The Neuropsychological Mechanisms of Treatment of Bipolar Disorder and Borderline Personality Disorder:

Activation Likelihood Estimation Meta-Analysis of Brain Imaging Research

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ABSTRACT

Objective: To explore the alteration of brain regions after treatments for bipolar disorder (BD) and borderline personality disorder (BPD) in order to discover the underlying neural mechanisms of therapies.

Data Sources: An electronic search of the PubMed, Embase, Cochrane Library, and Web of Science databases from inception until June 2021 was conducted.

Study Selection: Articles reporting the results of changes in brain activation after treatment, to assess the effects of therapy relative to a before-treatment condition, were included. A total of 1,592 records were retrieved, with 34 studies ultimately included.

Data Extraction: Activation coordinates were extracted from each study. We used activation likelihood estimation meta-analysis to evaluate the similarities and differences in the activation of different brain regions in patients with BD and BPD after treatment with psychotherapy and drug therapy.

Results: Most brain regions with abnormal activation were improved after treatments for BD and BPD. The brain activity changes produced by psychotherapy were mostly in the frontal areas, while drug therapy primarily impacted the limbic areas. In BD, treatments were associated with activation alterations in the inferior frontal gyrus, superior temporal gyrus, and cingulate gyrus, while in BPD, treatments were associated with activation alterations in the supramarginal gyrus, middle frontal gyrus, and parahippocampal gyrus.

Conclusions: These results suggest that drug therapy might have a bottom-up effect, while psychotherapy might have a top-down effect. This study may contribute to the clinical prediction of treatment efficacy in BD and BPD and to the identification of more accurate neuroimaging biomarkers for treatment of the two disorders.

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Bipolar disorder (BD), a type of mood disorder, refers to disease that includes both manic episodes and depressive episodes and has an incidence as high as 5%.[1] The symptoms of BD sometimes lead to severe emotional disruption, destroying an individual's ability to perform basic daily functions and make correct judgments.[2] Borderline personality disorder (BPD) consists of a universal pattern of interpersonal relationship, self-image, and emotional instability and significant impulsivity.[3] The incidence of BPD can be as high as 5.9%.[4] It usually starts no later than early adulthood and exists in various contexts.[5] According to the *DSM-5*,[3] two of the diagnostic criteria for BPD are emotional instability due to significant mood reactivity and inappropriately strong anger or difficulty controlling anger, which are similar to symptoms of BD. This leads to difficulties in the diagnosis of and differentiation between BD and BPD. Thus, it is crucial to distinguish these two diseases.

In severe cases of BD, the probability of confusing BD with BPD is particularly high, especially with bipolar II disorder[6]; this is mainly due to the emphasis on the similarities rather than the differences between BD and BPD.[7,8] A recent study demonstrated that up to 21.6% of BD patients have BPD comorbidities.[9] Thus, the comorbidity rate of these two diseases is very high, and emotional instability and impulsivity are the most important common features of BD and BPD.[10] Underestimating the boundary between BD and BPD also increases the risk of improper or harmful drug exposure.[11] The blurred boundary between BD and BPD is one of the reasons it is important to study the relationship between these two diseases.

Mood stabilizing drugs are considered to be the key therapeutic intervention for BD, while psychotherapy is the key treatment for BPD.[12] Hence, in the present research study, we only investigated the effect of drug therapy and psychotherapy on BD and BPD. To treat BD, psychotherapists use a variety of approaches, such as cognitive behavioral therapy, mindfulness-based cognitive therapy, psychoeducation, and family-focused therapy.[13] In terms of medication, lamotrigine, risperidone, divalproex, and quetiapine are often considered.[14] Some studies have evaluated the effectiveness of psychotherapies[15,16] or pharmacotherapies[17,18] for BD. However, the underlying neurologic mechanism for the treatment of BD and BPD is unclear. Although some studies have compared the relationship between BD and BPD,[19,20] they did not the explore the similarities and differences in brain mechanisms

Clinical Points

- Bipolar disorder and borderline personality disorder are difficult to diagnose and differentiate, and their comorbidity rate is very high.
- For patients with these disorders in whom either drug therapy or psychotherapy is not effective, combining both types of therapy is a viable consideration.
- After psychotherapy, the frontal lobe and temporal lobe were the primary brain regions in which activation changed, indicating a top-down effect of this therapy type. After drug therapy, the limbic area was the region in which activation changed, indicating a bottom-up effect.

between these two disorders after treatment. BD patients have a different disease course and therapy response than BPD patients, and misdiagnosis may result in patients receiving ineffective treatment[12]; therefore, it is particularly important to explore the neural mechanisms of the treatment of these two diseases.

In recent years, a large number of neuroimaging studies have found some cerebral structural and functional alterations related to the pathogenesis of BD and BPD. Most BPD studies indicated that structural differences in the amygdala, hippocampus, and cingulate cortex are involved in affective deficits, and alterations in the dorsolateral prefrontal and limbic regions have also been identified.[21,22] Supramarginal gyrus and angular gyrus demonstrate the experienced trauma association with BPD.[21] Although there is a similarity of clinical signs shared by both disorders, BPD primarily affects the fronto-limbic network, in particular the amygdala and hippocampus, while BD affects both cortical and subcortical areas.[22,23] Abnormalities in the amygdala explain the hypersensitivity to emotionally salient stimuli in BPD patients, especially negative stimuli.[22] Previous functional studies have suggested a link between amygdala hyperactivation and emotional dysregulation, and alterations in the amygdala and parahippocampal gyrus were reported as more frequent in BPD than in BD.[24–26] Neuroimaging studies suggest that dysfunctional fronto-limbic brain regions underlie the emotional dysfunction in BPD.[27] Several studies have associated the impulsivity of bipolar disorder with dysfunctions in the interplay of cortical-limbic circuits.[25,28]

Although some studies have focused on brain activity after treatment, the results have been mixed. In some studies, the hippocampus was found to have increased activation in BD patients after treatment.[29] However, in another study, decreased activity was found in the same area after psychoeducation.[30] Bertsch et al[31] found increased activity in the amygdala in BPD patients after treatment, and Carmona i Farrés et al[32] found increased activity in the insula after dialectical behavioral therapy (DBT). Lischke et al[33] found decreased activity in the amygdala and insula in BPD patients. Thus, one of the aims of the present study was to explore whether similar changes in brain activity occur after treatment for BD and BPD.

