taken into consideration Age and gender differences were assessed *via* *t*-test. Note that, three controls were excluded because they did not fill the CTQ questionnaire. All the data were extracted from the Clinical Research Imaging Centre in Edinburgh (OpenNeuro database, accession number ds000214) (Poldrack and Gorgolewski, 2017). The recruitment took place in outpatient and support services from around Edinburgh.

The exclusion criteria were the presence of neurological disease, or mental illness rather than BPD (SCID-II, SCID-IV), and the use of psychoactive substance, pregnancy, MRI contraindications. The BPD diagnosis was verified using Structured Clinical Interview for DSM-IV (SCID-II). The CTQ was administered to both patients and controls, although three control subjects did not fill the questionnaire. Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) was administered to assess the current symptoms only to BPD. See **Figure 1**. Demographic information about participants are displayed in **Table 1**. A high-resolution T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) scan was acquired for each participant *via* 3T Siemens Magneton (Verio) MRI scanner with TR = 2300 ms, TE = 2.98, 160 slices.

TABLE 1 | Demographic information about participants. Values in round brackets are the standard deviations.

	DEMOGRAPHIC INFORMATION		
	BPD	**HC**	***p*-values**
Participants	20	13	
Age (yrs)	36.75 (±8.61)	32.53 (±8.3)	$p = 0.63$
Gender	$F = 17$	$F = 11$	$p = 0.48$
Education	≥8	≥8	
Screening	Neurological disease, psychoactive substance, mental illness (SCID-II, SCID-IV)	Neurological disease, psychoactive substance, mental illness (SCID-II, SCID-IV)	
Exclusion criteria	Diagnosis in at least two different psychiatric categories, pregnancy, MRI contraindications, neurological disease	Diagnosis in one diagnostic category, pregnancy, MRI contraindications, neurological disease	

Preprocessing

After quality check of the images to exclude artifacts, all data were preprocessed using the segmentation routines provided by the Computational Anatomy Toolbox (CAT12)[1], a toolbox available for SPM12 software[2] in the MATLAB environment. Segmentation of gray and white matter, and cerebrospinal fluid was thus obtained. Modulated normalized writing option was chosen. Diffeomorphic Anatomical Registration through Exponential Lie algebra (DARTEL) tools, a potential alternative to SPM's traditional registration approaches that operates using a whole-brain approach, was used (Yassa and Stark, 2009; Grecucci et al., 2016; Pappaianni et al., 2018). Normalization to MNI space with spatial smoothing [full-width at half maximum of Gaussian smoothing kernel (8)] was then applied on DARTEL images.

