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Neural Correlates of Affective Disturbances: A Comparative Meta-analysis of Negative Affect Processing in Borderline Personality Disorder, Major Depressive Disorder, and Posttraumatic Stress Disorder

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ABSTRACT

BACKGROUND: Borderline personality disorder (BPD), major depressive disorder (MDD), and posttraumatic stress disorder (PTSD) are prominent examples of mental disorders with affective disturbances. Notably, all three disorders share a generally heightened negative affect, which is presumably the result of shared neural abnormalities in affective processing. In this meta-analysis, we aimed to identify transdiagnostic and disorder-specific abnormalities during the processing of negative compared with neutral stimuli.

METHODS: We synthesized neuroimaging findings of affect processing in BPD, MDD, and PTSD and calculated combined coordinate- and image-based meta-analyses. The analysis comprised 70 distinct study samples with a total of 31 unthresholded statistical parametric maps. Twenty-four studies had a focus on BPD (431 individuals with BPD, 436 healthy control subjects [HCs]), 32 studies on MDD (789 individuals with current MDD, 870 HCs), and 14 studies on PTSD (247 individuals with PTSD, 245 HCs).

RESULTS: Findings showed limbic hyperactivations in BPD and PTSD compared with limbic activation of HCs. In contrast, patients with MDD showed blunted amygdala activation in comparison with that of HCs. Additionally, the calculation of overlapping brain abnormalities in BPD, MDD, and PTSD highlighted transdiagnostic hyperactivation of the right median cingulate gyri and hypoactivation of the right middle frontal gyrus and the right middle occipital gyrus. Finally, disorder-specific comparisons also illustrate unique abnormalities for each mental disorder.

CONCLUSIONS: The present results support shared and disorder-specific neural abnormalities in patients with affective disturbances.

Keywords: Affect, Borderline personality disorder, fMRI, Major depressive disorder, Meta-analysis, Posttraumatic stress disorder, Valence

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Borderline personality disorder (BPD), major depressive disorder (MDD), and posttraumatic stress disorder (PTSD) are prominent examples of mental disorders with affective disturbances. Besides a marked diagnostic comorbidity (1–3), these three mental disorders also share a generally heightened negative affect (4–6), which may be related to shared abnormalities in the processing of aversive situations (7). These abnormalities in affective processing may include both a heightened reactivity to negative stimuli along with impairments in automatic top-down processes, and impairments in the implementation and maintenance of voluntary emotion regulation strategies (8).

To gain a better understanding of affective disturbances in psychopathology, numerous studies focused on neural processing of negative affective stimuli. Neuroimaging studies of affective processing in MDD illustrated heightened activations of limbic areas along with attenuated activation of the dorsolateral prefrontal cortex (dlPFC) and rostral parts of the anterior cingulate cortex compared with activation in healthy control subjects (HCs) (9,10), but in their recent work, Müller *et al.* (11) critically discussed a marked heterogeneity of neuroimaging findings in MDD. However, neurobiological models of depression assume that enhanced activation of limbic areas is the result of an inadequate modulation by prefrontal areas (12,13). Similar models were proposed for affective disturbances in BPD (14). In line with these propositions, a previous meta-analysis of ours illustrated enhanced activation of the left amygdala and posterior cingulate cortex in BPD, along with blunted activity of the bilateral dlPFC in comparison with that in HCs (15). Finally, findings in PTSD likewise suggest frontolimbic abnormalities during the processing of affective stimuli, i.e., decreased activity in the dorsal and ventral anterior

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cingulate cortex as well as in the ventromedial PFC, with increased amygdala activity (16–18).

Taken together, previous results in BPD, MDD, and PTSD highlight a substantial overlap of neural abnormalities during processing of negative stimuli. In addition to overlapping brain abnormalities, patients with these three mental disorders also show an altered functioning of the hypothalamic-pituitary-adrenal axis (19–21). Relatedly, it was proposed that genetic variations in serotonin-transporter genes (22–24) along with high rates of childhood maltreatment (25–28) may result in an increased risk for the selected disorders (22,29). However, until now, no study has directly compared these mental disorders, and there were few attempts to disentangle shared and disorder-specific deficits of neural abnormalities in such affect-related psychopathology.

An initial meta-analysis by Etkin and Wager (16) compared processing of negative stimuli in different anxiety disorders, namely PTSD, social anxiety disorder, and specific phobia. Patients with these mental disorders showed greater activity in (para-)limbic brain regions than did healthy individuals. Only patients with PTSD showed blunted activation of dorsal and rostral anterior cingulate brain regions in comparison with that in HCs. In addition, a recent meta-analysis across multiple Axis I disorders focused on experiments of cognitive control and highlighted blunted activation of the ventrolateral PFC, intraparietal sulcus, dorsal cingulate cortex, and anterior insula in psychopathology (30). Meta-analyses of gray matter volume also highlighted shared abnormalities in psychopathology, such as reduced gray matter in the dorsal anterior cingulate gyri (31,32).

In this study, we investigated transdiagnostic and disorder-specific neural abnormalities during the processing of negative affective stimuli. More specifically, we focused on heightened reactivity to negative stimuli along with impairments in automatic top-down processes (8). To this end, we synthesized data from patients with BPD, MDD, and PTSD in a combined image- and coordinate-based meta-analysis (33,34). We hypothesized that there would be abnormalities in the salience network (including limbic regions) (35).

