scientific reports

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# Assessment of neurotransmitter-related structural brain changes in borderline personality disorder: an MRI study

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**Borderline personality disorder (BPD) is characterized by grey matter (GM) alterations in areas related to emotion regulation, impulsivity and metacognitive abilities. Dysfunction of specific neurotransmitters, including serotoninergic and dopaminergic systems, is thought to be involved, but evidence is currently limited. In this exploratory study, we tested for associations between GM alterations in BPD, the spatial distribution of neurotransmitter systems, and clinical features in a sample of 58 patients with BPD and 28 healthy controls (HC). GM volume alterations were assessed on 3T MRI using voxel-based morphometry (i) in BPD patients compared to HC and (ii) between BPD subgroups defined based on clinical features followed by spatial correlations between regional GM differences and atlas-based neurotransmitter maps. We observed smaller GM volumes in BPD patients compared to HC in the limbic, temporo-parietal, frontal medial, olfactory, and cerebellar regions ($p_{FDR}<0.05$), but no association between these GM abnormalities and neurotransmitter maps of serotoninergic, dopaminergic, noradrenergic, glutamatergic, GABAergic, opioid and endocannabinoid systems ($p_{FDR}>0.05$). Our results do not support the notion of a direct relationship between BPD-related GM alterations and specific major neurotransmitter systems, highlighting the need for additional studies to determine the pathophysiologic mechanisms underlying structural changes.**

**Keywords** Borderline personality disorder, Structural magnetic resonance imaging, Neurotransmitter systems

Borderline personality disorder (BPD) is a psychiatric condition affecting approximately 1–3% of the general population, characterized by emotion dysregulation, impulsivity, unstable interpersonal relationships, and higher rates of self-harm and suicidal behaviour[1]. BPD frequently co-occurs with other psychiatric diseases, including anxiety, depression, eating disorder, and substance abuse[2]. Both environmental and genetic factors are thought to contribute to the disease pathogenesis. Specifically, early life adversity (e.g., childhood trauma, exposure to an invalidating environment) can interact with predisposing factors (e.g., personality traits, genetic inheritance, neurobiological vulnerability), to shape brain development and predispose individuals to the

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disorder[1,3]. In recent years, neuroimaging studies have significantly contributed to improving our understanding of the pathophysiological mechanisms underlying BPD by examining brain alterations associated with core symptoms. Several structural and functional magnetic resonance imaging (MRI) studies have reported reduced grey matter (GM) volumes and aberrant activity/connectivity in key areas of the fronto-limbic and default-mode circuits, including the anterior cingulate cortex, orbitofrontal cortex, amygdala and hippocampus, insula, posterior cingulate and parietal cortices[4]. These abnormalities have been associated with core BPD symptoms, including impulsivity and emotion regulation[4,5], supporting their clinical relevance. Nevertheless, the biological mechanisms underlying these associations remain poorly understood.

The core features of the disease have been associated with dysfunction in specific neurotransmitter systems, primarily serotoninergic and to a lesser degree the dopaminergic, noradrenergic and GABAergic systems (for reviews, see[6,7]. Neuroimaging, pharmacological-challenge, and neurochemical studies converge to support the role of serotoninergic dysfunction in relation to two core hallmarks of BPD, impulsivity and aggression. In vivo positron emission tomography/single photon computed emission tomography (PET/SPECT) studies reported an association between aggression, impulsivity and serotoninergic binding or transporter in fronto-limbic areas[8–11], while pharmacologic challenge studies showed reduced serotonergic inhibition in regions controlling impulsivity in BPD[12,13]. Biomarker studies also provide some support to the hypothesis of a link between impulsivity, affective instability and serotonergic dysfunction as assessed with cerebrospinal fluid 5-HIAA or prolactin[14,15]. The specificity of serotoninergic dysfunction to BPD however remains debated, given the clinical overlap with other psychiatric conditions, including depression, bipolar disorder and attention deficit hyperactivity disorder (ADHD)[16–18]. Some studies suggest a certain degree of specificity, for example a study reporting that the association between serotonergic dysfunction and impulsivity is present in BPD but not in patients with major affective diseases[13], and reviews of neuroimaging studies suggesting distinct patterns of impulse-related prefrontal cortex dysfunction in BPD compared to ADHD[19,20].

In addition to the serotoninergic system, dopamine and noradrenaline dysfunction have also been linked to core BPD features, although evidence is less consistent. Genetic studies highlighted a possible role of dopamine receptor polymorphisms (e.g. DAT1, DRD2, DRD4) in impulsive and self-damaging behaviors[21,22]. Prior neuroimaging and neurophysiological studies suggested an association between motor impulsivity in BPD and functional abnormalities between the locus coeruleus (a noradrenergic nucleus) and the ACC[23], and altered arousal regulation in patients compared to controls[24] and obsessive compulsive disorder[25]. One study reported elevated monoamine oxidase A (MAO-A) density, an enzyme that catabolizes multiple neurotransmitters (serotonin, dopamine, and norepinephrine), which was associated with BPD symptoms and severity[26]. However, molecular imaging studies assessing specifically the dopaminergic or noradrenergic systems (e.g., through radioligands targeting dopamine receptors or norepinephrine transporters) are still lacking.