Data Analysis

Machine learning based on MKR method was carried out in the Pattern Recognition for Neuroimaging Toolbox (PRoNTo) (Schrouff et al., 2013, 2018) and Matlab scripts. BPD and HC were analysed separately to predict the psychological variables (questionnaires scores). Multiple Kernel Learning (MKL; Schrouff et al., 2014) simultaneously learns the contribution of each brain region, previously defined by an atlas, to the decision. Thus, MKL lead to improved generalization performance and identifies a subset of relevant brain regions for the predictive model. To do this MKL combines the information coming from each voxel of different brain regions. To avoid computational complexity, kernels, or similarity matrices, are computed to reduce the input space in a few dimensions. Different brain areas correspond to a different kernel. After weights estimation, every region is ordered according to its contribution to the model; thus, it can be defined as a hierarchical model (regions contributing more vs. regions contributing less). Whole brain analyses were performed using a general brain mask provided inside PRoNTo. Age and gender were regressed out to avoid confoundings. The procedure was split into a training and a testing phase. The predictive function was calculated during the training phase where the algorithm learns to predict the psychological variables of interest (CTQ scores, etc.) from structural data. Whereas, during the test phase, the algorithm was used to predict the outcome in an independent dataset. To avoid splitting the data in a training and in a test set, thus reducing the number of subjects available for each calculation, leave one subject out cross-validation was performed. In this method, the total number of subjects minus one is used for the training phase. Then the performance is assessed by predicting the excluded subject. This is iteratively repeated for every subject, so that every subject has been used for training and testing the model in the end. Then the average performance is calculated across all the testing performances. The hyperparameters were set to 0.0001 0.01 1 10 100 1000. The parameter with the highest performance (balanced accuracy, BA) is then applied to assess the model (Schrouff et al., 2013). Statistical significance of the classifications was tested using permutation testing with 1500 permutations with random assignment of group class to input image. The resulting null-hypothesis distribution was used to calculate the *p*-value of the accuracies, or the proportion of permutations that yielded a greater accuracy than the accuracy found for the classification models. The Automated Anatomical Labeling (Tzourio-Mazoyer et al., 2002) atlas, built using the WFU- Pickup Atlas toolbox of SPM and consisting of 116 brain regions was used to explore regional contribution of each classification model. Being MKR approach a hierarchical model of the brain, it was possible to derive weights contribution of each region to the decision function. Regions were ranked according to their contribution to the model and averaged across folds. Only regions with >1% contribution to the decision function f are displayed. Additional morphometric analyses were run in SPM12 software (see text footnote 2) in the MATLAB environment. SurfIce software was used to plot the brain maps.[3]

RESULTS

Child Trauma Questionnaire

For BPD patients the MVPA returned a significant correlation with the subscale CTQ-Sexual abuse equal to 0.37, $p = 0.04$, the mean squared error (MSE): 2.50, $p = 0.03$, Normalized MSE: 0.62, $p = 0.03$. Areas showing a stronger contribution to the model are bilaterally the Caudate, the Heschl, the amygdala, the right supplementary area, the left putamen and right Rolandic operculum, various portions of the cerebellum (see **Table 2** and **Figure 1**). The other subscales (Emotional neglect, physical neglect, emotional abuse, physical abuse) did not returned significant results (all $p > 0.05$).

For HC subjects the MVPA returned a significant correlation with the subscale CTQ-Emotional neglect equal to 0.52, $p = 0.009$, MSE: 0.46, $p = 0.01$, Normalized MSE: 0.18, $p = 0.01$. Areas showing a stronger contribution to the model are several portions of the cerebellum, the precentral gyrus, some portions

[1]http://www.neuro.uni-jena.de/cat/

[2]http://www.fil.ion.ucl.ac.uk/spm/software

[3]https://www.nitrc.org/projects/surfice/

TABLE 2 | ROI weights and voxel sizes of the circuit predicting the CTQ-Sexual abuse for BPD.

Label	Significance (%)	Volume (Voxels)
Caudate_L	2.0336	2212
Heschl_L	1.6133	549
Amygdala_L	1.5737	487
Supp_Motor_Area_R	1.5166	5336
Putamen_L	1.5113	2255
Heschl_R	1.4855	513
Rolandic_Oper_R	1.4844	2946
Cerebelum_7b_R	1.4741	692
Cerebelum_Crus2_L	1.4177	4105
Cerebelum_Crus2_R	1.3772	3901
Caudate_R	1.3768	2330
Calcarine_L	1.3180	5182
Frontal_Inf_Oper_R	1.2756	2838
Vermis_9	1.2705	388
Temporal_Mid_L	1.2520	11409
Postcentral_R	1.2367	6986
Hippocampus_L	1.2251	2221
Rolandic_Oper_L	1.2123	2402
Vermis_4_5	1.1954	1489
Paracentral_Lobule_R	1.1864	1608
Cuneus_L	1.1582	3484
Cerebelum_Crus1_R	1.1441	4791
Occipital_Mid_R	1.1389	4649
Temporal_Inf_R	1.1280	7209
Pallidum_L	1.1107	637
Amygdala_R	1.1078	571
Temporal_Inf_L	1.1022	7081
SupraMarginal_R	1.0642	3768
Angular_R	1.0474	3628
ParaHippocampal_L	1.0473	2344
Parietal_Inf_R	1.0390	2671

Only regions with at least 1% contribution to the model are reported.

of the occipital and the medial and orbitofrontal parts of the frontal lobes (see **Table 3**). The other subscales (Sexual abuse, physical neglect, emotional abuse, physical abuse) did not return significant results (all $p > 0.05$).

