Association between the fronto-limbic network and cognitive and emotional functioning in individuals with bipolar disorder: a systematic review and meta-analysis

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Association Between the Fronto-Limbic Network and Cognitive and Emotional Functioning in Individuals With Bipolar Disorder
A Systematic Review and Meta-analysis

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IMPORTANCE Individuals with bipolar disorder (BD) experience cognitive and emotional dysfunctions. Various brain circuits are implicated in BD but have not been investigated in a meta-analysis of functional magnetic resonance imaging (fMRI) studies.

OBJECTIVE To investigate the brain functioning of individuals with BD compared with healthy control individuals in the domains of emotion processing, reward processing, and working memory.

DATA SOURCES All fMRI experiments on BD published before March 2020, as identified in a literature search of PubMed, Embase, Web of Science, Cochrane Library, PsycInfo, Emcare, Academic Search Premier, and ScienceDirect. The literature search was conducted on February 21, 2017, and March 2, 2020, and data were analyzed from January 2021 to January 2022.

STUDY SELECTION fMRI experiments comparing adult individuals with BD and healthy control individuals were selected if they reported whole-brain results, including a task assessing at least 1 of the domains. In total, 2320 studies were screened, and 253 full-text articles were evaluated.

DATA EXTRACTION AND SYNTHESIS A total of 49 studies were included after selection procedure. Coordinates reporting significant activation differences between individuals with BD and healthy control individuals were extracted. Differences in brain region activity were tested using the activation likelihood estimation method.

MAIN OUTCOMES AND MEASURES A whole-brain meta-analysis evaluated whether reported differences in brain activation in response to stimuli in 3 cognitive domains between individuals with BD and healthy control individuals were different.

RESULTS The study population included 999 individuals with BD (551 [55.2%] female) and 1027 healthy control individuals (532 [51.8%] female). Compared with healthy control individuals, individuals with BD showed amygdala and hippocampal hyperactivity and hypoactivation in the inferior frontal gyrus during emotion processing (20 studies; 324 individuals with BD and 369 healthy control individuals), hyperactivation in the orbitofrontal cortex during reward processing (9 studies; 195 individuals with BD and 213 healthy control individuals), and hyperactivation in the ventromedial prefrontal cortex and subgenual anterior cingulate cortex during working memory (20 studies; 530 individuals with BD and 417 healthy control individuals). Limbic hyperactivation was only found during euthymia in the emotion and reward processing domains; abnormalities in frontal cortex activity were also found in individuals with BD with mania and depression.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis revealed evidence for activity disturbances in key brain areas involved in cognitive and emotion processing in individuals with BD. Most of the regions are part of the fronto-limbic network. The results suggest that aberrations in the fronto-limbic network, present in both euthymic and symptomatic individuals, may be underlying cognitive and emotional dysfunctions in BD.

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Bipolar disorder (BD) is a severe psychiatric disorder characterized by recurrent depressive and manic episodes.[1] These mood fluctuations contribute considerably to functional impairments, including dysfunction in education and work.[2] In addition to affective symptoms, individuals with BD show cognitive impairments and emotion regulation deficits during episodes and also during euthymia.[3-5] As a result, several of these deficits in individuals with BD may be considered trait-associated characteristics of BD. Abnormalities in a variety of brain regions and related circuitry could be underlying cognitive and emotion regulation deficits in individuals with BD, with studies in general describing predominantly aberrations in the fronto-limbic network,[6-9] a group of interconnected neural regions including the prefrontal cortex (PFC), amygdala, anterior cingulate cortex (ACC), hippocampus, and nucleus accumbens.[10]

Individuals with BD appear to show amygdala hyperactivation during emotion processing across multiple tasks that evoke emotional responses.[11] In addition, recent work shows reduced functional connectivity between the ventrolateral PFC, ACC, orbitofrontal cortex (OFC), and limbic areas, which points toward a more complex aberrant interplay between frontal and limbic structures instead of amygdala hyperactivity alone.[10] In addition to emotion, individuals with BD show increased activity in fronto-limbic regions during reward processing, such as in the PFC, ACC, and striatum.[12-14] Studies of working memory in individuals with BD have reported deviant frontal cortex activity,[15-17] including medial frontal gyri hyperactivation[18] and dorsolateral PFC (dlPFC) hypoactivation.[19-21]