The glutamatergic and GABAergic pathways have also been hypothesized to contribute to BPD abnormalities due to their role in modulating impulsivity and cognitive functions such as memory and self-referential processes[27,28]. Previous magnetic resonance spectroscopy (MRS) studies in BPD reported higher glutamate binding in the insula, ACC and prefrontal cortex in patients, and an association between higher binding, impulsivity and the risk of suicide[29–31]. One study reported a negative association between GABA binding and impulsivity[30], suggesting that a failure to inhibit GABA may contribute to BPD symptomatology through excessive excitation. However, because similar alterations were also reported in patients with ADHD[30], these findings seem to be relatively non-specific to BPD. Conversely, a recent PET study assessing metabotropic glutamate 5 receptor confirmed that glutamatergic binding is abnormally higher in BPD and that this pattern is specific to BPD compared to major depressive disorder[32].

Finally, some anecdotal evidence suggests that the endocannabinoid and opioid systems may play a role in BPD, given that these neurotransmitters are expressed in fronto-limbic areas related to the modulation of emotion, stress and pain, such as the amygdala, prefrontal cortex, and thalamus[33,34]. However, evidence is currently limited as only two studies investigated cannabinoid receptor agonists, reporting conflicting findings: one study showed that higher receptor binding in the prefrontal cortex was associated with hostility[35], while another found no group differences and a negative (rather than positive) association with aggressive behaviour[36]. Only one PET study assessed opioid dysregulation, reporting greater receptor availability and heightened emotional reactivity in BPD, possibly reflecting compensatory up-regulation and increased sensitivity to negative stimuli[37].

While these results, particularly those involving serotoninergic pathways, are in line with the hypothesis of neurotransmitters involvement in BPD[7,38] and are congruent with isolated genetic studies[39] and pharmacological evidence that drugs targeting this system may be effective in managing BPD symptoms[40], the literature is fragmented and inconsistent. One limitation of current PET/SPECT and MRS studies is that they typically allow assessment of only a limited number of neurotransmitters per experiment, which constrains their ability to comprehensively evaluate multiple systems. Moreover, the use of PET/SPECT in clinical practice is challenging due to the high cost and specialized equipment required for these techniques, as well as the limited availability of specific radiotracers and the risks associated with radiation exposure. In recent years, the JuSpace tool has been developed to integrate PET- or SPECT-derived maps of major neurotransmitters with other imaging data, such as structural and functional MRI. This approach enables to indirectly investigate neurotransmitter systems by assessing the spatial co-localization of structural and functional MRI alterations with the normative distribution of neurotransmitters derived from PET/SPECT atlases from healthy adults[41], without the need to acquire individual PET/SPECT data. This approach has already been used to investigate structural-molecular associations in patients with depression[42,43], schizophrenia[44] and addiction[45,46] whereas to our knowledge no study has yet applied it to patients with BPD.

In this study, we aimed to investigate if GM alterations in BPD co-localize with the expression of specific neurotransmitters and if such alterations are associated with clinical features of BPD patients. Based on the above

background, we expected to observe a spatial correspondence primarily with serotoninergic and glutamatergic/GABAergic systems, and secondarily with dopaminergic, noradrenergic, and endocannabinoid/opioid systems.

## Results

### Baseline demographic and clinical features

Demographic and clinical characteristics of the BPD patients and healthy controls (HC) are summarized in Table 1. The two groups were comparable for gender distribution and age, while patients with BPD had significantly less years of education than HC ($p < 0.001$). BPD patients showed higher scores than HC on scales of symptomatology (ZAN-BPD), emotion dysregulation (DERS), disease severity (SCL-90-R), depression (BDI-II), impulsiveness (BIS) and traumatic experiences (CTQ) (all $p < 0.001$; Table 1). BPD patients showed a mean illness duration of 12 ± 8 years, with high prevalence (> 45%) of substance use (alcohol and drugs), traumatic experiences, self-harm behaviors, and suicide attempts (Suppl. Table 2). The majority of BPD patients (74%) were under pharmacological treatment (Suppl. Table 2). More details on the clinical characteristics, pharmacological treatments, specific comorbidities, and Axis II diagnoses are reported in Suppl. Table 2.

### Voxel-based morphometry analysis

At the global level, BPD patients showed significantly smaller GM volume compared HC (659 ± 39 vs. 682 ± 27, t = 3.09, $p = 0.003$), while no group differences were found in white matter volumes (497 ± 27 vs. 494 ± 24, t = 0.43, $p = 0.669$). The voxel-based morphometry (VBM) analysis revealed smaller GM volume in BPD patients relative to HC in subcortical limbic areas (right amygdala), posterior parietal cortex (right angular gyrus, left inferior parietal lobule and postcentral gyrus), temporal areas (bilateral middle and superior lateral cortex, left inferior gyrus), medial frontal superior gyrus, bilateral olfactory cortex and left cerebellum ($p_{FDR} < 0.05$; Fig. 1A; Table 2). No significant clusters were detected for the opposite contrast (HC < BPD).

The VBM comparison between BPD patients with high symptomatology (ZAN-BPD scores ≥ 16) compared to HC showed a similar pattern of GM reduction, again involving posterior parietal/sensorimotor, temporal, and limbic regions, and additionally the left orbitofrontal and middle cingulate cortex ($p_{FDR} < 0.05$; Fig. 1B; Table 3).

No difference was detected for the comparison between BPD patients with higher DERS scores compared to HC at $p_{FDR} < 0.05$ threshold, significant clusters emerging only at $p < 0.001$ uncorrected, mainly involving limbic/subcortical regions (left hippocampus and thalamus), parietal and sensorimotor areas (bilateral angular gyri, left inferior parietal lobule and postcentral gyrus), temporal regions (bilateral middle temporal gyri and temporal poles), and cerebellar regions (data not shown).