Zanarini Rating Scale for Borderline Personality Disorder

For BPD patients the MVPA returned a significant correlation with the subscale Zanarini Interpersonal problems, sector equal to 0.39, $p = 0.04$, MSE: 2.32, $p = 0.04$, Normalized MSE: 0.46, $p = 0.04$. Areas showing a stronger contribution to the model (see **Table 4** and **Figure 2**). The other subscales (Affective sector, Impulsivity sector, Cognitive sector) did not returne significant results (all $p > 0.05$).

Additional Analyses

To understand the effect of diagnosis on the overall volumetric pattern, we also computed a simple Voxel-based morphometry. The contrast BPD > HC (FWE corrected) returned the following areas: right inferior occipital gyrus\right cerebellum, right supplementary motor cortex\right superior frontal gyrus, left superior frontal gyrus, right putamen\caudate, right supramarginal gyrus, right middle frontal gyrus, right orbito-frontal cortex, left middle temporal gyrus. The contrast HC > BPD (FWE corrected) returned the following areas: left post central gyrus, right precentral gyrus\superior frontal gyrus, right superior parietal lobe\precuneus.

TABLE 3 | ROI weights and voxel sizes of the circuit predicting the CTQ-Emotional neglect for HC.

Label	Significance (%)	Volume (Voxels)
Cerebelum_7b_R	2.0262	692
Vermis_9	1.8854	388
Cerebelum_9_L	1.5372	1407
Cerebelum_Crus2_L	1.4105	4105
Cerebelum_9_R	1.4088	1320
Cerebelum_Crus2_R	1.3980	3901
Heschl_L	1.3388	549
Cingulum_Mid_R	1.3229	5244
Cerebelum_Crus1_L	1.3014	5334
Precentral_R	1.2832	6310
Occipital_Inf_L	1.2767	2264
Cerebelum_8_R	1.2642	2603
Cerebelum_7b_L	1.2502	863
Cerebelum_4_5_L	1.2483	2715
Cingulum_Ant_R	1.2218	3123
Frontal_Mid_R	1.1987	9213
Frontal_Mid_Orb_R	1.1778	1583
Frontal_Inf_Tri_R	1.1656	3654
Occipital_Mid_R	1.1603	4649
Cerebelum_8_L	1.1493	2619
Vermis_3	1.1471	522
Frontal_Mid_L	1.1403	11129
Frontal_Inf_Orb_R	1.1205	3635
Temporal_Inf_L	1.1099	7081
Cerebelum_10_R	1.1086	286
Fusiform_R	1.1074	5731
Angular_L	1.0897	2739
Vermis_4_5	1.0742	1489
Paracentral_Lobule_L	1.0715	2490
Angular_R	1.0657	3628
SupraMarginal_L	1.0509	2879
Cerebelum_4_5_R	1.0329	1938
Parietal_Sup_L	1.0182	4364
Postcentral_R	1.0155	6986
Rectus_L	1.0145	1780
Temporal_Pole_Mid_R	1.0123	1810
Temporal_Sup_L	1.0008	5312

Only regions with at least 1% contribution to the model are reported.

DISCUSSION

The neural correlates of the Borderline Personality Disorder (BPD) clinical features are mostly unclear. So far, several

TABLE 4 | ROI weights and voxel sizes of the circuit predicting the Zanarini-Interpersonal sector for BPD.