We found that studies on both disorders have shown differences in the alterations of brain regions after different treatments, and there is no unified study. Though it is not yet clear what brain regions are significantly activated after psychotherapy or drug therapy, it is suggested that psychotherapy affected advanced functional brain areas, such as the frontal area, while drug therapy affected limbic areas in most studies. To the best of our knowledge, no meta-analysis has studied the neural mechanism of BD and BPD after various treatments, which we want to explore. Thus, in this study, we also hypothesized that psychotherapy affects mostly the frontal regions and drug therapy affects mostly the limbic regions, such as cingulate gyrus. Some brain regions of neural circuit associated with emotional regulation, such as amygdala, are affected in both BD and BPD after treatments. In sum, the aims of this meta-analysis were to identify the brain activation changes in the treatment of BD and BPD, evaluate the similarities and differences of the neurologic mechanisms of these two disorders caused by the treatments, and determine the distinctions between different types of treatments (psychotherapy and drug therapy). This information can help clinicians distinguish treatment efficacy between BD and BPD and clarify the neural mechanism of treatment for these two diseases.

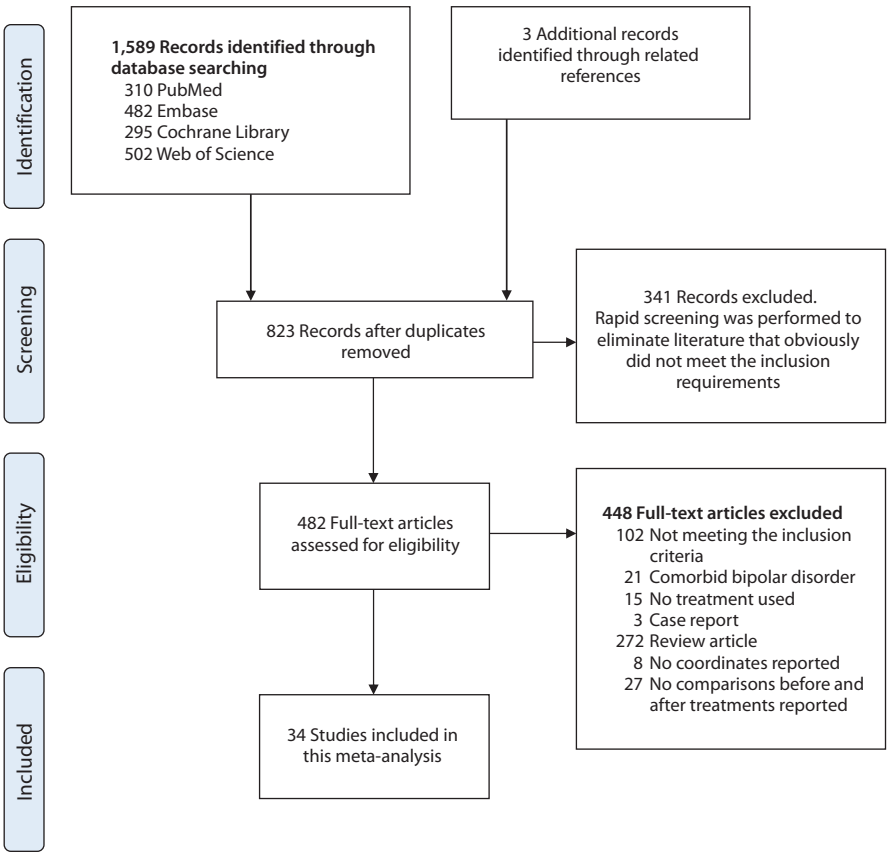
METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[34]; it was organized by adhering to previously recommended guidelines for transparent and comprehensive reporting of methodology and results. The PROSPERO ID of the protocol for this systematic review is CRD42021246626.

Literature Search

To identify relevant studies, a comprehensive systematic search was conducted in the PubMed, Embase, Cochrane Library, and Web of Science databases. Eligible studies on BD published until June 10, 2021, were identified based on the following keyword groupings (subject word and random word): (*a*) "bipolar disorder," "fMRI," "drug therapy" and (*b*) "bipolar disorder," "fMRI," "psychotherapy." Eligible studies on BPD were based on the following keyword groupings: (*a*) "borderline personality disorder," "fMRI," "drug therapy" and (*b*) "borderline personality disorder," "fMRI," "psychotherapy." When using psychotherapy and drug therapy keywords, we also added specific psychological treatments and medicines that are commonly used. Psychological treatments were cognitive behavioral therapy, mindfulness-based cognitive therapy, dialectical behavior therapy, family-focused therapy, cognitive therapy, group therapy, mentalization-based treatment, transference focused therapy, schema therapy, emotion-focused treatment, supportive therapy, counseling, psychoeducation, and interpersonal therapy. Medicines were antidepressants, antipsychotics, mood stabilizers, and lithium.

Figure 1. Flow Diagram of Study Selection



To ensure that we did not miss the matching literature, we also manually searched existing meta-analysis and review references on related topics. After removing duplicates, all the abstracts were screened for suitability by 2 independent raters.

Inclusion criteria for the eligible studies were (1) patients with a clinical diagnosis of BD or BPD according to the *DSM-5*; (2) neuroimaging studies using functional magnetic resonance imaging (fMRI); (3) the study employed the entire brain and not just a region of interest analysis; (4) the 3-dimensional (3D) coordinates of the peak activations in the stereotactic space of the Montreal Neurologic Institute (MNI) or Talairach were reported; (5) the research required treatment or intervention for patients with BD or BPD, and the type of treatment or intervention included pharmacologic or psychological therapies; (6) the study reported the results of changes in brain activation after treatment, assessing the effects of therapy relative to a before-treatment condition.

A study was excluded if it (1) was a review or a meta-analysis of the literature, (2) used a single case report format, or (3) used normal subjects as the control group and reported brain activation differences between the patient group and the healthy control group.

Data Extraction

We evaluated the interrater reliability of the title and abstract screening ($\kappa = 0.90$) and full-text screening ($\kappa = 0.91$). They both reflected excellent agreement. Data extraction was completed by 2 reviewers (J. L. and M. L.). In addition to extracting basic information about the study (sample size, average age, sex, years of education, disorder type, treatment, treatment time), we also extracted the coordinates of the results and coordinate space.