METHODS AND MATERIALS

Search Strategy and Inclusion Criteria

Studies were identified by the investigators through a literature search of articles published on or before October 25, 2017, using web interfaces to Cochrane, PsycINFO, and PubMed databases. We used variants of the keywords "borderline personality disorder," "depression," and "post-traumatic stress disorder" combined with "emotion," "valence," or "affect," and "neuroimaging" or "fMRI" (for specific search strategies, see the Supplement). The retrieved results were scanned by two researchers, who checked reference sections and citations to identify further articles of interest. A systematic approach compliant with Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines was adopted (see the Supplement).

Functional magnetic resonance imaging studies were included if 1) all individuals in patient samples met diagnostic criteria for a primary diagnosis of BPD, current (but not remitted) MDD, or PTSD according to the DSM (third edition or later) or ICD-10; 2) patients were compared with a sample of HCs; 3) samples had a mean age of ≥18 and ≤65 years; 4) participants completed an experimental paradigm with a negatively valenced and a neutral condition; 5) whole-brain results with stereotactic coordinates for between-group comparisons of negative minus neutral contrasts (and not, for instance, in comparison with a resting or fixation cross condition) either were reported initially or were provided subsequently by the investigators. Studies involving psychotherapeutic or pharmacological interventions or training procedures (e.g., cognitive control training) were included only if baseline data were available. Study samples with comorbidity of schizophrenia, bipolar disorder (regardless of current phase), neurological diseases, or primary physical diseases were excluded. If the article did not report results of relevant whole-brain contrasts, we asked authors for further information. All authors were invited to provide unthresholded statistical parametric maps (SPMs). For flowcharts of the search and selection process, see the Supplement.

Contrast Selection

We focused on the between-group results of a negatively valenced condition in comparison with a neutral baseline condition but not in comparison with a resting or fixation cross condition. This contrast selection allows investigators to more clearly attribute differences in brain activations to the negative valence rather than to additional processes, such as visual processing.

Negative conditions were defined as participants' being presented negative visual stimuli (e.g., facial expressions, scenes, words) or other stimuli used to elicit negative affect (e.g., script-driven imagery). For tasks with concurrent cognitive requirements (e.g., tasks with varying levels of working memory load), we used "negative > neutral" contrasts that were independent of these cognitive demands (e.g., collapsed across working memory load). To ascertain a greater homogeneity at the level of experimental paradigms, studies of pain processing, rumination induction, or social rejection were excluded.

In cases where more than one contrast was available (e.g., fearful and angry facial expressions compared with a neutral condition), the images of these contrasts were combined in a single image (36). This procedure was relevant for four studies (37–40). For a detailed description of all included paradigms and contrasts, see Supplemental Table S1.

Statistical Analyses

The Seed-based d Mapping software (SDM version 5.141) (33,41,42) was used to calculate a combined coordinate and image-based meta-analysis. SDM accounts for peaks' effect sizes and weights studies by intrastudy variance and interstudy heterogeneity. Positive and negative effects are recreated in the same image to counteract effects of studies reporting findings in opposite directions.

SDM allows investigators to combine image- and coordinate-based study maps for statistical analyses. Importantly, the inclusion of unthresholded SPMs substantially increases the power of the respective analyses (33). For coordinate-based results, two researchers independently extracted coordinates and effect sizes from whole-brain

results. Findings from more liberally thresholded brain regions (e.g., regions of interest) were not taken into account. If an effect size was not reported, the significance level of a study was used to calculate the minimum effect size. Coordinates reported in Talairach space were converted into Montreal Neurological Institute space by means of Lancaster transformation. Activation foci were smoothed with an anisotropic kernel of 20-mm full width at half maximum to improve the recreation of effect size maps and to address spatial errors, e.g., those caused by the use of different cluster sizes between studies (42). For three studies, a null effect size was assumed for all voxels (43–45). After preprocessing, study maps were used to calculate random-effects models taking into account sample size and intra- and between-study variance. Statistical significance was determined using randomization tests (50 randomizations).

First, we calculated separate meta-analyses for each disorder based on the respective group comparisons (patient group vs. HC group) of the contrast "negative > neutral." Additional models with medication status as a meta-regressor were calculated to analyze activation patterns for unmedicated samples. Second, to assess effects between mental disorders, a linear meta-regression model with BPD, MDD, and PTSD was calculated to analyze group comparisons. These group comparisons were masked by the results of an initial model including all patient groups, thus assessing the main effect of group (compare with Supplemental Table S4). Only abnormalities that survived thresholding with an SDM Z value of 1, a voxel-level (height) threshold of $p < .005$, and a cluster-level (extent) threshold of $k \geq 20$ voxels are reported. This threshold corresponded to $p < .05$ corrected for multiple comparisons in a mega-analysis (19). Between-study variance was analyzed to assess significant heterogeneity. Robustness of main findings was estimated via jackknife analyses, and only robust abnormalities are discussed in this article (for full information, see Tables 1–6). In addition, we provide the results of Egger tests for all clusters.