### Spatial correlation of GM volume alterations with neurotransmitters distribution

JuSpace toolbox was used to investigate spatial correlations between neurotransmitter maps and significant GM alterations in BPD patients. For the comparison between BPD patients and HC, GM alterations were not correlated with serotoninergic, dopaminergic, glutamatergic/GABAergic, noradrenergic, cannabinoid or opioid receptors/transporter (all $p_{FDR} > 0.884$; Fig. 2A; see Methods for details on receptor and transporter maps). All correlation coefficients were close to zero (Fisher's z Spearman rho range = -0.042 to 0.033; Suppl. Table 3) and remained non-significant even at a more lenient (i.e., uncorrected) threshold (all $p > 0.258$).

Similarly, no significant association emerged between GM alterations and neurotransmitters for the comparison between BPD with higher symptomatology (ZAN-BPD ≥ 16) and HC after multiple comparisons

| Variable | BPD $N = 58$ | HC $N = 28$ | Test value | $p$ |
|---|---|---|---|---|
| Sociodemographic features | | | | |
| Age, years | 29.3 ± 7.9 | 28.5 ± 6.8 | W = 771 | 0.709 |
| Sex, N female (%) | 51 (87.9) | 23 (82.1) | – | 0.515 |
| Education, years | 12.9 ± 3.1 | 17.3 ± 2.1 | W = 1381.5 | < 0.001 |
| Clinical features | | | | |
| DERS, total score | 124.0 ± 23.8 | 63.4 ± 11.8 | W = 14 | < 0.001 |
| ZAN-BPD, total score | 16.4 ± 5.10 | 2.1 ± 1.8 | W = 1.5 | < 0.001 |
| SCL-90-R, total score | 178.0 ± 67.1 | 23.1 ± 18.3 | W = 5 | < 0.001 |
| BIS, total score | 74.4 ± 12.1 | 51.7 ± 7.7 | t = −9.87 | < 0.001 |
| BDI-II, total score | 33.2 ± 11.9 | 3.25 ± 2.9 | W = 3 | < 0.001 |
| CTQ, total score | 57.3 ± 16.3 | 32.3 ± 5.33 | W = 93.5 | < 0.001 |
| Illness duration, years | 11.6 ± 7.6 | – | – | – |

**Table 1**. Demographic and clinical characteristics of the study groups. Values are reported as mean (M) and standard deviation (SD) or number (N) and percentage (%). Abbreviations. BDI-II = Beck Depression Inventory II; BIS = Barratt Impulsiveness Scale; BPD = borderline personality disorder; CTQ = Childhood Trauma Questionnaire; DERS = Difficulties in Emotion Regulation Scale; HC = healthy controls; SCL-90-R = Symptoms Check-list 90 Revised scale; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder. p values refer to Wilcoxon rank-sum test (continuous variables) or $\chi^2$ test/Fisher's exact test (categorical variables).