Activation Likelihood Estimation

Activation likelihood estimation (ALE) is a coordinate-based meta-analysis technique that models the voxel-wise spatial convergence of activation foci gleaned from published studies after they are modeled in common stereotactic space. This approach treats foci as 3-dimensional Gaussian probability distributions centered at the given coordinates.[35] The width of the probability distribution is determined by empirical estimates of the between-subject or between-template variance associated with each single focus, resulting in a random-effects analysis.

GingerALE software (version 2.3.1) from the BrainMap Project was used to conduct the ALE meta-analyses of the eligible studies.[36] This meta-analysis was conducted in MNI space with the Lancaster transformation applied to the coordinates originally reported in Talairach space.[36,37] For inconsistent coordinates in different spaces, we used the function provided by GingerALE to convert the coordinates from Talairach space to MNI space. ALE results were reported onto an MNI brain template using the

Table 1. Demographics and Clinical Details of Included fMRI Studies

Study	Number of patients	Average age (y)	Sex (F/M)	Education (y)	Type	Treatment	Time	Coordinate space	Number of foci
Deckersbach et al, 2018[41]	32	40.28 (13.58)	16/16	15.07 (1.58)	BD	CBT/SP	18 weeks	MNI	7
Ives-Deliperi et al, 2013[42]	23	37.6 (9.3)	14/9	NR	BD	MBCT	8 weeks	Talairach	2
Meusel et al, 2013[43]	73	48.19 (9.0)	58/15	15.6 (3.52)	BD	Cognitive remediation	10 weeks	Talairach	14
Diler et al, 2013[29]	10	15.6 (0.9)	8/2	NR	BD	Individual psychotherapy and medication	6 weeks	MNI	6
Favre et al, 2013[30]	16	40.4 (11.8)	9/7	NR	BD	Psychoeducation therapy	3 months	MNI	8
Venza et al, 2016[44]	27	45.8 (12.9)	16/11	16.0 (1.8)	BD	Cognitive training	4 weeks	MNI	1
Diler et al, 2013[45]	10	15.6 (0.9)	8/2	NR	BD	Individual psychotherapy and medication	6 weeks	MNI	5
Garrett et al, 2021[46]	40	13.57 (2.73)	20/20	NR	BD	FFT	5 months	MNI	5
Haldane et al, 2008[47]	12	42.1 (11.8)	7/5	NR	BD	LTG	6 weeks	Talairach	6
Jogia et al, 2008[48]	12	42.1 (11.8)	7/5	NR	BD	LTG	12 weeks	Talairach	8
Marchand et al, 2007[49]	10	43.4 (11.9)	0/10	NR	BD	Psychiatric medications	11 months	MNI	2
Passarotti et al, 2011[50]	17	14.29 (2.05)	12/5	NR	BD	SGA and LTG	14 weeks	Talairach	5
Pavuluri et al, 2012[69]	22	12.37 (2.08)	6/16	NR	BD	Risperidone and divalproex	6 weeks	MNI	22
Pavuluri et al, 2012[51]	21	12.77 (2.16)	9/12	NR	BD	Risperidone and divalproex	6 weeks	Talairach	6
Pavuluri et al, 2011[52]	24	12.65 (2.05)	8/16	NR	BD	Risperidone and divalproex	6 weeks	Talairach	7
Pavuluri et al, 2010[53]	17	14.3 (1.1)	11/6	NR	BD	SGA and LTG	14 weeks	Talairach	16
Yang et al, 2013[54]	13	13.25 (2.27)	4/9	NR	BD	Pharmacotherapy	16 weeks	Talairach	12
Miskowiak et al, 2016[55]	30	39 (12)	13/5	15 (4)	BD	EPO	14 weeks	MNI	5
Miskowiak et al, 2018[56]	18	39 (12)	13/5	15 (2)	BD	EPO	15 weeks	MNI	5
Chang et al, 2018[57]	23	15.66 (1.87)	9/14	NR	BD	Quetiapine	8 weeks	MNI	3
Strakowski et al, 2016[58]	42	18 (5)	17/25	NR	BD	Lithium and quetiapine	8 weeks	Talairach	3
Miskowiak et al, 2016[59]	62	40.97 (11.44)	41/21	15 (3.49)	BD	EPO	14 weeks	MNI	5
Dandash et al, 2018[60]	39	21.45 (2.20)	9/30	NR	BD	Quetiapine and lithium	12 months	MNI	1
Carmona i Farrés et al, 2019[32]	65	32.37 (7.88)	58/7	NR	BPD	DBT	10 weeks	MNI	2
Driessen et al, 2008[61]	13	33 (8.8)	13/0	11.1 (1.6)	BPD	DBT	1 year	Talairach	24
Niedtfeld et al, 2017[62]	52	26.79 (6.84)	52/0	NR	BPD	DBT	12 weeks	MNI	2
Paret et al, 2016[63]	8	33.6 (9.5)	8/0	NR	BPD	DBT	12 weeks	MNI	6
Perez et al, 2016[64]	10	27.8(NR)	10/0	NR	BPD	TFP	1 year	MNI	17
Schmitt et al, 2016[65]	32	28.09 (7.29)	32/0	NR	BPD	DBT	12 weeks	MNI	29
Schnell and Herpertz, 2007[66]	6	23.7 (4.8)	6/0	NR	BPD	DBT	12 weeks	Talairach	21
Winter et al, 2016[67]	31	28.17 (7.47)	31/0	NR	BPD	DBT	12 weeks	MNI	6
Bertsch et al, 2013[31]	38	24.05 (5.40)	38/0	11.65 (1.59)	BPD	Oxytocin	NR	MNI	5
Lischke et al, 2017[33]	47	26.47 (5.82)	47/0	NR	BPD	Oxytocin	NR	MNI	4
Metz et al, 2019[68]	17	26.82 (4.79)	17/0	11.76 (1.52)	BPD	Hydrocortisone	1 week	MNI	5

Abbreviations: BD = bipolar disorder, BPD = borderline personality disorder, CBT = cognitive behavior therapy, DBT = dialectical behavioral therapy, EPO = erythropoietin, F = female, FFT = family-focused therapy, fMRI = functional magnetic resonance imaging, LTG = lamotrigine, M = male, MBCT = mindfulness-based cognitive therapy, MNI = Montreal Neurologic Institute, NR = not reported, SGA = second-generation antipsychotic, SP = supportive psychotherapy, TFP = transference-focused psychotherapy.