Finally, we calculated the spatial overlap in neural abnormalities between BPD, MDD, and PTSD using procedures thoroughly described in Radua *et al.* (46). This analysis is

Table 1. Brain Regions Exhibiting Abnormal Activation During Negative Emotion Processing in BPD

	Peak				Cluster		Robustness		Bias Assessment
Region	MNI Space			Z	Size[a]	BAs[b]	Heterogeneity	Jackknife	Egger Test
Contrast: BPD > HC (Hyperactivation in BPD)									
Left posterior cingulate gyrus	−2	−50	26	3.02	900	7, 23, 26, 30	n.s.	24/24[c]	n.s.
Left angular gyrus	−48	−70	38	2.68	170	7, 39	n.s.	24/24[c]	n.s.
Left middle temporal gyrus	−52	0	−28	2.50	148	20–22	n.s.	24/24[c]	n.s.
Left amygdala, hippocampus	−20	−16	−24	2.57	116	28, 35	n.s.	24/24[c]	n.s.
Left inferior frontal gyrus, triangular	−36	16	28	2.30	62	48	n.s.	23/24	n.s.
Left inferior temporal gyrus	−54	−48	−10	2.37	52	20, 37	n.s.	19/24	n.s.
Left superior frontal gyrus, medial	2	64	20	2.39	49	10	n.s.	24/24[c]	n.s.
Right middle frontal gyrus, orbital	34	40	−14	2.17	48	47	n.s.	20/24	n.s.
Right superior frontal gyrus, dorsolateral	18	34	46	2.30	43	9	n.s.	19/24	n.s.
Left lenticular nucleus	−30	2	−12	2.24	39	48	n.s.	19/24	n.s.
Left corticospinal projections	−4	−34	−28	2.18	31		n.s.	19/24	n.s.
Right superior occipital gyrus	24	−96	14	2.10	26	18	n.s.	17/24	n.s.
Contrast: HC > BPD (Hypoactivation in BPD)									
Left postcentral gyrus	−62	−16	34	−3.02	1212	1–4, 6, 40, 43, 48	n.s.	24/24[c]	n.s.
Right superior parietal gyrus	24	−60	54	−2.01	98	7	n.s.	23/24	n.s.
Left supramarginal gyrus	−50	−42	30	−2.19	84	41, 48	n.s.	23/24	n.s.
Corpus callosum	−20	−54	54	−2.18	73		n.s.	23/24	n.s.
Right superior frontal gyrus, dorsolateral	24	−2	54	−2.02	77	6, 8	n.s.	22/24	sign.
Left precentral gyrus	−54	4	26	−2.13	70	6, 44	n.s.	24/24[c]	n.s.
Left inferior network, inferior longitudinal fasciculus	−24	−62	−4	−1.95	67		n.s.	20/24	n.s.
Undefined	0	4	12	−2.04	64		n.s.	19/24	n.s.
Left precentral gyrus	−34	−2	52	−1.83	47	6	n.s.	18/24	n.s.
Right middle frontal gyrus	36	40	24	−2.11	37	46	n.s.	20/24	n.s.
Left middle temporal gyrus	−52	−26	−2	−1.92	26	21	n.s.	16/24	n.s.
Right insula	40	−4	4	−1.72	21	48	n.s.	13/24	n.s.
Right insula	32	0	14	−1.84	20	48	n.s.	12/24	n.s.

BA, Brodmann area; BPD, borderline personality disorder; HC, healthy control subjects; MNI, Montreal Neurological Institute; n.s., nonsignificant; sign, significant.

[a]Size is provided in voxels per cluster.

[b]Only BAs with ≥10 voxels are reported.

[c]Robust brain abnormalities, as determined by jackknife analyses, are exhibited in these regions.

Table 2. Brain Regions Exhibiting Abnormal Activation During Negative Emotion Processing in MDD

Region	Peak				Cluster		Robustness		Bias Assessment
	MNI Space			*Z*	Size[a]	BAs[b]	Heterogeneity	Jackknife	Egger Test
Contrast: MDD > HC (Hyperactivation in MDD)									
Corpus callosum, thalamus	−4	−28	16	2.82	91		n.s.	32/32[c]	n.s.
Right insula, right rolandic operculum	40	−12	18	2.40	83	48	sign.	32/32[c]	n.s.
Right postcentral gyrus	48	−26	34	2.21	81	2, 3	n.s.	30/32	n.s.
Right Rolandic operculum	54	2	8	2.28	40	48	n.s.	30/32	n.s.
Left median network	−6	−2	30	2.06	41		sign.	29/32	n.s.
Right inferior occipital gyrus	36	−84	−14	2.51	29	19	n.s.	29/32	sign.
Left median cingulate/paracingulate gyri	−2	18	32	1.95	33	24	sign.	22/32	n.s.
Right median cingulate/paracingulate gyri	6	−10	42	2.20	30	23	n.s.	25/32	n.s.
Left caudate nucleus, left anterior thalamic projections	−18	−2	24	2.87	25		n.s.	30/32	n.s.
Right anterior cingulate/paracingulate gyri	0	28	−4	2.06	28	11	n.s.	27/32	n.s.
Left superior longitudinal fasciculus III	−46	−4	16	2.33	24		n.s.	27/32	n.s.
Corpus callosum	−22	−58	14	2.03	24		n.s.	26/32	sign.
Left median cingulate/paracingulate gyri	0	−24	40	1.80	25	23	n.s.	19/32	n.s.
Corpus callosum, right precuneus	20	−56	30	2.11	20		n.s.	19/32	n.s.
Contrast: HC > MDD (Hypoactivation in MDD)									
Right inferior temporal gyrus	56	−60	−6	−2.60	212	21, 37	n.s.	32/32[c]	n.s.
Left superior parietal gyrus	−26	−78	46	−2.37	93	7, 19	n.s.	32/32[c]	sign.
Left precentral gyrus	−42	0	52	−2.32	70	6	n.s.	31/32	n.s.
Right amygdala	26	−4	−16	−2.02	71	34	n.s.	32/32[c]	n.s.
Right middle frontal gyrus	40	−4	56	−1.88	68	6	n.s.	30/32	n.s.
Left insula	−32	22	−6	−2.07	62	47	n.s.	31/32	n.s.
Left inferior frontal gyrus, triangular	−48	24	16	−2.19	40	45, 48	n.s.	30/32	n.s.
Left fusiform gyrus	−38	−48	−22	−2.00	32	37	n.s.	28/32	n.s.
Right inferior frontal gyrus, triangular	48	32	14	−2.10	31	45	sign.	26/32	n.s.
Left middle frontal gyrus	−46	46	0	−1.94	27	45	n.s.	26/32	n.s.
Left inferior frontal gyrus	−42	34	−14	−2.22	21	47	n.s.	26/32	n.s.
Left precentral gyrus	−52	4	44	−1.87	20	6	n.s.	21/32	n.s.