Labels	Significance (%)	Volume (Voxels)
Temporal_Pole_Mid_R	1.8963	1810
Vermis_9	1.7640	388
Temporal_Inf_R	1.7004	7209
Frontal_Inf_Oper_R	1.4985	2838
Occipital_Inf_R	1.3648	2411
Cerebelum_Crus1_R	1.3329	4791
Angular_R	1.3270	3628
Cerebelum_7b_R	1.3118	692
Fusiform_R	1.2755	5731
ParaHippocampal_R	1.2542	2557
Cerebelum_Crus2_R	1.1956	3901
Frontal_Sup_R	1.1873	8047
Vermis_1_2	1.1838	109
Cerebelum_9_L	1.1797	1407
Occipital_Sup_R	1.1739	3166
Temporal_Mid_R	1.1722	8803
Parietal_Inf_R	1.1675	2671
Lingual_R	1.1434	5574
Cerebelum_9_R	1.1147	1320
Fusiform_L	1.1135	5282
SupraMarginal_L	1.1046	2879
Cingulum_Ant_L	1.0933	3248
Precuneus_R	1.0850	7251
Occipital_Mid_R	1.0745	4649
Frontal_Mid_R	1.0669	9213
Cingulum_Post_R	1.0316	763
Cerebelum_Crus1_L	1.0220	5334
SupraMarginal_R	1.0189	3768

Only regions with at least 1% contribution to the model are reported.

neuroimaging studies have tried to unveil its neurofunctional and structural correlates, although using mass univariate approaches (see for instance: Herpertz et al., 2001; Völlm et al., 2004; Doell et al., 2020). To overcome previous methodological limitations, in the present study, we explored whether the main BPD features can be predicted by structural cerebral pattern by using a novel neuroimaging approach, combining clinical scales with multivariate pattern analysis (MVPA) based on Multiple Kernel Regression (MKR). More specifically, we explored the possibility that separate sets of areas would predict the main clinical features of BPD.

Evidence in the literature has shown that traumatic experiences are recognized as a risk factor for various psychiatric disorders (Widom et al., 2007; Chen et al., 2010), as well as the development of psychosis later in life (Thompson et al., 2014; Varese et al., 2012). Our results also corroborated this evidence on BPD patients, reinforcing the hypothesis that sexual abuse may be at the etiopathogenesis of the disorder (de Aquino Ferreira et al., 2018). Our results have shown that a complex cortico-subcortical set of areas predicted traumatic life events, such as the sexual abuse subscale, in BPD patients. Among all traumas, sexual trauma is the most common, severe and most associated with receiving a BPD diagnosis when adult. In line with previous studies, the set of areas predicting sexual abuse in BPD patients mainly involves subcortical regions such as the Caudate, Putamen and Amygdala (Herpertz et al., 2001; Xu et al., 2016). Morphometric alterations of striatum and putamen are associated with several neuropsychiatric disorders characterized by impulsive behavior, affect instability, and substance abuse (Luo et al., 2019; Lapomarda et al., 2021a,b). Notably, putamen is part of a cortical-striatal-thalamic circuit (Luo et al., 2019) that has been consistently implicated in affective processes of different psychiatric disorders (Fettes et al., 2017). In addition, the cerebellum, *via* connection with the basal ganglia and prefrontal cortex, is responsible for affective evaluation (Pierce and Péron, 2020; Piretti et al., 2021). Recent results have pointed out that the cerebellum may have a relevant role for emotions (Adamaszek et al., 2017; Pappaianni et al., 2018; Sorella et al., 2019; Lapomarda et al., 2021b). The contribution of the Heschl's gyrus is also noticeable as it may increase function of posterior and anterior insula (Craig, 2005, 2009) in trauma-exposed patients contributing to multisensory dysfunctions in schizoaffective/schizophrenic patients (Quidé et al., 2017) psychotic patients (Aas et al., 2016) and is implicated in distorted internal dialoge in Eating disorders, and verbal hallucinations in schizophrenia. Furthermore, functional and volume abnormalities in amygdala and basal ganglia, for instance, has been suggested as the neural basis of the characterizing emotion dysregulation in BPD (Dadomo et al., 2016, 2018; Schulze et al., 2016; Grecucci et al., 2017; Frederickson et al., 2018; Grecucci et al., 2020). It is also interesting to note that the involvement of right lateralized set of cortical structure such as the right Rolandic Operculum, Paracentral Lobule and Inferior parietal regions (i.e., supramarginal and angular gyri) testimonies the bodily-related nature of the experienced trauma. Indeed, it has been hypothesized that these cortical areas would subserve the bodily-self-consciousness and altered emotional imitation (Grecucci et al., 2011; Salvato et al., 2020), which is typically altered in some psychiatric syndromes (Brugger and Lenggenhager, 2014).