Inconsistent findings are common across all emotional and cognitive domains. As a result, a robust hypothesis on fronto-limbic dysfunction in individuals with BD is lacking.[22] Not surprisingly, and probably associated with aberrant brain activity, individuals with BD show behavioral deficiencies in terms of decreased task performance during emotion and reward processing, as well as during cognitive tasks that demand working memory activity.[4,23-26] In addition to decreased task performances, fronto-limbic network deficiencies may also be involved in aberrant psychological mechanisms in individuals with BD, such as state-independent emotional hyper-reactivity, rumination, and the intense pursuit of goals and focus on achievement.[27-29]

Cognitive and emotion tasks that involve fronto-limbic brain activity have been intensively studied. Emotion processing involves attentional processes toward emotional stimuli, their interpretation, and the regulation of activated emotions (ie, the ability to monitor and modify the occurrence, intensity, and duration of an ongoing response to emotional stimuli).[30] Activations in subcortical regions are associated with modulating and generating emotions, whereas frontal regions are involved in the evolution and regulation of emotional responses.[10,26] The 3 primary functions of reward processing include associative learning (classical conditioning and operant reinforcement), incentive salience (motivation and desire), and positively valenced emotions (pleasure and hedonic).[31] In particular, pleasure coding has been described in association with activation in the OFC,[32] whereas ACC activity is associated with reward anticipation.[33] In addition to the ACC, the ventral striatum has a key function in anticipation of reward stimuli and is part of a complex circuit involving limbic regions, such as the amygdala, attributing feelings toward the experienced reward.[34] Working memory is seen as a platform where information temporarily can be held, manipulated, and then used to adjust goal-directed behavior.[35,36] Studies of working memory have pointed to the involvement of the dlPFC, dorsal and anterior ACC, and parietal cortex.[37] The dlPFC is associated with the integration and retrieval of information that is stored.[38] The ACC is implicated in evaluative processes to adjust and adapt the received information depending on demand.[39] In addition to fronto-limbic regions, the parietal cortex seems to be a workspace for processing sensory and perceptual information.[40-42] In sum, tasks associated with emotion processing, reward processing, and working memory are all dependent on an adequate activation of fronto-limbic brain regions and can therefore be used to assess functioning in this network.

Although there is an increasing number of fMRI studies suggesting fronto-limbic functional abnormalities in individuals with BD, a meta-analysis specifically focusing on this brain network in individuals with BD, to our knowledge, has not yet been performed. A meta-analysis of fronto-limbic network activity in individuals with BD is important, as malfunctioning of this brain network can be considered as reflecting part of the pathophysiology of cognitive and emotional impairments in individuals with BD. Therefore, we conducted a systematic review and meta-analysis of fMRI studies in individuals with BD investigating emotion processing, reward processing, or working memory, domains that all rely on proper fronto-limbic network activity. By performing this systematic review and meta-analysis, we aimed to aggregate the evidence to be able to draw more rigorous conclusions regarding potential abnormalities in the fronto-limbic network in individuals with BD. Moreover, we wanted to elucidate whether trait (ie, euthymia) or state (ie, mania or depression) may be associated with potential fronto-limbic network alterations.

Key Points

Question Do individuals with bipolar disorder show aberrant brain activities in regions of the fronto-limbic network compared with healthy control individuals?

Findings This systematic review and meta-analysis consisting of 49 functional magnetic resonance imaging studies (999 individuals with bipolar disorder and 1027 healthy control individuals) examining brain activity in 3 domains (emotion processing, reward processing, and working memory) found robust activity disturbances in brain regions, mostly within the fronto-limbic network.

Meaning Aberrations in the fronto-limbic network may underlie cognitive and emotional dysfunctions in individuals with BD.