BA, Brodmann area; HC, healthy control subjects; MDD, major depressive disorder; MNI, Montreal Neurological Institute; n.s., nonsignificant; sign., significant.

[a]Size is provided in voxels per cluster.

[b]Only BAs with ≥10 voxels are reported.

[c]Robust brain abnormalities, as determined by jackknife analyses, are exhibited in these regions.

based on the actual *p* values from the three individual meta-analyses. For this statistical analysis, we used a threshold of $p < .05$. Results were visualized with the BrainNet Viewer (47). Brain maps of all analyses are available at https://neurovault.org/collections/SOXNEZTF/.

RESULTS

In total, we included 70 distinct study samples comprising 31 unthresholded SPMs (BPD: 14 SPMs; MDD: 13 SPMs; PTSD: 4 SPMs). These studies investigated 1467 patients with mental disorders and 1551 HCs (38–40,43–45,48–113). Twenty-four studies focused on BPD (431 individuals with BPD, 436 HCs), 32 studies on current MDD (789 individuals with current MDD, 870 HCs), and 14 studies on PTSD (247 individuals with PTSD, 245 HCs). Weighted means of sociodemographic characteristics were age, BPD: 28.7 years; MDD: 35.6 years; and PTSD: 30.9 years; gender, BPD: 81.0% female; MDD: 66.2% female; and PTSD: 63.6% female; and percentage of patients taking psychotropic medication, BPD: 23.2%; MDD, 23.9%; and PTSD: 12.6%. Detailed demographic characteristics for each study are presented in Supplemental Table S2.

Results for Individual Disorders

In a first step, we calculated simple meta-analyses comparing individual mental disorders to HCs (Figure 1 and Tables 1–3; for an additional analysis comparing all patients with HCs, see Supplemental Table S3).

Borderline Personality Disorder. In comparison with HCs, patients with BPD showed enhanced activity in the left amygdala and hippocampus, the left posterior cingulate gyrus, the left middle temporal gyrus, and the medial PFC. Relatively decreased activity in BPD was found in the left pre- and postcentral gyrus.

Major Depressive Disorder. Relative to HCs, patients with MDD showed enhanced activity in the right posterior

Table 3. Brain Regions Exhibiting Abnormal Activation During Negative Emotion Processing in PTSD

Region	Peak MNI Space			Peak *Z*	Cluster Size[a]	Cluster BAs[b]	Robustness Heterogeneity	Robustness Jackknife	Bias Assessment Egger Test
Contrast: PTSD > HC (Hyperactivation in PTSD)									
Left inferior network; inferior frontal gyrus, orbital and triangular	−32	32	−2	3.21	1659	6, 9, 38, 44, 45, 47, 48	sign.	14/14[c]	n.s.
Cerebellum, vermic lobule IV/V	−2	−46	2	3.36	384	27, 29	n.s.	14/14[c]	n.s.
Left arcuate network, posterior segment; middle temporal gyrus	−52	−28	0	3.44	373	21, 22	n.s.	14/14[c]	n.s.
Right striatum, right amygdala	18	10	−8	3.63	270	48	n.s.	14/14[c]	n.s.
Corpus callosum	−18	50	24	2.79	200	9, 10, 46	sign.	12/14	n.s.
Left anterior thalamic projections	−12	12	2	3.15	177		n.s.	14/14[c]	n.s.
Left inferior network; left striatum	−38	0	−24	3.20	163	20, 48	n.s.	14/14[c]	n.s.
Right middle frontal gyrus	36	40	24	2.93	123	46	n.s.	13/14	n.s.
Corpus callosum	10	28	40	2.65	113	32	n.s.	10/14	n.s.
Right supplementary motor area	10	14	62	2.66	54	6	n.s.	10/14	n.s.
Right precuneus	10	−72	50	2.71	35	7	n.s.	10/14	n.s.
Left thalamus	−2	−18	12	2.53	31		n.s.	10/14	n.s.
Contrast: HC > PTSD (Hypoactivation in PTSD)									
Left postcentral gyrus	−60	−8	40	−1.56	248	3, 4, 43	n.s.	14/14[c]	sign.
Right postcentral gyrus	56	−4	24	−1.38	228	4, 6, 43	n.s.	11/14	n.s.
Right superior temporal gyrus	68	−30	4	−1.16	176	21, 22, 42	n.s.	11/14	n.s.
Right insula	36	−4	8	−1.27	119	48	n.s.	11/14	n.s.
Left postcentral gyrus	−32	−38	68	−1.08	56	1, 3	sign.	12/14	sign.

BA, Brodmann area; HC, healthy control subjects; MNI, Montreal Neurological Institute; n.s., nonsignificant; PTSD, posttraumatic stress disorder; sign., significant.