Mango software package. Based on the recommendations of Eickhoff et al,[38] we applied a *P* value threshold at $P < .001$ and a minimum cluster of 250 mm^3.

ALE Meta-Analyses

This study focused on the effects of brain activation changes in BD and BPD patients as well as the influences of different treatments. Therefore, we performed the following meta-analysis: (1) based on the type of disorder, the included studies were divided into 2 groups—a BD group and a BPD group—to evaluate the consistency of changes in brain regions after treatment for different diseases; (2) based on treatment methods, the included studies were divided into 2 groups—psychotherapy studies and drug therapy studies—to evaluate the consistent activation of and changes in the brain areas of patients with BD and BPD receiving different treatments. Each meta-analysis has its own ALE result graph and cluster report.

This study reports the activation clusters of brain regions and their maximum ALE values for each meta-analysis. The maximum ALE value represents the activation probability of the brain area.[39] To better present the data results, we used Mango software (http://ric.uthscsa.edu/mango/) to superimpose the coordinates into a standard brain.[40]

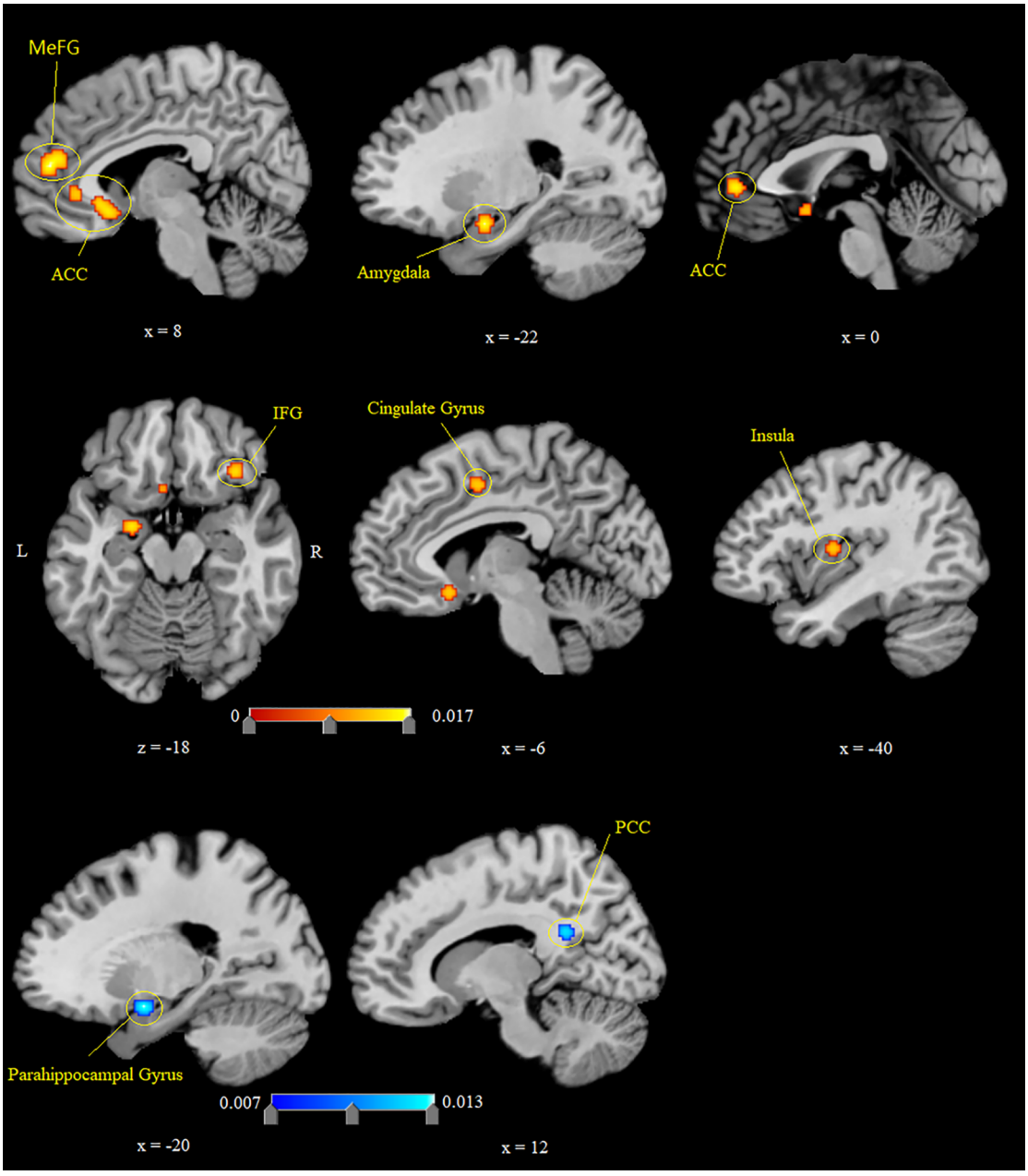
RESULTS

Literature Search

The flow diagram of the selection process based on the PRISMA statement is shown in Figure 1. The preliminary search identified 1,589 articles and 3 additional articles after a reference search. After removing duplicates, we obtained 823 articles. Of these, 341 articles were excluded on the basis of title and abstract. After the full-text articles were evaluated, 34 articles met the inclusion criteria and were considered eligible.

The demographics, imaging status, treatment methods, coordinate space, and methodological details extracted from each study are shown in Table 1. The results reported the changes before and after treatment in each group. Therefore,

Figure 2. Similar Changes in Brain Regions Modulated by Different Treatments[a]



[a]Red indicates areas with increased activation; blue indicates areas with reduced activation; color rulers indicate the ALE values.
Abbreviations: ACC = anterior cingulate cortex, ALE = activation likelihood estimation, IFG = inferior frontal gyrus, MeFG = medial frontal gyrus, PCC = posterior cingulate cortex.