Methods

Literature Search and Selection

For the selection procedure, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline[43,44] was followed (eTable 1 in Supplement 1). The PRISMA flowchart depicting the process for the systematic literature search and selection of the studies is shown in the eFigure in Supplement 1. The literature search was conducted on February 21, 2017, and March 2, 2020, in the databases of PubMed, Embase, Web of Science, Cochrane Library, PsycInfo, Emcare, Academic Search Premier, and ScienceDirect. The following keywords were used in the literature search: *bipolar disorder*, *manic depression*, *functional magnetic resonance imaging* (*fMRI*), *mania*, and *bipolar depression* (eMethods in Supplement 1). Articles were eligible if written in English and with populations aged between 18 and 65 years. All control individuals were physically and neurologically healthy, with no current psychopathology. Exclusion criteria for all participants were medical or neurological illnesses that might influence brain function and any contraindications for receiving an MRI scan. Literature reviews, meta-analyses, methodological articles, case reports, letters, conference abstracts, and editorials were excluded. Selection of literature was conducted using 3 main inclusion criteria: task-related fMRI studies on BD with whole-brain analyses; studies had to include a task assessing at least 1 of the domains (ie, emotion processing, reward processing, or working memory); and studies that compared adult individuals with BD with healthy control individuals. fMRI studies using a region-of-interest analysis approach, those only assessing functional connectivity, and resting-state studies were excluded. Studies including only participants with high risk of BD, relatives with BD, offspring with BD, or BD in childhood (ie, younger than 18 years) were also excluded. Finally, the studies were grouped into at least 1 of the 3 domains. Data were analyzed from January 2021 to January 2022.

For each study, data were extracted (ie, first author, year of publication, mean age, sex, number of individuals with BD and healthy control individuals, mood state, contrasts, details about tasks, imaging results as coordinated clusters [x, y, z] in voxels, and details of the fMRI paradigm), which were used for description and further analyses. The fMRI studies were allocated to the 3 task domains (ie, emotion processing, reward processing, and working memory). Two fMRI studies examined 2 different domains and were therefore included in 2 different analyses.[13,45]

Statistical Analysis

Meta-analyses were conducted using GingerALE version 3.0.2.[43,44] Differences in brain activation among regions associated with each domain were analyzed separately using the activation likelihood estimation method. The activation likelihood estimation approach uses modeling of activation locations (foci) by a 3-dimensional gaussian function, calculating the overlap of the distributions across experiments using the spatial uncertainty of the foci.[44] It forms a probabilistic map of the likelihood that each voxel was activated by an experiment.

The analyses for each domain involved 2 analyses of contrasts. First, we analyzed the activation in brain areas that were more active in brains of individuals with BD compared to those of healthy control individuals, indicating hyperactivation in individuals with BD. Second, we analyzed the activation in brain areas that were more active in the brains of healthy control individuals compared to those of individuals with BD, indicating hypoactivation in individuals with BD. The voxel-level familywise error method ($P = .05$) was used for the correction of all analyses and contrasts of different domains. The number of threshold permutations was set at 1000, and the P value threshold at .05 with a minimum cluster size of suprathreshold voxels exceeding 100 mm^3. Next, we performed sensitivity analyses focused on mood states. For each domain, we analyzed the effect of mood states separately (ie, euthymic, manic, and depressive). A similar procedure was followed for these analyses.

Results

In total, 49 whole-brain-based fMRI studies were included, which accrued 999 individuals with BD (551 [55.2%] female) and 1027 healthy control individuals (532 [51.8%] female). The included studies (per domain) and their clinical specifications are listed in eTable 2 in Supplement 1. All meta-analytical results are presented in **Tables 1** and **2**.

Emotion Processing

For emotion processing, 20 studies were included, with a total of 324 individuals with BD (155 [47.8%] female) and 369 healthy control individuals (170 [46.1%] female). Individuals with BD had different mood states; 116 (35.8%) were in a euthymic state, 70 (21.4%) were in a depressive state, 44 (13.6%) were in a manic state, 1 (0.3%) was in a mixed state, and state was not specified for the remaining 93 (28.7%). The emotion processing domain included emotion tasks with a variety of paradigms, including emotionally salient stimuli (eg, affect induction, emotional perception of facial emotions or prosody, emotion regulation, emotion recognition, emotion memory, and inhibition tasks).