[a]Size is provided in voxels per cluster.

[b]Only BAs with ≥10 voxels are reported.

[c]Robust brain abnormalities, as determined by jackknife analyses, are exhibited in these brain regions.

insula, the right Rolandic operculum, and a cluster comprising the thalamus. Notably, we observed decreased activity in the right amygdala of patients with MDD relative to that in HCs. Relatively decreased activity in MDD compared with that in HCs was also characteristic for the right inferior temporal gyrus and the left superior parietal gyrus.

Table 4. Brain Regions Exhibiting Abnormal Activation During Negative Emotion Processing in BPD Compared With MDD and Vice Versa[a]

Region	Peak MNI Space			Peak *Z*	Cluster Size[b]	Cluster BAs[c]	Robustness Jackknife	Bias Assessment Egger Test
Contrast: BPD > MDD								
Left amygdala, hippocampus	−24	−10	−12	2.41	314	34, 35	56/56[d]	n.s.
Left inferior network, inferior longitudinal fasciculus	−50	−6	−24	2.60	185	21, 22	56/56[d]	n.s.
Left angular gyrus	−42	−72	44	2.64	124	7, 39	56/56[d]	n.s.
Left inferior frontal gyrus, orbital	−42	34	−14	2.60	101	45, 47	56/56[d]	n.s.
Right amygdala, hippocampus	34	−2	−20	2.32	97	34	54/56	n.s.
Left inferior frontal gyrus, opercular and triangular	−34	14	30	2.45	67	44, 48	56/56[d]	n.s.
Left inferior network, uncinate fasciculus	−28	30	−10	2.35	52	47	55/56	n.s.
Contrast: MDD > BPD								
Left postcentral gyrus	−40	−34	50	−2.91	1089	2–4, 6, 7, 40, 43, 48	56/56[d]	sign.
Right superior parietal gyrus	24	−62	50	−2.37	145	7	56/56[d]	n.s.
Left precentral gyrus, corpus callosum	−54	4	24	−2.18	69	6	56/56[d]	n.s.
Left anterior thalamic projections	0	2	10	−1.99	28		46/56	n.s.

BA, Brodmann area; BPD, borderline personality disorder; MDD, major depressive disorder; MNI, Montreal Neurological Institute; n.s., nonsignificant; sign., significant.

[a]Analyses were informed by the main effect of group. Thus, only clusters overlapping with robust results of this main effect are presented.

[b]Size is provided in voxels per cluster.

[c]Only BAs with ≥10 voxels are reported.

[d]Robust brain abnormalities, as determined by jackknife analyses, are exhibited in these regions.

Table 5. Brain Regions Exhibiting Abnormal Activation During Negative Emotion Processing in BPD Compared With PTSD and Vice Versa[a]

Region	Peak MNI Space			Peak Z	Cluster Size[b]	Cluster BAs[c]	Robustness Jackknife	Bias Assessment Egger Test
Contrast: BPD > PTSD								
No suprathreshold clusters								
Contrast: PTSD > BPD								
Left middle temporal gyrus	−54	−26	−2	−3.88	387	21, 22	38/38[d]	n.s.
Left inferior frontal gyrus, triangular part	−52	4	26	−3.35	359	6, 44, 45, 48	38/38[d]	n.s.
Left precentral gyrus	−36	0	54	−2.75	358	6, 8, 9	38/38[d]	n.s.
Left anterior thalamic projections	−14	12	4	−2.74	332	25	38/38[d]	n.s.
Right superior parietal gyrus	24	−62	52	−2.96	310	7	38/38[d]	n.s.
Right middle frontal gyrus	36	40	24	−3.61	258	45, 46	38/38[d]	n.s.
Right striatum	20	12	−8	−3.39	149	48	38/38[d]	n.s.
Left postcentral gyrus	−44	−36	52	−2.74	156	2, 3, 40	37/38	n.s.
Left inferior network, inferior fronto-occipital fasciculus	−36	32	−4	−2.75	155	47, 48	35/38	n.s.
Left middle frontal gyrus, corpus callosum	−18	52	22	−2.90	145	9, 46	38/38[d]	n.s.
Right thalamus	4	−20	6	−2.60	87		36/38	n.s.

BA, Brodmann area; BPD, borderline personality disorder; MNI, Montreal Neurological Institute; n.s., nonsignificant; PTSD, posttraumatic stress disorder.

[a]Analyses were informed by the main effect of group. Thus, only clusters overlapping with robust results of this main effect are presented.

[b]Size is provided in voxels per cluster.

[c]Only BAs with ≥10 voxels are reported.

[d]Robust brain abnormalities, as determined by jackknife analyses, are exhibited in these brain regions.

Posttraumatic Stress Disorder. Compared with HCs, patients with PTSD showed enhanced activations in orbital and triangular parts of left inferior frontal gyrus, the bilateral striatum (encompassing parts of the right amygdala), and the left middle temporal gyrus. The left postcentral gyrus showed a robust hypoactivation in PTSD.

Moderating Variable. Analyses of unmedicated samples mostly replicated the results presented above. Regarding limbic abnormalities, we found bilateral hyperactivation in BPD, right-lateralized hypoactivation in MDD, and hyperactivation of the left amygdala and right striatum in PTSD. For a detailed overview of brain activations per mental disorder, see statistical maps provided at NeuroVault.