The other subscales of the CTQ were not predicted by any other set of areas testifying that physical abuse, emotional abuse, physical neglect, and emotional neglect are not peculiar features of BPD. Interestingly, we found that a set of areas in the healthy brain predicted the CTQ subscale of emotional neglect. This finding provides evidence on the impact on the brain of specific relationship patterns in which the significant other disregarded, ignored, invalidated, or unappreciated individual's affectional needs.

Lastly, our findings have shown that a specific set of regions predicts interpersonal problems in BPD patients. This evidence confirms the pivotal contribution of interpersonal problems in BPD, which are considered as the most characteristic and discriminative feature of the disorder (Fossati et al., 1999; Johansen et al., 2004; Gunderson, 2007). Patients affected by BPD frequently experience unstable and intense relationships with an alternation between idealization and devaluation (Lazarus et al., 2020). They also experience high interpersonal sensitivity and efforts to avoid abandonment (Domes et al., 2009; American Psychiatric Association [APA], 2013). In particular, the contribution the temporal lobe and cerebellar regions, involved in the set of predictor areas, are suggestive of such behavioral outcome in patients with BPD. Interpersonal skills (e.g., theory of

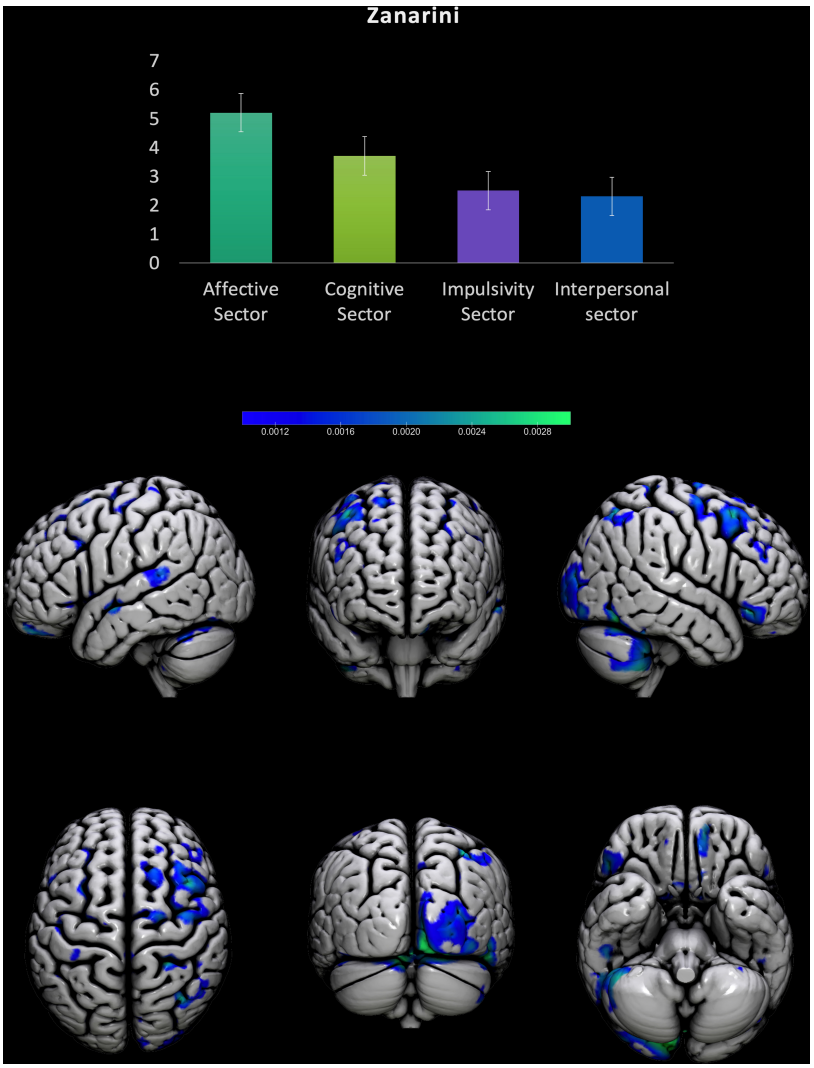

FIGURE 2 | Results from the prediction of Zanarini scales for BPD patients. Upper part, results from the Zanarini sectors scores for BPD patients. Lower part, surface plots of the significant regions predicting Interpersonal problems subscale in BPD patients.

mind) have been mostly associated with temporal pole activity in healthy and pathological subjects. Furthermore, temporal region have also been associated with social well-being (Gallagher and Frith, 2003; Giovagnoli et al., 2011; Kong et al., 2016). The cerebellar contribution to the prediction of this interpersonal behavioral problem in BPD confirms the role of this region in affective and interpersonal life. For instance, it has been demonstrated that lesion to "limbic cerebellum" (i.e., vermis) dysregulation of affect (Schmahmann et al., 2007). Moreover, the role of the cerebellum in social interaction has been highlighted (Leggio and Olivito, 2018). Notably, the majority of the areas found (with the exception of the left post central gyrus, the right precentral gyrus\superior frontal gyrus, and the right superior parietal lobe\precuneus) showed increased GM for BPD compared to HC, partially confiming, but also expanding previous Voxel-based morphometric analyses (see the review of Yu et al., 2019).