Hyperactivation was shown in all individuals with BD compared with healthy control individuals (Table 1) in part of the left hippocampus, the left and right anterior temporal cortices, and the left amygdala (**Figure 1**A-D). Hypoactivation in individuals with BD was found only in the right inferior frontal gyrus (IFG) compared to healthy control individuals (Figure 1E).

The results regarding mood states (Table 2) revealed hyperactivation in the left parahippocampal gyrus and hypoactivation in the left IFG in individuals with BD who were in a euthymic state. During mania, we found hyperactivation in the left thalamus and hypoactivation in the right IFG in individuals with BD. Individuals with BD showed hyperactivation in the left parietal lobe during depressive state.

Table 1. Activation Likelihood Estimation Meta-analytical Results of Whole Brain–Based Studies[a]

Anatomical label	Peak coordinates			BA	*z* Value	Cluster size, mm^3	ALE value
	x	y	z				
Emotion processing domain							
Bipolar disorder > healthy control							
Left hippocampus	−18	−14	−10	28	6.70	864	0.029
Right superior temporal gyrus	48	14	−10	38	6.06	176	0.025
Left superior temporal gyrus	−56	−16	6	41	5.86	176	0.025
Left amygdala	−28	−2	−12	NA	5.52	160	0.022
Healthy control > bipolar disorder							
Right inferior frontal gyrus	42	22	0	47	6.38	232	0.024
Reward processing domain							
Bipolar disorder > healthy control							
Left orbitofrontal cortex	−46	30	0	47	6.22	344	0.024
Working memory domain							
Bipolar disorder > healthy control							
Left subgenual anterior cingulate	−6	34	−10	32	6.82	696	0.032
Left ventromedial prefrontal cortex	−2	46	−10	10	6.63	624	0.031

Abbreviations: ALE, activation likelihood estimation; BA, Brodmann area; NA, not applicable.

[a] Talairach coordinates are reported. The voxel-level familywise error method (*P* = .05) was used for the correction of all analyses and contrasts of different domains. The number of threshold permutations was set at 1000 and the *P* value threshold at .05, with a minimum cluster size of suprathreshold voxels exceeding 100 mm^3.

Reward Processing

Nine studies on reward processing were included, with a total of 195 individuals with BD (129 [66.2%] female) and 213 healthy control individuals (111 [52.1%] female). In this selection of studies, 117 individuals with BD (60.0%) were in a euthymic state, 65 (33.3%) were in a depressive state, 10 (5.1%) were in a manic state, and 3 (1.5%) were in a mixed state. The reward processing domain paradigms included monetary incentive, gambling, card number guessing, and Roulette tasks.

Taking all individuals with BD together (Table 1), only hyperactivation in the left OFC was shown compared to healthy control individuals (**Figure 2**). For the euthymic mood state in individuals with BD, hyperactivation was found in the left parahippocampal gyrus, ACC, MFG, and right temporal gyrus compared to healthy control individuals. Individuals who were in a depressive mood state showed hyperactivation in the left IFG and in the right superior temporal gyrus (Table 2). A meta-analysis in individuals with BD in a manic state could not be performed due to a lack of power.

Working Memory

We included 20 studies with 530 individuals with BD (267 [50.4%] female) and 417 healthy control individuals (251 [60.2%] female) for working memory. There were 178 individuals (36.1%) in a euthymic state, 171 (34.7%) in a depressive state, 124 (25.1%) in a manic state, and state was not specified for 57 (10.8%). Most of the studies used a letter n-back task, and a few studies a delayed match to sample task.

Overall, hyperactivation in individuals with BD was found in the left subgenual ACC and ventromedial PFC (**Figure 3**) compared to healthy control individuals (Table 1). With regard to mood states, no difference in individuals with BD in a euthymic state were found compared to healthy control individuals. Individuals who were in a manic state showed hyperactivity in the left ACC and hypoactivation in the left IFG during working memory. Individuals with BD in a depressed state showed hyperactivation in the left PFC and ACC, and hypoactivation was found in the right parietal lobe and left cerebellum (Table 2).