Table 6. Brain Regions Exhibiting Abnormal Activation During Negative Emotion Processing in MDD Compared With PTSD and Vice Versa[a]

Regions	Peak MNI Space			Peak Z	Cluster Size[b]	Cluster BAs[c]	Robustness Jackknife	Bias Assessment Egger Test
Contrast: MDD > PTSD								
No suprathreshold clusters								
Contrast: PTSD > MDD								
Left inferior network; left inferior frontal gyrus, triangular and orbital	−38	26	−6	−3.63	2511	6, 9, 38, 44, 45, 47, 48	46/46[d]	n.s.
Right striatum; right amygdala	16	8	−8	−3.29	518	34, 48	46/46[d]	n.s.
Cerebellum, vermic lobule IV/V	−2	−48	2	−3.16	322	27, 29	46/46[d]	n.s.
Left inferior parietal gyri	−34	−68	48	−2.85	252	7, 19, 39	44/46	n.s.
Left middle temporal gyrus	−56	−24	−4	−3.32	209	21, 22	46/46[d]	n.s.
Left superior frontal gyrus, dorsolateral; corpus callosum	−16	52	26	−3.00	222	9, 46	46/46[d]	n.s.
Left striatum; left anterior thalamic projections	−12	10	4	−3.02	210	25	46/46[d]	n.s.
Left middle temporal gyrus; left amygdala; left hippocampus	−36	0	−22	−3.07	185	21, 48	46/46[d]	n.s.
Right middle frontal gyrus	36	40	24	−2.96	102	46	46/46[d]	n.s.

BA, Brodmann area; MDD, major depressive disorder; MNI, Montreal Neurological Institute; n.s., nonsignificant; PTSD, posttraumatic stress disorder.

[a]Analyses were informed by the main effect of group. Thus, only clusters overlapping with robust results of this main effect are presented.

[b]Size is provided in voxels per cluster.

[c]Only BAs with ≥10 voxels are reported.

[d]Robust brain abnormalities, as determined by jackknife analyses, are exhibited in these areas.

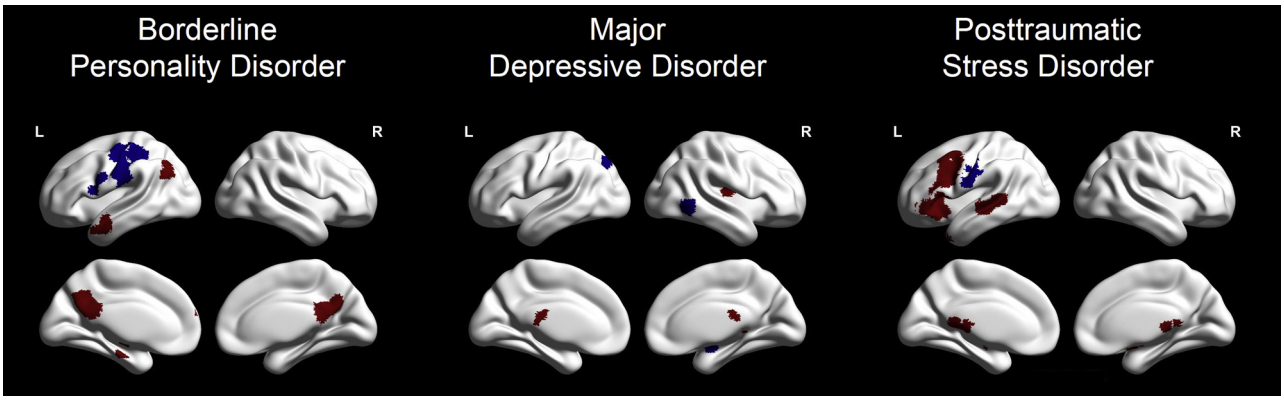

Figure 1. Visualization of abnormal emotion processing in individual mental disorders. Relative to healthy control subjects, enhanced neural activations in patient samples are presented in red, whereas decreased activations are presented in blue. Results are thresholded at $p < .005$ (uncorrected) and $k > 20$ voxels. L, left; R, right.

Comparison of Mental Disorders

Next, statistical comparisons between patient groups were calculated (see Figure 2). We report only clusters overlapping with the main effect of an analysis including all patient groups (for comparison, see Supplemental Table S4).

Comparison of BPD and MDD. Compared with persons with MDD, individuals with BPD showed increased activations in the left amygdala and hippocampus, different parts of the left inferior frontal gyrus (including ventrolateral PFC), and the left angular gyrus (Table 4). The results showed also an increased activation of the right amygdala and hippocampus, but this finding was less robust, as indicated by jackknife analyses.

The reverse contrast showed enhanced activations of the right posterior parietal cortex (Brodmann area [BA] 7), the left ventral premotor cortex (BA 6), and the postcentral gyrus in MDD compared with those in BPD.

Comparison of BPD and PTSD. Statistical comparisons yielded enhanced activations in PTSD compared with those in BPD of the left inferior frontal gyrus (triangular), the left middle temporal gyrus, and right striatum (Table 5). Enhanced activations in PTSD were also observed in the bilateral middle frontal gyrus (including parts of the left superior frontal gyrus, dorsolateral), the ventral premotor cortex (BA 6), and the right posterior parietal cortex (BA 7).

Comparison of MDD and PTSD. Compared with persons with MDD, individuals with PTSD showed enhanced activations in the left inferior frontal gyrus (including ventrolateral PFC) as well as the bilateral amygdala and hippocampus (Table 6). Enhanced activations were also observed in the left superior frontal gyrus, dorsolateral prefrontal gyrus, and right middle frontal gyrus.