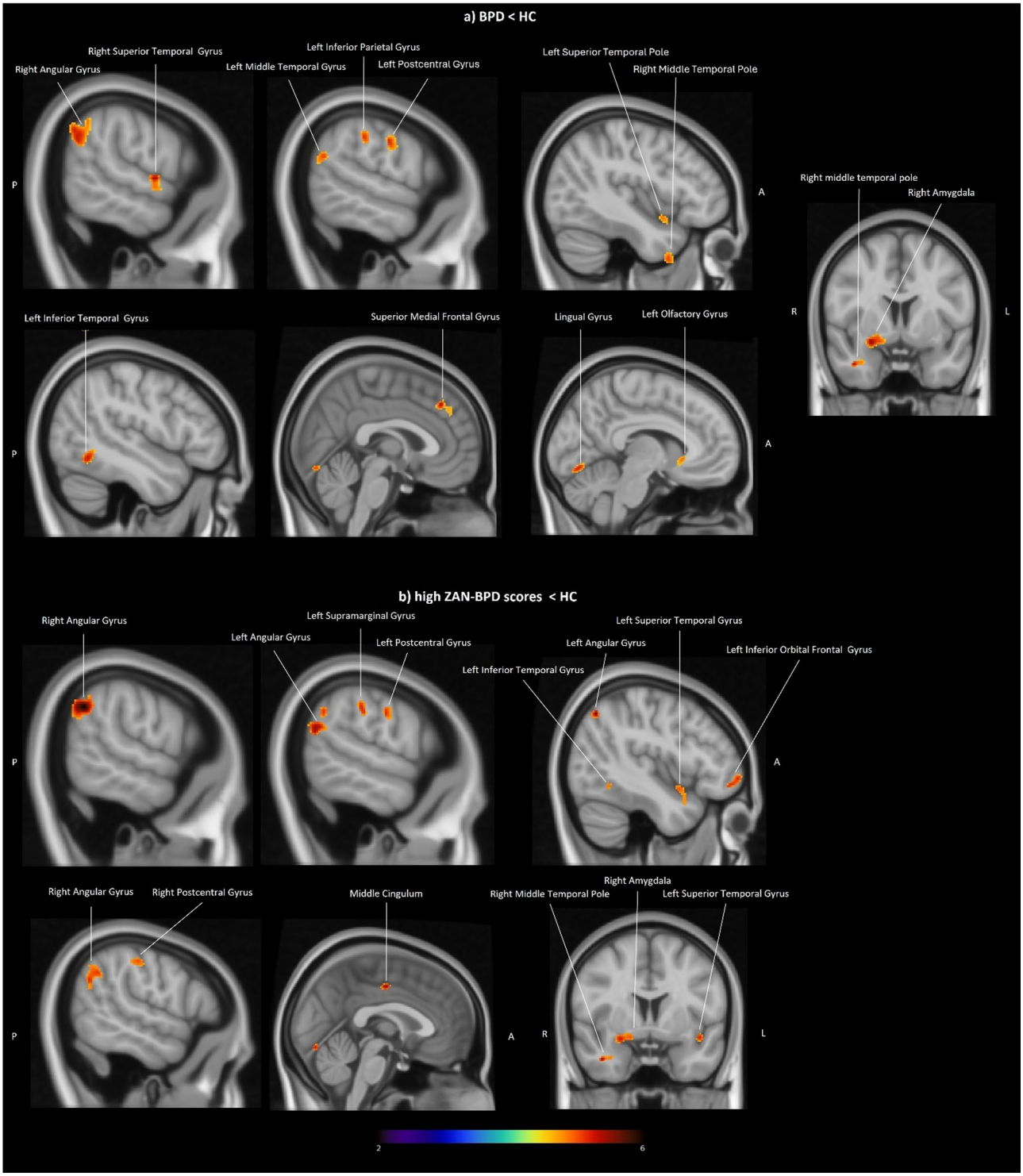



**Fig. 1**. Clusters of smaller GM volume in (**a**) BPD patients compared to HC and (**b**) BPD patients with higher symptomatology (ZAN-BPD ≥ 16) compared to HC, as detected using VBM (adjusted for intracranial volume and education). Statistical maps are thresholded at $p < 0.05$, FDR-corrected for multiple comparisons. Cluster peak voxel coordinates for (**a**) and (**b**) are provided in Tables 2 and 3, respectively.

correction (all $p_{FDR}$>0.789; Fig. 2B). Correlation coefficients were also close to zero (mean Fisher's z-transformed correlation coefficient range = -0.052 to 0.054; Suppl. Table 3) and remained non-significant at more lenient thresholds (all $p > 0.145$).

To assess the potential confounding effect of comorbidities and medication use on the above associations, additional JuSpace sensitivity analyses were performed. Specifically, comorbidities and medication use were coded as binary variables (based on their presence/absence) and their effect regressed out from the normalized,

| Brain region | Cluster size | Peak MNI coordinates | | | T | $p_{FDR}$ |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Right angular gyrus | 792 | 58 | −54 | 36 | 5.24 | 0.034 |
| | | 50 | −60 | 38 | 4.78 | 0.034 |
| | | 63 | −48 | 42 | 4.46 | 0.034 |
| Right Amygdala | 774 | 26 | 3 | −12 | 5.15 | 0.034 |
| | | 0 | −9 | −12 | 4.57 | 0.034 |
| | | 8 | 22 | −6 | 4.43 | 0.034 |
| Cerebellum 6 Left | 319 | −3 | −80 | −14 | 5.03 | 0.034 |
| | | −9 | −75 | −9 | 4.88 | 0.034 |
| | | −15 | −81 | −14 | 4.85 | 0.034 |
| Left postcentral gyrus | 291 | −60 | −10 | 34 | 4.92 | 0.034 |
| | | −64 | −14 | 24 | 4.34 | 0.035 |
| Left inferior temporal gyrus | 208 | −42 | 10 | −46 | 4.49 | 0.034 |
| | | −38 | 3 | −44 | 4.10 | 0.041 |
| | | −51 | 12 | −38 | 4.07 | 0.042 |
| Right middle temporal pole | 171 | 40 | 4 | −32 | 6.21 | 0.010 |
| Left inferior temporal gyrus | 166 | −50 | −54 | −10 | 4.93 | 0.034 |
| Right superior temporal gyrus | 131 | 62 | −3 | 3 | 5.05 | 0.034 |
| Superior medial frontal gyrus | 129 | 2 | 34 | 42 | 4.95 | 0.034 |
| | | 0 | 42 | 32 | 3.98 | 0.045 |
| Left olfactory gyrus | 122 | −6 | 20 | −3 | 4.27 | 0.037 |
| | | −9 | 14 | −12 | 4.12 | 0.040 |
| | | −14 | 8 | −15 | 3.87 | 0.047 |
| Left middle temporal gyrus | 123 | −57 | −58 | 24 | 4.58 | 0.034 |
| | | −54 | −66 | 18 | 4.24 | 0.037 |
| Left superior temporal pole | 119 | −34 | 6 | −18 | 4.58 | 0.034 |
| Left inferior parietal gyrus | 114 | −57 | −30 | 39 | 4.63 | 0.034 |

**Table 2**. Clusters of smaller GM volume in the whole BPD cohort compared to HC on voxel-wise comparisons (adjusted for intracranial volume and education). Coordinates are reported in Montreal Neurological Institute (MNI) space. Cluster-level significance threshold at $p < 0.05$, FDR-corrected.

modulated, and smoothed GM maps at the voxel level prior to JuSpace analysis. The resulting residualized GM maps were then used as input for the spatial correlation analyses. No significant association emerged between GM alterations and any neurotransmitter maps for either the comparison between BPD patients and HC or between BPD with higher symptomatology (ZAN-BPD ≥ 16) and HC after multiple comparisons corrections (all $p_{FDR} > 0.05$), nor at more lenient thresholds (all $p > 0.28$ and $p > 0.14$, respectively).