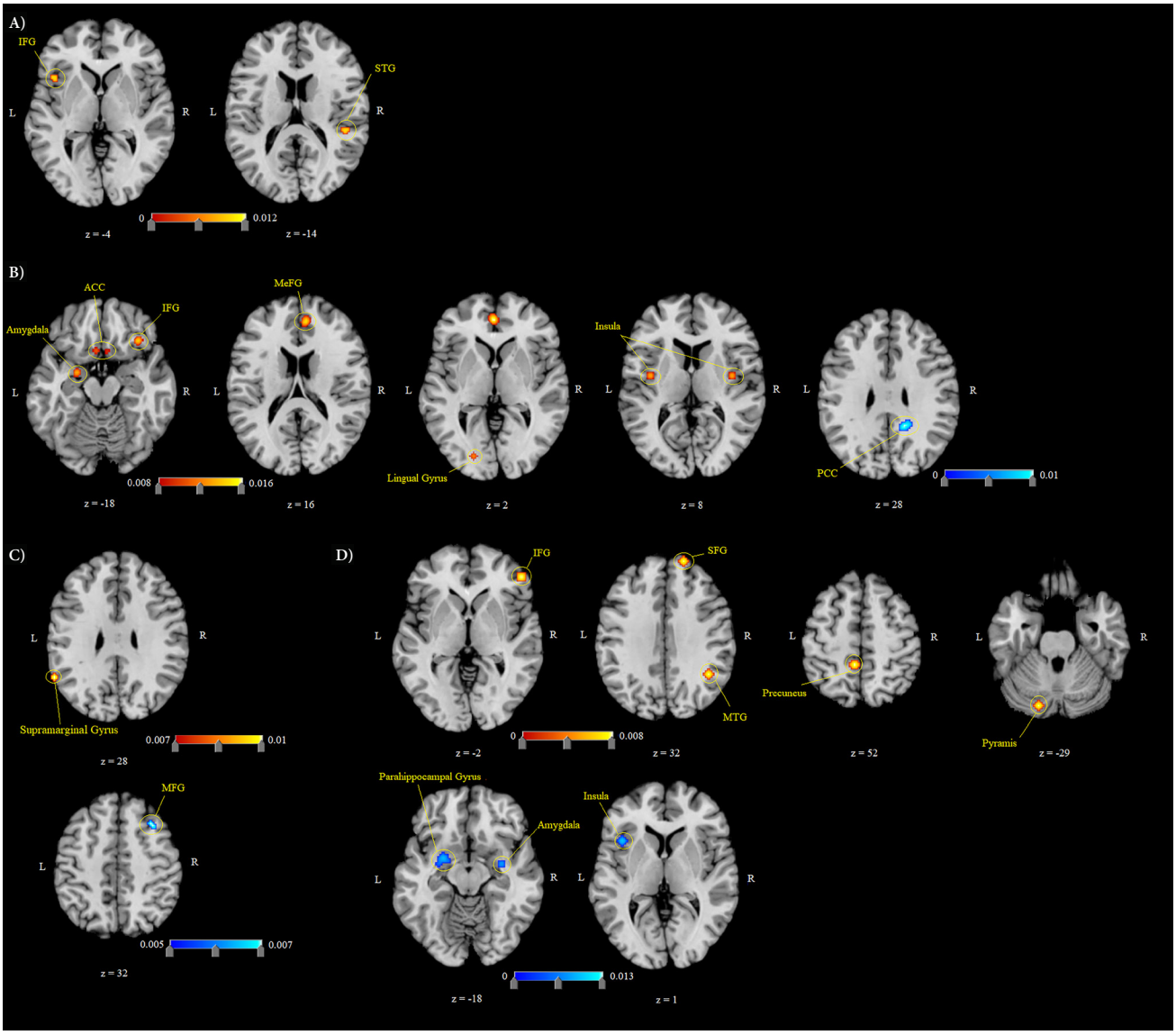
these documents are divided into substudies of multiple samples, so all the documents contain a total of 34 small studies, which are all written in English. Twenty-three of the studies are on BD, and 11 are on BPD. When categorized by treatment, 14 of the 34 studies used psychotherapy, 18 studies used drug therapy, and 2 studies used a combination of 2 treatment methods.

Similar Changes in Brain Regions Modulated by Different Types of Treatment

A total of 34 studies were included in the ALE meta-analysis, resulting in 912 subjects. A total of 186 activity increase points and 90 activity decrease points were extracted from these studies. After combining the calculations, there were 12 increased activation clusters and 2 decreased activation clusters.

To elucidate the brain regions modulated by treatment, we first conducted meta-analyses to identify the convergent increased or decreased activation brain regions. Treatments were associated with activity increases in the bilateral anterior cingulate cortex (ACC), right medial frontal gyrus (MeFG), left amygdala, right inferior frontal gyrus (IFG), left cingulate gyrus (CG), left insula, and right claustrum. Treatments were associated with activity decreases in the left

Figure 3. Brain Activity in Bipolar Disorder (BD) and Borderline Personality Disorder (BPD): (A) Brain Activity in BD After Psychotherapy, (B) Brain Activity in BD After Drug Therapy, (C) Brain Activity in BPD After Psychotherapy, and (D) Brain Activity in BPD After Drug Therapy[a]



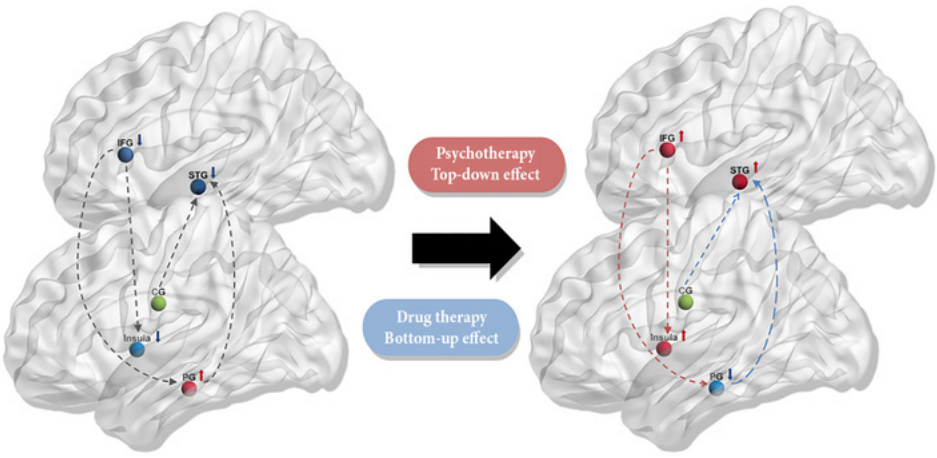
[a]Red indicates areas with increased activation; blue indicates areas with reduced activation; color rulers indicate the ALE values.
Abbreviations: ACC = anterior cingulate cortex, ALE = activation likelihood estimation, IFG = inferior frontal gyrus, MeFG = medial frontal gyrus, MFG = middle frontal gyrus, MTG = middle temporal gyrus, PCC = posterior cingulate cortex, SFG = superior frontal gyrus, STG = superior temporal gyrus.

parahippocampal gyrus (PG) and right posterior cingulate cortex (PCC) (Figure 2, Supplementary Table 1).