Discussion

In the current systematic review and meta-analysis, we investigated brain functioning in individuals with BD compared to that of healthy control individuals within cognitive domains related to emotion processing, working memory, and reward processing. Our findings revealed significant differences in brain activity in individuals with BD, mostly within the fronto-limbic network. Specifically, limbic activation alterations were only manifest in individuals with BD in a euthymic state, whereas more widespread frontal dysfunctions were also found during depression and mania. As such, aberrant limbic activity during cognitive and emotion processing may be a trait-associated BD characteristic; on the other hand, disruptions in frontal cortex activity may be associated with state-related factors.

During emotion processing, we found that individuals with BD showed hyperactivation in the hippocampus, parts of the temporal cortex, and amygdala and hypoactivation in the right IFG (as part of the PFC) when all affective states were pooled together. This is in line with an earlier meta-analysis[7] and a systematic review[11] that focused on emotion processing and found abnormal activity in the fronto-limbic network. Our results regarding the emotion processing domain can be functionally interpreted. For instance, amygdala hyperactivation

Table 2. Activation Likelihood Estimation Meta-analytical Results of Whole Brain–Based Studies per Mood State[a]

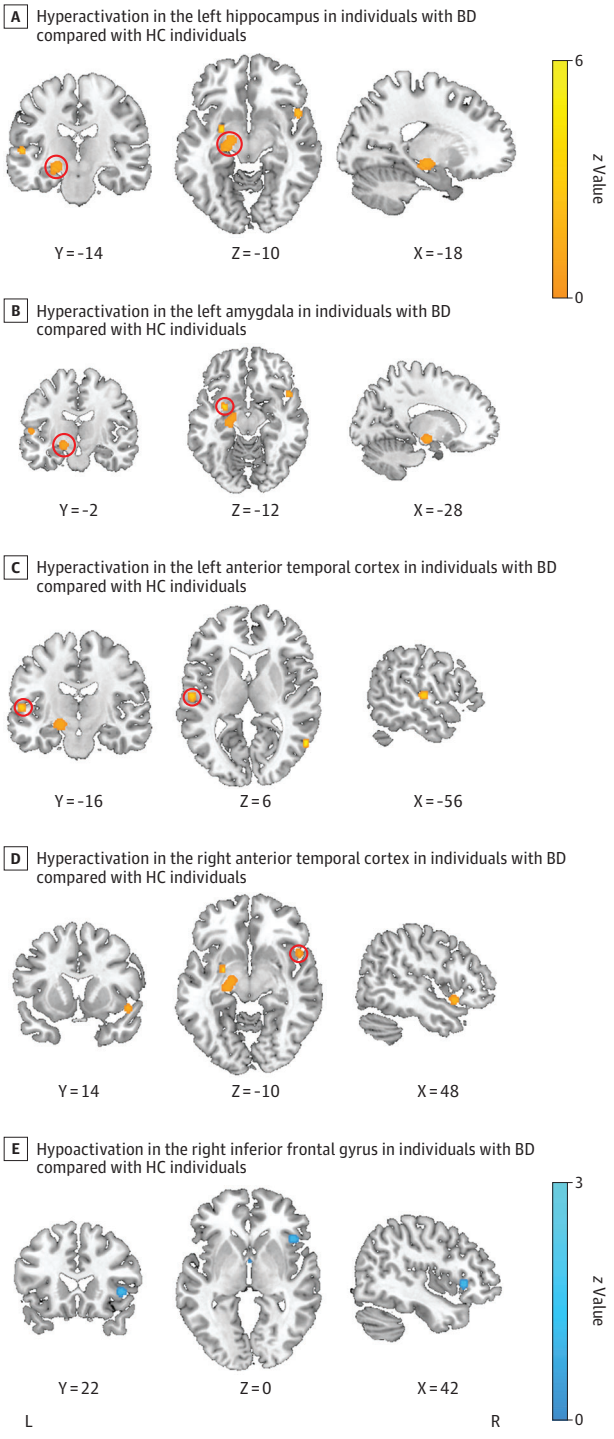
Anatomical label	Peak coordinates			BA	*z* Value	Cluster size, mm^3	ALE value
	X	Y	Z				
Emotion processing domain							
Euthymia							
Bipolar disorder > healthy control							
Left parahippocampal gyrus	−24	−20	−10	28	5.62	216	0.019
Healthy control > bipolar disorder							
Left inferior frontal gyrus	−56	10	26	9	5.28	168	0.014
Mania							
Bipolar disorder > healthy control							
Left thalamus	−4	−32	10	NA	5.91	312	0.018
Healthy control > bipolar disorder							
Right inferior frontal gyrus	46	26	−2	47	5.31	224	0.014
Depression							
Bipolar disorder > healthy control							
Left angular gyrus (parietal lobe)	−32	−56	32	39	5.63	104	0.018
Reward processing domain							
Euthymia							
Bipolar disorder > healthy control							
Left parahippocampal gyrus	−22	−42	−10	36	5.81	152	0.019
Left anterior cingulate	−16	42	0	32	5.81	152	0.019
Left medial frontal gyrus	−16	48	−6	10	5.81	152	0.019
Right middle temporal gyrus	60	−4	−8	21	5.81	152	0.019
Depression							
Bipolar disorder > healthy control							
Left inferior frontal gyrus	−48	28	−1	47	5.46	100	0.017
Right superior temporal gyrus	48	−22	−2	22	5.65	100	0.018
Working memory domain							
Mania							
Bipolar disorder > healthy control							
Left anterior cingulate	−6	40	4	32	6.26	400	0.022
Healthy control > bipolar disorder							
Left middle frontal gyrus	−30	−6	56	6	8.30	624	0.037
Depression							
Bipolar disorder > healthy control							
Left prefrontal cortex	−2	46	−10	10	7.18	504	0.028
Left anterior cingulate	−4	36	−4	32	5.76	112	0.019
Healthy control > bipolar disorder							
Right parietal lobe	8	−66	56	7	5.70	112	0.018
Left cerebellum	−30	−52	−32	NA	5.71	104	0.019