Finally, to assess if the negative results were influenced by methodological factors, we conducted sensitivity analyses using (i) surface-based cortical thickness and (ii) high-resolution functional parcellations to measure GM alterations. These analyses did not reveal any significant difference between BPD patients and HC, nor between BPD patients with higher symptomatology (ZAN-BPD ≥ 16) and HC (all $p_{FDR} > 0.05$). Results remained non-significant also when the effect of medication use and comorbidities were regressed out from the GM maps prior to analysis (all $p_{FDR} > 0.05$).

## Discussion

In this study, we investigated whether GM changes in BPD are associated with the expression of neurotransmitters implicated in BPD - primarily serotoninergic and glutamatergic/GABAergic, but also dopaminergic, noradrenergic, and endocannabinoid/opioid systems. Our VBM analysis confirmed the presence of GM alterations in BPD patients compared to HC, in line with previous MRI studies[47,48]. Specifically, we observed lower GM tissue in core regions of the fronto-limbic circuit, including the amygdala and medial frontal cortex, but contrary to our hypothesis these GM alterations were not associated with the availability of the major neurotransmitters, nor in the whole sample nor when considering clinical subgroups. Several explanations must be considered when interpreting these negative results. Specifically, different biological mechanisms, limited statistical power, methodological factors, and clinical heterogeneity may have contributed to attenuate these associations.

Our null findings were unexpected given that the pattern of GM alterations included key components of the emotional-affective fronto-limbic network (i.e., amygdala, orbitofrontal, medial superior frontal cortex), which are densely innervated by serotonergic fibers[49,50], glutamatergic, GABAergic and dopaminergic neurons[51–54], as well as areas involved in social cognition and mentalization, such as lateral temporal cortices, which are critical for empathic abilities. However, we did not observe structural alterations in other fronto-limbic areas previously

| Brain region | Cluster size | Peak MNI coordinates | | | T | $p_{FDR}$ |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| Right angular gyrus | 583 | 60 | −52 | 34 | 5.95 | 0.026 |
| | | 48 | −62 | 36 | 5.12 | 0.028 |
| | | 52 | −51 | 42 | 4.82 | 0.028 |
| Left postcentral gyrus | 580 | −62 | −12 | 34 | 5.38 | 0.028 |
| | | −66 | −12 | 26 | 5.01 | 0.028 |
| | | −66 | −21 | 27 | 4.67 | 0.031 |
| Right angular gyrus | 206 | 44 | −69 | 46 | 5.10 | 0.028 |
| Left inferior orbital frontal gyrus | 185 | −42 | 46 | −9 | 4.82 | 0.028 |
| | | −45 | 54 | −4 | 4.78 | 0.029 |
| Right amygdala | 153 | 26 | 3 | −14 | 4.87 | 0.028 |
| | | 16 | 2 | −12 | 4.52 | 0.033 |
| Left middle temporal gyrus | 129 | −58 | −62 | 22 | 5.09 | 0.028 |
| Left superior temporal gyrus | 117 | −42 | 3 | −12 | 4.83 | 0.028 |
| | | −42 | 9 | −20 | 4.41 | 0.035 |
| Left angular gyrus | 116 | −42 | −66 | 46 | 5.38 | 0.028 |
| Left inferior temporal gyrus | 107 | −46 | −56 | −10 | 4.87 | 0.028 |
| Left supramarginal gyrus | 91 | −58 | −28 | 36 | 4.70 | 0.031 |
| Right middle temporal pole | 89 | 40 | 4 | −32 | 6.18 | 0.026 |
| | | 33 | 2 | −28 | 4.20 | 0.041 |
| Left angular gyrus | 83 | −51 | −62 | 34 | 5.19 | 0.028 |
| | | −58 | −56 | 34 | 4.64 | 0.031 |
| Right postcentral gyrus | 68 | 57 | −22 | 45 | 4.42 | 0.035 |
| Middle cingulum | 67 | 0 | −14 | 45 | 5.25 | 0.028 |
| Vermis | 63 | 0 | −80 | −14 | 4.85 | 0.028 |
| | | −2 | −74 | −8 | 4.33 | 0.036 |
| Right postcentral gyrus | 60 | 51 | −14 | 40 | 4.42 | 0.035 |
| | | 57 | −9 | 36 | 4.20 | 0.041 |

**Table 3**. Clusters of smaller GM volume in BPD patients with high ZAN-BPD scores compared to HC on voxel-wise comparisons (adjusted for intracranial volume and education). Coordinates are reported in Montreal Neurological Institute (MNI) space. Cluster-level significance threshold at $p < 0.05$, FDR-corrected.

reported to show serotoninergic, glutamatergic and GABAergic abnormalities in PET and MRS studies, such as the ACC[10,26,29,30], while we observed GM abnormalities in postcentral gyrus and inferior parietal lobule areas that, together with the amygdala, form a limbic-motor circuit involved in the emotional modulation of perceptual and motor processes[55]. It is therefore possible that this composite structural pattern, spanning multiple large-scale circuits, may be less dependent on serotoninergic and glutamatergic/GABAergic neurotransmitters than the typical fronto-limbic circuit. Another possible explanation may be that GM abnormalities in BPD are not driven by neurotransmitter dysregulation, but rather by other processes, such as developmental, stress-related or neuroinflammatory mechanisms associated to abnormal fronto-limbic maturation[56] or chronic inflammation leading to subsequent neural loss[57].