Results of Different Disorders and Treatments

The studies were categorized based on the treatment method: psychotherapy or drug therapy. Information about the activated brain regions after treatment is presented in Supplementary Table 2. In the BD group, after receiving psychotherapy, the activity of the IFG and the superior temporal gyrus (STG) increased (Figure 3A). After drug therapy, the activity of the ACC, MeFG, IFG, amygdala, lingual gyrus (LG), angular gyrus (AG), insula, and claustrum increased, and the activity of the PCC decreased (Figure 3B). In the BPD group, after psychotherapy, the activity of the supramarginal gyrus (SG) increased, and the activity of the middle frontal gyrus (MFG) decreased (Figure 3C). After drug therapy, the activity of the IFG, middle temporal gyrus (MTG), superior frontal gyrus (SFG), and precuneus increased, and the activity of the PG, insula, and amygdala decreased (Figure 3D). Information about the activated brain regions after treatment is presented in Supplementary Table 3. The results of activity in the brain regions after psychotherapy and drug therapy for BD and BPD are shown in Supplementary Table 4. These results suggest that psychotherapy and drug therapy use different therapy mechanisms.

Figure 4. Hypothetical Model of Psychotherapy and Drug Therapy[a,b]



[a]Blue represents decreased activity, red represents increased activity, and green indicates that the area has experienced activation and deactivation.
[b]Before treatments, both disorders showed abnormally reduced activation of the IFG, STG, ACC, and insula and increased activation of the PG and PCC. Psychotherapy reduces PG and PCC activity by increasing the activity of the IFG and STG (psychotherapy produces a top-down effect by activating the activity of the frontal area and temporal area). Drug therapy increases brain activity in the IFG and STG by reducing the activity in the PG and ACC and increasing the activity in the insula (drug therapy produces a bottom-up effect by reducing the limbic area).
Abbreviations: ACC = anterior cingulate cortex, CG = cingulate gyrus, IFG = inferior frontal gyrus, PCC = posterior cingulate cortex, PG = parahippocampal gyrus, STG = superior temporal gyrus.

DISCUSSION

To the best of our knowledge, this is the first ALE meta-analysis of brain imaging research to explore the similarities and differences in the neurobiological results of psychotherapy and drug therapy for BD and BPD. Thirty-four studies met the filtering criteria, including 23 studies on BD and 11 on BPD. We used the ALE method to analyze the consistency of brain activation in these studies. The distinction under different conditions was further explored by disorder types and treatments.

Similar Changes in Brain Regions After Different Treatments

Previous studies have found that both disorders have functional and structural abnormalities in the default mode network (DMN).[70,71] The present study found that the activation of the brain area of the neural circuit changed after the treatments.

The PCC is an important part of the DMN; it plays a crucial role in memory and self-reference processing.[72] A study found that the activation within the PCC was greater in the BPD patients in comparison to the healthy controls, but less activation was seen in the amygdala.[73] BD seems to be associated with changes in the frontal and posterior DMN structures, especially the prefrontal lobe and PCC.[70] Additionally, damage to the PG may lead to abnormalities in emotion processing and cognition, which are part of the DMN.[74] Altered activity in the regions of the DMN may reflect the barriers of interpersonal and emotional adjustment, and these changes could underlie the core symptoms in BPD.[71] The present study found that the neural circuit of DMN changed after the two types of treatment. This suggests that treatment may change these brain activation levels by acting on the abnormal brain neural circuit, so as to "normalize" its activity and improve symptoms.

In the fronto-limbic network, prefrontal cortices (such as dorsolateral prefrontal cortex [DLPFC] and MeFG) and marginal structures (such as the amygdala and ACC) are most often involved in the regulation of emotions.[75] Malhi et al[76] suggested that fronto-limbic network dysfunction underpins both BD and BPD. Our study found that the function of the fronto-limbic network (MeFG, ACC, and amygdala) improved after treatment. This further suggests that the treatment may change these abnormal brain neural circuits in BD and BPD.

Brain Areas Activated in BD and BPD

We found that after treatments, the activated brain areas of BD and BPD are different. These results demonstrate that there are more brain areas in which the activity changes in BD than in BPD. This difference may be due to differences in the patients' neurobiology, or it may be due to the limited number of articles using fMRI scans after treatment. Although emotional instability is a conspicuous feature of both disorders, their mechanisms are different. The emotional regulation defect of BPD is related to abnormal activity in the frontal and limbic areas.[77]

Our results indicated that activated brain areas after psychotherapy are different between BD and BPD. It has been proven that supramarginal gyrus is related to mood regulation and empathy for pain.[78] When patients with BPD viewed angry faces, they showed lower activation in the left SG.[79] This may indicate that the treatment improved empathy in BPD, activating the associated brain regions. ACC is an important brain region for evaluating

and controlling subjective emotional response.[78,80] Studies reported abnormal function activation of the frontal-limbic system in BD patients, including ACC.[81] We found that after drug therapy, activity was increased in the precuneus in BPD. Precuneus, which is vital in the DMN, participates in reflection, self-related processing, empathy, self-consciousness, and episodic memory.[82,83] One study preliminarily demonstrated that there were differences in the DMN between BPD patients and controls.[84] Treatment was found to decrease activation in the amygdala in this study, perhaps because treatment regulates overreaction to emotions of BPD. A study by Herpertz et al[85] found that BPD patients showed greater activation in the amygdala compared to the control group, probably reflecting an attempt to reconcile response to strong emotions. While amygdala was found to have increased activation in BD, this may indicate that treatment improved the depressive state of BD and shifted the patient's reactions to emotions to a normal state. The results are consistent with previous findings that indicated individuals with BPD have abnormalities in the temporal lobe and limbic regions associated with emotional instability.[86] In the BPD group, the activation of SFG and PG changed after treatment, demonstrating that treatment regulates a patient's mood by altering abnormal brain regions. After treatments, the activity of the insula was found to increase in the BD group and decrease in the BPD group. This may be because in BD, insufficient emotional regulation is a problem. For emotional stimulation, the BD group showed dysfunction of the limbic brain network, including the amygdala, insula, and other brain areas.[87] In the BPD group, it is easier to notice negative emotions before treatment, leading to increased activation in the insula; therefore, after treatment, the activation of the insula in the BPD group decreased.