Abbreviations: ALE, activation likelihood estimation; BA, Brodmann area; NA, not applicable.

[a] Talairach coordinates are reported. The voxel-level familywise error method (P = .05) was used for the correction of all analyses and contrasts of different domains. The number of threshold permutations was set at 1000 and the P value threshold at .05, with a minimum cluster size of suprathreshold voxels exceeding 100 mm^3.

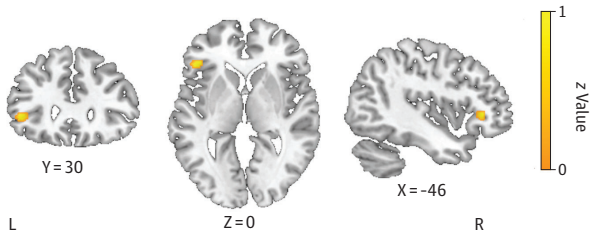
may be interpreted as reflecting a state of oversensitivity, resulting in increased amygdala responses even when there is no need for such a response. The amygdala has a crucial role in emotion generation (ie, perception and arousal), identification of emotional stimuli,[46-48] and emotion regulation.[49] In addition to amygdala hyperactivation during emotion processing, we also found increased activation in the hippocampus. Besides its crucial role in memory, this region is also involved in socioemotional processing and the production of affective states.[48,50] Further, hyperactivation was found in the temporal cortex, which is notably involved in social and emotion processing, recognition, and semantic memory.[51] Our results regarding emotion processing also encompassed hypoactivation in the IFG, which is known to be associated with inhibitory control.[52] Inhibition is a major subcomponent of executive function and is defined as the ability to suppress the process of irrelevant stimuli and dominant response when appropriate.[53] The inability to inhibit responses is, among other

Figure 1. Meta-analytic Maps of Brain Functional Changes in the Emotion Processing Domain



Red circles show area of hyperactivation. BD indicates bipolar disorder; HC, healthy control.

Figure 2. Meta-analytic Maps of Brain Functional Changes in the Reward Processing Domain



Hyperactivation in the left orbitofrontal cortex in individuals with bipolar disorder compared with healthy control individuals.