Other factors that may have contributed to these null results include limited statistical power and methodological factors that may have reduced our ability to detect subtle associations between brain structure and neurotransmitters. First, our sample size was modest, especially for the analyses in clinical subgroups, and the groups were unbalanced, which further limited statistical power. Moreover, JuSpace enables an indirect assessment of neurotransmitter distribution and may be less powered than studies using PET/SPECT sequences to directly assess neurotransmitters levels/activity. Among methodological factors, the use of GM volumes and structural atlases in JuSpace analysis may have limited the sensitivity to detect subtle effects. However, when we used cortical thickness analysis (as opposite to GM volumes), and high-resolution functional parcellation (rather than anatomical atlases), the results were unchanged, suggesting that our findings were not substantially influenced by these methodological choices. Alternatively, task-based or resting-state functional imaging may prove more sensitive than structural MRI in detecting correlation with neurotransmitters since these are dynamic processes that may relate more closely to state-dependent features (e.g., behaviour) than to relatively stable structural measures.

Another potential confound is represented by clinical heterogeneity, as comorbidities were common among patients, with approximately 30% presenting depression or eating disorders. As neurotransmitters seem to be sensitive to specific symptom clusters, previous PET/MRS studies reporting associations specifically with impulsivity, aggression, and mood symptoms[58], this variability might have masked potential associations. Moreover, pharmacological treatment and substance use may interact with neurotransmitters, potentially

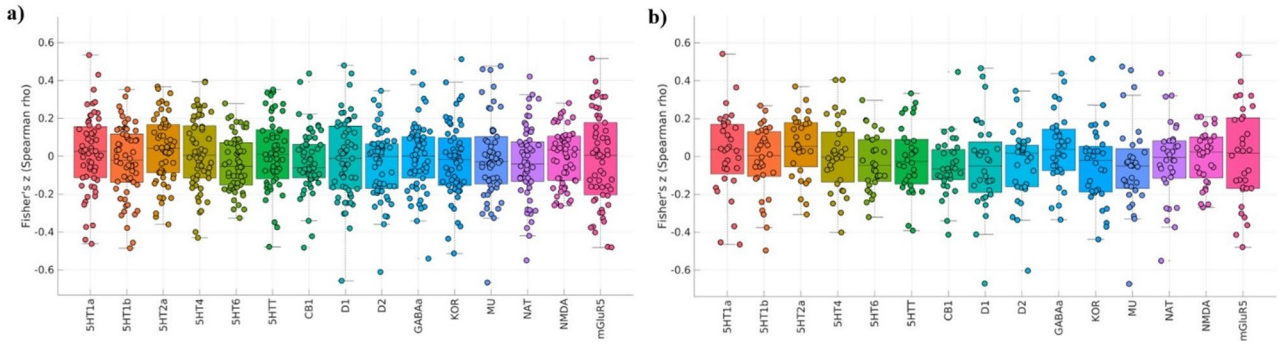



**Fig. 2**. Spatial correlation analysis between GM alterations (adjusted for intracranial volume and education) in BPD patients and neurotransmitter maps included in the JuSpace toolbox. (**a**) BPD patients compared to HC and (**b**) BPD patients with higher symptomatology (ZAN-BPD ≥ 16) compared to HC. Fisher's *Z*-transformed correlation coefficients with respective neurotransmitter maps are displayed. Error bars represent the parametric 95% confidence interval of the mean. None of the correlations survived multiple comparisons correction ($p_{FDR} < 0.05$). 5HT1a=serotonin 5-hydroxytryptamine receptor subtype 1a; 5HT1b=serotonin 5-hydroxytryptamine receptor subtype 1b; 5HT2a=serotonin 5-hydroxytryptamine receptor subtype 2a; 5HT4 = serotonin 5-hydroxytryptamine receptor subtype 4; 5HT6 = serotonin 5-hydroxytryptamine receptor subtype 6; 5HTT= serotonin transporter; BPD = borderline personality disorder; CB1 = cannabinoid receptor type 1; D1 = dopamine D1; D2 = dopamine D2; GABAa=gamma-aminobutyric acid type a; GM = grey matter; HC = healthy controls; KOR = κ-opioid receptor; MU = μ-opioid receptor; NET=noradrenaline transporter; NMDA = N-methyl-D-aspartate receptor; mGluR5 = metabotropic glutamate receptor 5; ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

obscuring the detection of associations. In our sample, 30–40% of BPD patients were taking antidepressants or mood stabilizers, and 10–30% were under serotonin selective (SSRI) or non-selective (SNRI) reuptake inhibitors, which influence dopamine, serotonin, and noradrenergic levels, respectively. However, when we accounted for these factors in sensitivity analyses the results remained unchanged. Specifically, no significant GM differences emerged when directly comparing BPD patients with versus without comorbidities, nor between BPD with versus without medication use (data not shown). Moreover, JuSpace results did not differ when comorbidities and medication use were included as covariates in the models, suggesting that these clinical confounds did not significantly impact our results. Drug abuse may also have an impact on brain structure and specific neurotransmitters such as the opioid and endocannabinoid systems. While current substance abuse was an exclusion criterion for the study, 60% of participants reported an history of drug abuse, thus we cannot exclude a long-term impact of this factor on brain measures. Future studies involving drug-free participants or drug-challenge paradigms are needed to better understand the contribution of drug-abuse on brain associations.