To summarize, we propose that treatment achieves a therapeutic effect by regulating the activity of the DMN circuit and mood-related brain regions to "normalize" them. Specifically, the brain regions with abnormally increased activation showed decreased activation after treatment, and brain regions with abnormally decreased activation showed increased activation after treatment to relieve the symptoms of these disorders and achieve therapeutic results.

Brain Areas Activated by Different Treatments

This separate meta-analysis found differences in the activated brain regions between the 2 types of treatment. The frontal lobe and temporal lobe were the primary brain areas in which the activity changed after psychotherapy; after drug therapy, the brain activity changed mostly in the limbic area, including the CG and PG. These results may suggest that drug therapy and psychotherapy work through different mechanisms.

Psychotherapy changed the activity mostly in the frontal lobe, which is related to cognitive control, emotion, and memory. Kupferschmidt and Zakzanis[88] found weak frontal lobe activity in untreated BD, and they also observed differences in the brain activation of STG between the BD and the healthy group. The STG was found to be correlated to emotion processing deficits and other symptoms.[89] Our study found that in the BPD group psychotherapy decreased activity in the MFG, which is a part of the DLPFC that plays a vital role in emotional regulation and inhibition of unneeded memories.[90] This suggests that psychotherapy could enable BPD patients to manage their emotions and improve symptoms of mood instability. In motion tasks, BD patients showed poorly controlled balance,[91] which may indicate that abnormality in the IFG leads to dysmotility in BD. Given that the frontal lobe and temporal lobe are activated by treatment, we can speculate that psychotherapy could restore the brain activity of BD and BPD patients to a normal state.

After drug therapy, activity was increased in the IFG in both BD and BPD patients. The potential neurobiology of mood regulation disorders with BD is assumed to involve an abnormal increase in the limbic regions and decreased activation of the frontal lobe.[92] It has been reported that IFG in BD was deactivated during emotional face processing, and this was ameliorated by medication.[93] In BPD, dysregulation of emotion is associated with reduced IFG activation.[94] IFG is part of the ventrolateral prefrontal cortex (VLPFC). In view of VLPFC's role in the regulation of emotions,[95] we assume that deficits in the emotional regulation of BD and BPD patients can be ameliorated by IFG activation due to drug therapy. In addition to emotional regulation deficits, BD is characterized by cognitive impairment.[96] MeFG has been shown to play a role in cognitive control.[97] Low activation of specific subregions in a cognitive control network located in the MeFG has been described in BD.[98] Drug therapy increased activity in the MeFG, which may indicate BD patients can more effectively regulate their emotions after undergoing therapy. However, we found decreased MeFG activity in BPD; this could be due to the fact that, before treatment, BPD patients are keen about avoiding negative emotions, so they use more cognitive control resources. It is known that BPD displays an overlap of some symptoms with BD, such as affective instability. Functional studies have shown abnormal bilateral DLPFC and amygdala activation in BPD and abnormal frontal and amygdala activation in BD.[99] There are various abnormalities in the prefrontal attention network and mechanism of inhibitory control, which may lead to impulsivity and poor regulation of top-down emotion. In our meta-analysis, we found alterations of frontal areas and limbic areas in both disorders. It may be inferred that treatments worked by targeting the common brain regions to achieve the effect of treating common symptoms.

A review[100] summarized the effect of drug therapy on BD and found that it can affect the brain activation of the prefrontal lobe in emotion processing and non-emotional cognitive tasks. In our results, drug therapy increased brain activity in the IFG in the BD group. The right IFG is related to emotion and cognitive control.[101] In the present study, we found that ACC, MeFG, and IFG were involved in

processing emotions in BD, and the insula was activated after drug therapy in both the BD and BPD groups, showing that this area plays a role in the wider regulation of antidepressant response and relief.[102] Additionally, we found that activity was decreased in the PCC and increased in the ACC after drug therapy in the BD group. Abnormal activation of the CG can be used as a potential diagnostic marker and neurofeedback target for depression,[103] while the activation of the CG changed after drug therapy. These findings suggest that these brain areas could be markers for determining the effect of treatment.

Taken together, these results suggest that, for BD and BPD, activation of the frontal area, including the IFG, STG, and MFG, changed after psychotherapy, while activation of PG and CG changed after drug therapy. The brain activity changes produced by psychotherapy are mostly in the frontal areas, which is related to advanced brain function, like cognitive control, emotional regulation, and memory, while drug therapy primarily impacts the limbic area, which is related to emotion and attention. The difference may be due to the fact that these two treatments work with distinct mechanisms such that drug therapy has a bottom-up effect, especially reducing the excessive activity of the peripheral structure, while psychotherapy has a top-down effect, which tends to increase the activity in and recruitment of the frontal area.[104] Drug therapy can quickly relieve symptoms; psychotherapy provides broader symptom improvement and longer-lasting effects after treatment.[105]

We can speculate that both types of treatment regulate the activity of related brain regions and might "normalize" functional brain abnormalities in specific ways, so as to achieve the therapeutic effect. Based on the emotional circuit, we propose the hypothesis of the respective mechanisms of psychotherapy and drug therapy (Figure 4) on the basis of the meta-analysis results. Psychotherapy produces a top-down effect by increasing the activity of the frontal area and temporal area, and drug therapy produces a bottom-up effect by decreasing the activity of the limbic area, resulting in greater activation in the IFG and less activation in the PG. These treatments have an effect on the patient's emotional circuit in their own ways to "normalize" the corresponding brain region activation, thereby alleviating the symptoms.

Limitations

This analysis has some limitations. First, the number of studies using fMRI after administering different types of therapies is limited and unbalanced across different conditions. As far as we know, only a few have used fMRI scans to compare the data measured before and after treatment; This limited the number of articles we included in the analysis. Second, most of the BPD subjects in the included articles are women, which limits the applicability of the results of this analysis. Third, we included only 1 imaging method and 2 types of treatment. In future studies, we can consider other neuroimaging methods and include non-invasive brain stimulation therapies in order to explore the effect and mechanism of that kind of treatment. Furthermore, due to the limitation of the number of studies, when exploring the differences in the consistency of the changes under different conditions, only 1 condition can be controlled at a time. This may be affected by the interaction of other regulatory factors, such as age and gender.