Moderating Variables. We ran several statistical analyses to assess the potentially moderating effects of age, gender, and psychotropic medication on group differences. Except for a cluster in the left postcentral gyrus, all clusters remained significant (see Supplemental Table S4).

Transdiagnostic Abnormalities

Finally, we calculated the overlap between abnormal brain activations of patients with BPD, MDD, and PTSD. This analysis illustrated a hyperactivation of the right median cingulate gyrus (Montreal Neurological Institute [MNI] coordinates: 8, −16, 40) as well as hypoactivations of the right middle frontal gyrus (MNI coordinates: 42, 4, 52) and the right middle occipital gyrus (MNI coordinates: 38, −76, 2). For a visualization, see Supplemental Figure S5.

DISCUSSION

This meta-analysis investigated shared and disorder-specific neural abnormalities of negative affect processing in three mental disorders with prominent affective disturbances (BPD, MDD, and PTSD). To this end, we synthesized 70 studies comprising a total of 1467 patients and 1551 HCs.

Results for Individual Mental Disorders

The meta-analyses for individual mental disorders provide a noteworthy pattern of abnormalities within the amygdala, which represents a key node of the salience network and is crucial for the processing of salient stimuli (35,114). Compared with HCs, BPD and PTSD patients showed enhanced activity in the amygdala (left or right amygdala, respectively). This finding reinforces previous notions of increased processing of negative material in BPD and PTSD (14,115). Findings of previous studies provided some support for the idea that the left amygdala is involved in the conscious processing of negative stimuli and is based on reflective processes, whereas the right amygdala is more involved in automatic processing of affective stimuli (116–118). Thus, one might speculate that amygdala hyperreactivity reflects augmented negative appraisal of the presented stimuli in BPD, compared with an enhanced automatic affective response in PTSD.

Our finding of decreased activity in the right amygdala of patients with current MDD is at odds with previous meta-analytic results in this patient group (9–12). It is thus important to consider the methodological differences between our approach and previous meta-analyses in MDD. The most noteworthy difference is the use of an effect-size–based

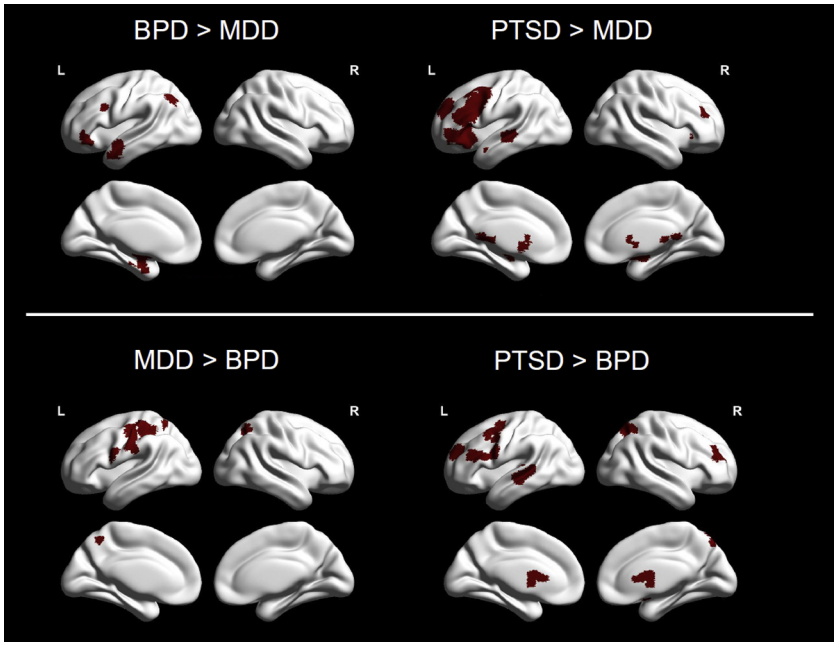

Figure 2. Visualization of disorder-specific effects in negative emotion processing. Enhanced activations between mental disorders are presented in red. Results are thresholded at $p < .005$ (uncorrected) and $k > 20$ voxels. BPD, borderline personality disorder; L, left; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; R, right.

approach and the inclusion of untresholded SPMs. This specific procedure was previously validated (33). In this validation study, the authors compared 1) effect-size–based methods, 2) effect-size–based methods using different percentages of unthresholded SPMs, and 3) peak probability methods with the results of a pooled analysis of original data. The results of this validation study showed a substantially higher overlap and sensitivity of the effect-size–based methods with the "true map" from the pooled analysis compared with peak probability methods. Importantly, the inclusion of unthresholded SPMs did further increase the spatial overlap and statistical sensitivity, while still providing an excellent control of false positives (33,34).

Furthermore, we focused on "negative > neutral" contrasts. Hence, main effects of group or results contrasting negative stimuli with a resting condition or with a positive condition were not included. Several studies reported increased limbic reactivity to negative and neutral stimuli in patients with MDD (40), resulting in a main effect of group rather than an interaction of valence by group. Thus, it is possible that divergent findings are also attributable to differences in contrast selection. Finally, we also checked whether activation patterns of the amygdala might be related to medication status in persons with MDD. Results of limbic hypoactivation remained significant when we analyzed persons with unmedicated MDD compared with HCs.