Several limitations of the study should be acknowledged. First, the study should be considered as exploratory given the small and unbalanced samples, and future studies with larger and multicentric cohorts are needed to investigate these associations more reliably. Furthermore, while we controlled for medication use in sensitivity analyses, residual confounding related to medication type, dosage, duration, and cumulative exposure cannot be excluded. Similarly, too few cases were available to conduct sub-group analyses based on specific comorbidities. Moreover, our sample included predominantly women, in line with previous studies and the higher prevalence of BPD in women. Since previous studies reported gender-specific neurotransmitter alterations in BPD[9], future studies are needed to determine whether distinct GM-neurotransmitter associations also emerge as a function of gender. Finally, our approach relies on normative PET atlases, which enable to assess multiple, although not all, neurotransmitter pathways. For example, no PET atlas is currently available for the MAO-A system, which has been reported to be affected in BPD in at least one study[26].

## Conclusions

In summary, our findings suggest that structural alterations in BPD may not be modulated by neurotransmitters. These results prompt further investigation into alternative mechanisms and pathways contributing to GM changes in BPD patients. Studies incorporating functional brain measures (e.g., resting-state functional MRI), focusing on more homogeneous subgroups (e.g., patients with aggressive behaviour, drug-free BPD, males vs. females) and including larger samples will be important to address current limitations and investigate specific brain-neurotransmitter associations.

## Methods

### Participants

This study was a secondary, cross-sectional analysis of data collected from the CLIMAMITHE study, a randomized clinical trial aimed at investigating the clinical and neurobiological effects of Metacognitive Interpersonal Therapy in patients with BPD. The study protocol was registered on ClinicalTrials.org (NCT02370316) and described in detail elsewhere[59,60]. For the present study, we included patients with BPD and HC with available structural MRI data at baseline, resulting in a sample of 88 participants (60 BPD and 28 HC). Inclusion criteria

for BPD were: (i) diagnosis of BPD according to DSM-IV-TR, (ii) age between 18 and 45 years, and (iii) provision of written informed consent. Exclusion criteria were: (i) a lifetime diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, organic mental syndromes, dementia, cognitive impairment, or relevant neurological signs; (ii) substance abuse or addiction within the 3 months preceding enrolment; (iii) pregnancy or lactation; and (iv) concurrent psychotherapy. HC were volunteers without cognitive impairment, psychiatric/neurologic conditions, or alcohol/substance abuse. The study was approved by the local ethic committee of the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli in Brescia, Italy (IRB number 67/2014). All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. The clinical assessment included the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD)[61] as a measure of severity of BPD symptoms, Difficulties in Emotion Regulation Scale (DERS)[62] as a measure of emotion dysregulation, the Symptoms Check-list 90 Revised scale (SCL-90-R)[63] for state-psychopathology, the Beck Depression Inventory II (BDI-II)[64] for depressive symptoms, the Barratt Impulsiveness Scale (BIS)[65] for impulsiveness, and the Childhood Trauma Questionnaire (CTQ)[66] for childhood traumatic experiences assessment. Data on demographics, pharmacotherapy, and clinical history (including comorbidities, substance abuse, suicide attempts, and aggressive behaviour) were also collected.

## MRI protocol

MRI data were acquired on a 3.0 Tesla Siemens Magnetom Skyra system (Siemens Medical, Erlangen, Germany) equipped with a 64-channel RF head coil at the Neuroradiology Unit of the ASST Spedali Civili Hospital, Brescia (Italy). Structural 3D magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted sequences were collected with the following parameters: TR/TE = 2300/2.03 ms; field of view = 256 mm; voxel size = $1.0 \times 1.0 \times 1.0$ mm$^3$; 176 contiguous slices; matrix = $256 \times 256$.

## Data processing and analysis

After the conversion of MRI images from DICOM to NIFTI format, data were analyzed using the Computational Anatomy Toolbox (CAT12; version 12.9, https://neuro-jena.github.io/cat//) implemented in the Statistical Parametric Mapping package (SPM 12; revision 7606, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running on the MATLAB R2024b platform (The MathWorks, Natick, MA, USA). The voxel-based morphometry (VBM) pipeline followed standard procedures[67] and included four steps: (i) spatial normalization: 3D T1-weighted images were corrected for bias-field inhomogeneities, spatially normalized via affine and nonlinear transformations, and segmented in native space into GM, WM, and cerebrospinal fluid (CSF)[68]. Segmented images were then normalized to the Montreal Neurological Institute (MNI) template. (ii) Modulation: local tissue volumes were preserved by compensating for deformations introduced during normalization. (iii) Smoothing: GM maps were smoothed with an isotropic Gaussian kernel of 6 mm full-width at half maximum (FWHM). (iv) Volume extraction and quality control: total GM, WM, and CSF volumes were extracted for each subject. Image quality was assessed using CAT12 metrics (Image Quality Rating, IQR), which evaluates noise, bias, and resolution, providing a rating scale range from 0 to 100. Images classified as "excellent" (range: 90–100) or "good" (range: 80–90) were retained. Based on these criteria, two BPD images were excluded, resulting in 58 BPD patients and 28 HC included in the final analyses.

Voxel-wise differences in GM volumes between groups were tested using a general linear model (GLM) in SPM12, including Total Intracranial Volume (TIV) as nuisance variable to account for individual differences in head size. Education was also included as a covariate since it differed between patients and controls. Comparisons with HC were conducted for the whole BPD group and for BPD subgroups defined according to key clinical scales, as follows: (i) BPD patients vs. HC, (ii) BPD patients with higher symptomatology (ZAN-BPD $\geq 16$) vs. HC, and (iii) BPD patients with higher emotion dysregulation (DERS $\geq 124$) vs. HC. The thresholds to define high/low levels on the ZAN-BPD and DERS scales were defined according to the median (i.e., 50th percentile) value of the distribution. Results were thresholded at $p < 0.05$, corrected for multiple comparisons using the False Discovery Rate (FDR) across the whole brain.