CONCLUSION

In conclusion, we analyzed the similarities and differences in the activation of areas in the brain in BD and BPD groups after treatments, and we analyzed the disorder type, treatment method, and imaging task type as moderating variables. We found that the activation of brain areas in BD and BPD is consistent, but there are also differences in the activation of those areas after undergoing different types of treatment. The differences in brain regions activated by psychotherapy and drug therapy may be due to the different mechanisms of therapeutic action. We posit that drug therapy might have a bottom-up effect, while psychotherapy might have a top-down effect. This meta-analysis may contribute to prediction of treatment efficacy in BD and BPD and identification of more accurate neuroimaging biomarkers for the treatment of these two disorders.

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Supplementary Material

Article Title: The Neuropsychological Mechanism of Treatment of Bipolar Disorders and Borderline Personality Disorders: Activation Likelihood Estimation Meta-Analysis of Brain Imaging Research

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List of Supplementary Material for the article

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Supplementary Materials

Supplementary Table 1 Overall analysis of two disorders after treatments.

Brain Region	Hemisphere	BA	Cluster Size (mm^3)	MNI			ALE	Z
				x	y	z		
Overall increase:								
Anterior Cingulate	R	25	1248	6	18	-14	0.015	4.11
Medial Frontal Gyrus	R	9	1120	6	50	12	0.017	4.46
Amygdala	L	NA	496	-22	-4	-20	0.017	4.44
Anterior Cingulate	L	32	432	0	46	0	0.016	4.31
Anterior Cingulate	R	24	352	8	36	-2	0.014	3.92
Inferior Frontal Gyrus	R	47	328	36	26	-18	0.014	3.98
Cingulate Gyrus	L	24	272	-6	2	46	0.013	3.74
Insula	L	13	256	-40	-8	8	0.013	3.66
Claustrum	R	NA	256	38	-8	8	0.013	3.66
Overall decrease:								
Parahippocampal Gyrus	L	34	688	-20	-2	-18	0.013	4.49
Posterior Cingulate	R	30	416	12	-48	24	0.011	4.11

Supplementary Table 2 Analysis of psychotherapy and drug therapy in BD.

Brain Region	Hemisphere	BA	Cluster Size (mm^3)	MNI			ALE	Z
				x	y	z		
Psychotherapy increase:								
Inferior Frontal Gyrus	L	47	344	-46	18	-4	0.012	4.17
Superior Temporal Gyrus	R	41	296	46	-34	14	0.010	3.84
Drug therapy increase:								
Anterior Cingulate	R	25	1976	6	18	-14	0.014	4.57
Medial Frontal Gyrus	R	9	1016	8	46	16	0.015	4.69
Anterior Cingulate	L	32	800	0	46	0	0.016	4.93
Inferior Frontal Gyrus	R	47	792	36	26	-18	0.014	4.60
Amygdala	L	NA	472	-24	-4	-18	0.013	4.38
Medial Frontal Gyrus	L	9	464	-6	50	18	0.013	4.35
Inferior Frontal Gyrus	L	47	456	-34	24	-18	0.014	4.49
Lingual Gyrus	L	18	456	-20	-84	2	0.014	4.49
Insula	L	47	456	-39	-6	8	0.013	4.18
Angular Gyrus	L	39	448	-30	-54	44	0.013	4.33
Frontal Lobe	L	10	312	-44	44	-8	0.011	3.85
Medial Frontal Gyrus	R	6	288	6	-10	74	0.011	3.91
Drug therapy decrease:								
Posterior Cingulate	R	31	520	16	-46	28	0.010	4.43

Supplementary Table 3 Analysis of psychotherapy and drug therapy in BPD.

Brain Region	Hemisphere	BA	Cluster Size (mm^3)	MNI			ALE	Z
				x	y	z		
Psychotherapy increase:								
Supramarginal Gyrus	L	40	304	-60	-54	28	0.009	3.74
Psychotherapy decrease:								
Middle Frontal Gyrus	R	6	280	32	22	46	0.007	3.71
Drug therapy increase:								
Inferior Frontal Gyrus	R	46	384	51	41	-2	0.008	3.88
Middle Temporal Gyrus	R	39	352	42	-52	31	0.008	3.98
Superior Frontal Gyrus	R	8	352	18	56	31	0.008	3.98
Precuneus	L	7	352	-6	-43	52	0.008	3.98
Drug therapy decrease:								
Parahippocampal Gyrus	L	34	1560	-20	-2	-18	0.013	5.11
Insula	L	13	368	-40	16	1	0.010	4.13
Amygdala	R	NA	256	32	-6	-14	0.008	3.68

Supplementary Table 4 Analysis of psychotherapy and drug therapy in two disorders.

Brain Region	Hemisphere	BA	Cluster Size (mm^3)	MNI			ALE	Z
				x	y	z		
Psychotherapy increase:								
Superior Temporal Gyrus	R	41	400	50	-32	10	0.011	3.68
Inferior Frontal Gyrus	L	NA	280	-46	18	-4	0.012	3.85
Anterior Cingulate	R	24	264	6	36	-4	0.012	3.88
Psychotherapy decrease:								
Middle Frontal Gyrus	R	6	280	32	22	46	0.007	3.71
Drug therapy increase:								
Anterior Cingulate	R	25	1904	6	18	-14	0.014	4.47
Medial Frontal Gyrus	R	9	944	8	46	16	0.015	4.59
Anterior Cingulate	R	47	768	0	46	0	0.016	4.84
Inferior Frontal Gyrus	L	32	752	36	26	-18	0.014	4.49
Inferior Frontal Gyrus	L	47	456	-34	24	-18	0.014	4.39
Lingual Gyrus	L	18	456	-20	-84	2	0.014	4.39
Insula	L	NA	448	-39	-6	8	0.013	4.15
Claustrum	R	NA	448	38	-8	8	0.013	4.15
Amygdala	L	NA	432	-24	-4	-18	0.013	4.28
Medial Frontal Gyrus	L	9	400	-6	50	18	0.013	4.25
Angular Gyrus	L	39	384	-30	-54	44	0.013	4.23
Drug therapy decrease:								
Parahippocampal Gyrus	L	34	816	-20	-2	-18	0.013	4.64
Posterior Cingulate	R	30	440	12	-48	24	0.011	4.31