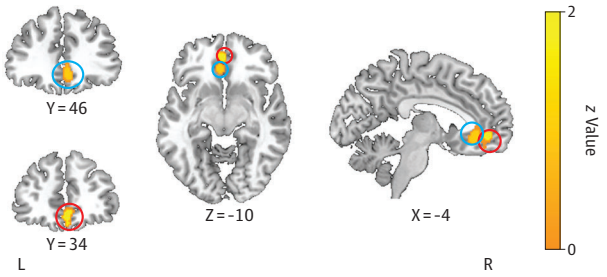
things, associated with impulsive behavior.[54] Moreover, individuals with BD might have difficulties in the identification of emotional stimuli (either negative or positive), leading to increased arousal and making it more difficult to regulate emotions; this in turn may provoke mood episodes.[55] From a network perspective, hypoactivity in inhibitory structures, such as the IFG, might be related to hyperactivity in the whole network related to the fronto-limbic system (as found here in the hippocampus, parts of the temporal cortex, and amygdala) that would normally be inhibited.[56]

For reward processing, our results showed hyperactivation in the OFC in individuals with BD. OFC activity is important for pleasure coding as well as reward outcome and for processing the experience of hyperhedonia.[32] This region forms the key in a hypersensitivity model of reward processing that was introduced based on a behavioral approach system hypothesis for individuals with BD.[57] The model of the behavioral approach system refers to the hypothesis that individuals with BD have a hypersensitive reward system that leads to overreaction or underreaction to reward-related cues. It states that excessive reward system activation leads to manic symptoms, whereas excessive deactivation gives rise to depressive symptoms.[57] This model is thought to be associated with hyperdopaminergia, which leads to high-risk, high-reward-seeking behavior observed during mania.[58] Our finding of OFC hyperactivation in individuals with BD is in line with this reward hypersensitivity model of BD.

To our best knowledge, no previous meta-analyses of neuroimaging studies have focused on the reward system in individuals with BD. To date, only a systematic review on imaging findings during reward processing in unaffected first-degree relatives has been performed.[59] Although relatives are nonaffected and do not have symptoms, these genetically at-risk individuals seem to show reward-related activity dysfunction similar to individuals with BD, that is, increased activity in the OFC in response to reward.[59] The fact that the current systematic review and meta-analysis found a similar OFC activity pattern in a large sample of individuals with BD as found in healthy relatives underlines the importance of these aberrations, as they may serve as an important element in the pathological pathway toward BD.

For working memory tasks, our results showed hyperactivation in the subgenual ACC and ventromedial PFC in individuals with BD compared to healthy control individuals. Interestingly, these regions are connected to limbic structures and are functionally involved in reward valuation and emotion regulation, but recent studies highlight their role in

Figure 3. Meta-analytic Maps of Brain Functional Changes in the Working Memory Domain



Hyperactivation in the left subgenual anterior cingulate (blue circles) and ventromedial prefrontal cortex (red circles) in individuals with bipolar disorder compared with healthy control individuals.

working memory as well. Both subgenual ACC and ventromedial PFC play an important role in integrating cognitive and emotional stimuli. For example, the ventromedial PFC structurally connects the amygdala with the dlPFC and functionally regulates the influencing effects of capacity-exceeding working memory load from the dlPFC and the mediating deleterious effects of emotional interference on cognitive processing in the amygdala.[60,61] In addition, the subgenual ACC is seen as another bridge between the dlPFC and amygdala and plays a role in emotion processing and attention.[62] The interconnection of these 2 regions to the dlPFC and the amygdala facilitates interactions between emotion and cognition.[61] Our results provide further support for the potential role of dysregulated mPFC and subgenual ACC activity as a direct contributor to poor working memory performance and deficiencies in emotional processing in individuals with BD.