## Spatial correlation with receptor/transporter density maps

We used the JuSpace toolbox (version 2.0;[41] to assess the spatial association between GM alterations and PET/SPECT-derived neurotransmitter maps. PET/SPECT maps corresponding to the following neurotransmitter systems were selected, as provided in the JuSpace toolbox: (a) serotonin 5-hydroxytryptamine receptor subtype 1a (5HT1a), (b) serotonin 5-hydroxytryptamine receptor subtype 1b (5HT1b), (c) serotonin 5-hydroxytryptamine receptor subtype 2a (5HT2a), (d) serotonin 5-hydroxytryptamine receptor subtype 4 (5HT4); (e) serotonin 5-hydroxytryptamine receptor subtype 6 (5HT6), (f) serotonin transporter (5HTT), (g) cannabinoid receptor type 1 (CB1), (h) dopamine D1 receptor (D1), (i) dopamine D2 receptor (D2), (l) gamma-aminobutyric acid type A receptor (GABAa), (m) κ-opioid receptor (KOR), (n) μ-opioid receptor (MU), (o) noradrenaline transporter (NET), (p) N-methyl-D-aspartate receptor (NMDA), (q) metabotropic glutamate receptor 5 (mGluR5). The characteristics of the specific maps used for the analysis are provided in the Suppl. Table 1.

Prior to JuSpace analysis, TIV and years of education were regressed out from the normalized, modulated, and smoothed GM images to remove their influence on brain images. The resulting maps were then used as input to JuSpace to extract the mean GM values from 119 predefined regions of interest (ROIs), based on the Neuromorphometrics Atlas (MICCAI 2012 Grand Challenge;[41]. Option 5 of the JuSpace toolbox was used to generate Z-scores GM maps for the contrasts of interest (e.g., BPD vs. HC) and Spearman correlation coefficients were then calculated between the Z-score maps and the spatial distribution of each neurotransmitter map. To allow parametric testing in the statistical analysis, correlation coefficients were Fisher's Z transformed. Negative correlations indicate that smaller GM volume in patients relative to HC is associated with higher receptor/

transporter availability in the reference PET/SPECT maps, suggesting selective vulnerability of neurotransmitter-enriched regions to disease-related structural alterations.

Sensitivity analyses were conducted to assess if JuSpace findings were influenced by (i) clinical heterogeneity and (ii) methodological factors. For the first analysis, the effect of comorbidities and medication (coded as binary variables according to their presence/absence) was regressed out from GM maps prior to JuSpace analysis. For the second analyses, we considered (i) surface-based cortical thickness measures instead of GM volumes and (ii) high-resolution functional parcellation schemes (i.e., 200, 300 and 400 regions;[69] instead of the Neuromorphometrics Atlas.

Surface-based morphometry (SBM) was performed using CAT12 toolbox. Cortical thickness was estimated using the projection-based thickness method, which reconstructs the central cortical surface while accounting for partial volume effects and sulcal blurring. Individual cortical thickness maps were resampled to a common template surface and smoothed using a Gaussian kernel of 12 mm FWHM. Group comparisons were performed in SPM12, using the same second-level statistical framework adopted for the VBM analyses. TIV was not included as a covariate, in line with standard SBM procedures, whereas education was included. Additional models were also tested including medication use and/or comorbidities as covariates.

## Statistical analyses

Statistical analyses for sociodemographic, clinical and volumetric data were performed using the R software (version 4.3.3; R Foundation For Statistical Computing, Vienna, Austria; https://www.r-project. org/) and the R studio GUI (version 1.3.1073; http://www.rstudio.com/; RRID: SCR_001905). For group comparisons, continuous variables were analyzed using the Student's t-test or the Wilcoxon–Mann–Whitney test, according to data distribution, while categorical variables were compared with the Pearson $\chi^2$ test. Statistical significance was set at $p < 0.05$ (two-tailed).

For statistical analysis of JuSpace output, exact permutation-based p-values (10,000 permutations randomly assigning group labels using orthogonal permutations) were computed to assess whether the observed GM-PET maps correlation coefficients significantly differed from zero. All results were corrected for multiple comparisons using the FDR method, accounting for the number of neurotransmitter maps tested.

## Data availability

The data supporting the findings of this study are available in Zenodo at https://zenodo.org/records/17965267.

Received: 19 December 2025; Accepted: 29 May 2026
Published online: 04 June 2026

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Conceptualisation: MP, BB, EP, RR; methodology: MP, EG, VB, GB, DC, JD, EP; formal analysis: EG, VB; data curation: EG, SM, LP, ML, AC, GN, AS, DC, RR; writing - original draft: MP, EG; writing - review and editing: MP, EG, VB, SM, LP, ML, GB, AC, GN, AS, RG, DC, MM, JD, BB, EP, RR; supervision: EP, RR. All authors approved the final version of the manuscript.

## Funding

The IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli acknowledges support from the Italian Ministry of Health (Ricerca Corrente 2025–2027). Juergen Dukart received funding from DFG (DU 2027/7 – 1 project number 549186835).

## Declarations

## Competing interests

The authors declare no competing interests.

## Additional information

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1038/s41598-026-56165-6.

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