Disorder-Specific Effects

As suggested by the findings discussed above, mental disorders differ in neural activity of the limbic system during negative affective processing. Specifically, patients with BPD or PTSD showed increased activations of the left amygdala-hippocampus region compared with those with MDD. The same pattern, albeit less robust, was found for the right amygdala-hippocampus region. In addition, patients with BPD and PTSD were characterized by enhanced activity in the ventrolateral PFC (BAs 44, 45, and 47). This brain region is involved in automatic as well as voluntary control of emotions (119,120) or the suppression of one's emotional responses (121). Enhanced recruitment of the ventrolateral PFC in BPD and PTSD might thus reflect a regulatory mechanism to deal with excessive affective responding.

In PTSD, processing of negative stimuli was uniquely characterized by enhanced activations of the dlPFC (BAs 9 and 46) and the striatum compared with those found in BPD and MDD. While the striatum is primarily associated with reward processing, there is increasing evidence that this structure plays a critical role in affective learning and decision making. More specifically, the striatum is thought to represent aversive prediction errors and to continuously update limbic regions with expectancy information (122). Enhanced amygdala-striatum activation might thus reflect an increased expectation and processing of negative outcomes, which would be in line with models of a generalized fear response in PTSD (123,124). In addition, patients with PTSD showed enhanced activity in the dlPFC (BAs 9 and 46) compared with those with BPD and MDD.

In comparison with persons with MDD and PTSD, patients with BPD were uniquely characterized by reduced activation in the ventral premotor cortex (BA 6) and the right posterior parietal cortex (BA 7). These abnormalities might contribute to increased impulsivity as well as pronounced difficulties in the voluntary control of negative emotions in BPD (125,126). Accordingly, previous studies illustrated that patients with BPD are more susceptible to interference by negative stimuli (72,87) and have difficulties in using attentional deployment or other cognitive strategies for the regulation of negative emotions

(69,111). Our finding of reduced dlPFC activation in BPD compared with that in PTSD also points to an additional disorder-specific effect in BPD regarding emotion regulation: as both diagnostic groups show amygdala hyperreactivity during negative emotion processing, and those with BPD show less dlPFC activation than those with PTSD, this finding is in line with previously discussed aberrations in prefrontal control regions in BPD (127,128).

Transdiagnostic Abnormalities

Compared with HCs, patients with affective disturbances showed enhanced activation of the median cingulate gyrus during processing of negative stimuli. This region is a part of the default mode network (DMN), and this finding supports the idea that DMN dysfunction is a main characteristic of patients with affective disturbances. The DMN is an interconnected system for self-related cognitive activity, including autobiographical memory, as well as for self-monitoring of emotional states (129–131). Thus, patients with BPD, MDD, and PTSD process negative stimuli in a more self-related way. As self-related processing of negative stimuli is typically related to neural activations of cortical midline structures (132), we conclude that negative stimuli might trigger ruminative thoughts or negative autobiographical content (133), thereby fueling negative affect.

Limitations

There are some limitations that need to be considered. First and foremost, the number of included studies and resulting sample sizes differed substantially between diagnostic groups (BPD: 24 studies; MDD: 32 studies; and PTSD: 14 studies). For peak probability meta-analyses, a minimum number of 20 experiments was determined to achieve sufficient power to detect moderate effects (134). The percentage of SPMs differed as well between groups (BPD: 58.33%; MDD: 40.63%; PTSD: 28.57%). These aspects might have affected the sensitivity of our analyses. Second, findings of disorder-specific effects relied on indirect comparisons of different disorders. Thus, patient groups were not matched regarding sociodemographic characteristics or to experimental paradigms. Although findings of analyses of covariance do not support a modulatory influence of sociodemographic variables, it might be argued that differences in experimental material have contributed to group differences. Most studies in MDD relied on facial expressions (faces, 56.3%; scenes, 25.0%), whereas most studies in BPD or PTSD applied scenes (BPD: faces, 29.2%; scenes, 41.7%; PTSD: faces, 28.6%; scenes, 50.0%). However, it is unlikely that the observed hypoactivation of the limbic system during negative emotion processing in MDD compared with that in patients with BPD or PTSD is primarily attributable to differences in experimental material. First, differences in experimental material could not affect analyses comparing persons with each mental disorder with HCs, because HCs were presented with the same stimuli in each study. The respective results illustrated a similar pattern of hyperactivations of the limbic system in BPD and PTSD but hypoactivation in patients with current MDD. Furthermore, previous research highlighted the finding that faces and scenes activate a shared network including the amygdala to a comparable extent (135). Third, median sample size of the included studies was 18.0 participants (range: 6–80 participants) for patient samples and 18.5 participants (range: 6–132 participants) for control samples. The reporting on small datasets is associated with increased between-study variance and reduced statistical power (136). The recruitment of bigger samples, however, represents a major challenge in clinical neuroscience. A solution for this problem may lie in open data repositories (e.g., NeuroVault) to aggregate primary data from multiple sites, or in concerted efforts to assess data across many labs (e.g., Enigma Consortium). Fourth, the lack of a positive condition leaves open the possibility that the results are not specifically related to negative valence, but to more general abnormalities in the arousal domain [cf. affective circumplex model (137)]. Fifth, the hippocampus and amygdala are two small and adjacent structures, which can be difficult to differentiate with brain imaging (138). Therefore, regional specificity of the reported abnormalities in the limbic system has to be interpreted with caution.

Conclusions

Taken together, the present meta-analysis of negative affect processing supports shared and disorder-specific neural abnormalities in patients with affective disturbances. More specifically, our findings point to enhanced limbic activation in BPD and PTSD, but blunted activation in MDD. Furthermore, results highlight a generally enhanced activation of the DMN. Finally, disorder-specific comparisons illustrate unique abnormalities for each mental disorder.

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