In addition to the whole BD group, analyses were also performed by mood state. Limbic hyperactivity was only found in individuals with BD in a euthymic state (parahippocampal), whereas abnormalities in frontal activation, although with a more widespread pattern, were also revealed during states of depression and mania. A tentative conclusion can be drawn that limbic hyperactivation during emotion and cognitive processing in individuals with BD may be a trait-dependent characteristic, whereas frontal cortex dysfunction may also be affected during states in individuals with BD. Functionally, failed frontal inhibitory control may be more pronounced when individuals experience a depressive or manic episode, while the aforementioned increased limbic oversensitivity may only occur during euthymia and may be a risk factor for provoking mood states.[55] Given power constraints, these conclusions should be interpreted with caution. It can therefore not be ruled out that increased limbic activity could be the case during mania or depression; however, the current systematic review and meta-analysis shows that frontal hypoactivation may be a more robust state-dependent finding. One could hypothesize that individuals with BD take high-dose or other medication during affective states compared to when they are in a euthymic state, which may normalize limbic activity.[63]

Two earlier meta-analyses with smaller numbers of inclusions investigated task fMRI studies in individuals with BD.[7,64] Our findings regarding emotional processing are consistent with limbic hyperactivation and IFG hypoactivation as found in 1 meta-analysis.[7] However, all kinds of paradigms related to a variety of cognitive functions were included, while the current systematic review and meta-analysis focused on working memory and emotion and reward processing with regard to the hypothesis of impaired fronto-limbic network activity in individuals with BD specifically. One other meta-analysis focused on the comparison between youth with BD and adults with BD.[64] Similar amygdala hyperactivation during emotional tasks and ACC hyperactivation during nonemotional tasks was found in youth with BD, which underlines the important role of these brain areas in the psychopathology of BD and suggests common trait-like abnormalities.

To the best of our knowledge, this is the first systematic review and meta-analysis showing robust fronto-limbic network abnormalities during emotion and cognitive functioning. The differentiation of 3 cognitive domains in association with fronto-limbic network functioning in individuals with BD allowed a better perspective on how neurocognitive abnormalities can coexist in parallel.

Limitations

Some limitations need to be noted. First, although significant results were revealed in the analyses per mood state, the number of individuals with BD for the different states was limited. As mentioned above, this may result in the negative finding of unincreased limbic activity during affective states. Future studies specifically focusing on state-associated emotional and cognitive functioning are required to increase the power of meta-analyses. Second, we were unable to perform sensitivity analyses and disentangle the potential effects of psychopharmaceuticals due to heterogeneity in medication.[65] Most individuals were treated with mood stabilizers as monotherapy or in combination with other psychotropics. However, a review in individuals with BD found no significant effect of medication on brain activation.[66] Third, clinical heterogeneity and demographic features often make it complicated to compare across studies. To obtain generalizable results, we included a broad range of studies, conditions, and multiple contrasts in 3 domains of interest, although individuals with cognitive impairment were excluded. Meta-analytic results help one to draw overriding conclusions and identify consistencies in the literature despite heterogeneity, though they might lack specificity as to the nature of any aberration. A further limitation is that we could not correct for specific participant factors, including symptomatology, such as psychosis. A few studies measured and reported psychotic symptoms, while others did not. Because of the lack of information, we did not model sex, medication, and comorbidity, factors that might be associated with brain activity in individuals with BD. However, it is known that particular mood states are associated with confounding fMRI results, specifically in the fronto-limbic network.[67] In the current analyses, we were able to tackle this important factor.

Conclusion

To our knowledge, the current study is the first systematic review and meta-analysis in individuals with BD investigating brain activity during cognitive and emotional tasks that demand proper fronto-limbic functioning. Studies have reported that the fronto-limbic network was affected in individuals with BD, both in the euthymic state and in symptomatic individuals. Regarding reward processing specifically, more studies are needed to replicate and expand our findings. Moreover, fMRI studies in individuals with BD would benefit from the standardization of reward paradigms. The field may be furthered by using novel approaches, such as multimodal analyses and pattern-recognition techniques. These advances have the potential to increase the clinical and scientific relevance of reward-processing fMRI paradigms in individuals with BD, which may result in their use during diagnostics or in investigating therapeutic targets. Longitudinal fMRI studies monitoring at-risk individuals as well as individuals with first-onset BD are needed to examine the development of cognitive impairment and its association with fronto-limbic findings over the course of BD.

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