CONCLUSION

Our work shows how combining clinical scales with multivariate pattern analysis (MVPA) based on Multiple Kernel Regression (MKR) provides important insights into which different aspects of BPD might link to different brain structures. Using two different specific instruments, to evaluate, respectively, the traumatic experiences lived during childhood and clinically relevant symptoms of borderline personality disorder we find a complex cortico-subcortical set of areas predict sexual trauma and interpersonal problems, that are the most common, severe and most associated symptoms in BPD. While further replication is warranted, due to the small sample size, our findings underscore the need to delve into structural brain patterns, not only based on symptom structure, but possibly also based on the persistent traumatic events inherent in many BPD patients. This study also contains some limitations. Firstly, the sample size is

quite small for this kind of analyses. Future studies may want to extend and possibly replicate these findings. Unfortunately, the availability of pure BPD patients is not common as for other psychiatric disorders. Furthermore, healthy subjects did not perform the Zanarini scale. Future studies may overcome these issues. Last, but not least, these results may lead in the next future to new treatment possibilities. We hypothesize that neurostimulation protocols specifically focused on the circuit outlined in this study may help to ameliorate emotional disturbances displayed by BPD patients after sexual trauma.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: OpenNeuro database, accession number ds000214.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HD: conceptualization, writing—original draft preparation, and writing—reviewing and editing. GS: writing—original draft preparation and writing—reviewing and editing. GL: preprocessing of MRI data and writing—reviewing and editing. ZC: writing—reviewing and editing. IM: conceptualization, writing—original draft preparation, and writing—reviewing and editing. AG: conceptualization, data curation, machine learning formal analysis, project management, and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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