Research Paper

Resting-state functional connectivity in individuals with bipolar disorder during clinical remission: a systematic review

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Background: Bipolar disorder is chronic and debilitating. Studies investigating resting-state functional connectivity in individuals with bipolar disorder may help to inform neurobiological models of illness. **Methods:** We conducted a systematic review with the following goals: to summarize the literature on resting-state functional connectivity in bipolar disorder during clinical remission (euthymia) compared with healthy controls; to critically appraise the literature and research gaps; and to propose directions for future research. We searched PubMed/MEDLINE, Embase, PsycINFO, CINAHL and grey literature up to April 2017. **Results:** Twenty-three studies were included. The most consistent finding was the absence of differences in resting-state functional connectivity of the default mode network (DMN), frontoparietal network (FPN) and salience network (SN) between people with bipolar disorder and controls, using independent component analysis. However, 2 studies in people with bipolar disorder who were positive for psychosis history reported DMN hypoconnectivity. Studies using seed-based analysis largely reported aberrant resting-state functional connectivity with the amygdala, ventrolateral prefrontal cortex, cingulate cortex and medial prefrontal cortex in people with bipolar disorder compared with controls. Few studies used regional homogeneity or amplitude of low-frequency fluctuations. **Limitations:** We found heterogeneity in the analysis methods used. **Conclusion:** Stability of the DMN, FPN and SN may reflect a state of remission. Further, DMN hypoconnectivity may reflect a positive history of psychosis in patients with bipolar disorder compared with controls, highlighting a potentially different neural phenotype of psychosis in people with bipolar disorder. Resting-state functional connectivity changes between the amygdala, prefrontal cortex and cingulate cortex may reflect a neural correlate of subthreshold symptoms experienced in bipolar disorder euthymia, the trait-based pathophysiology of bipolar disorder and/or a compensatory mechanism to maintain a state of euthymia.

Introduction

Bipolar disorder is a major mental illness characterized by discrete periods of depression and mania (bipolar disorder type I) or hypomania (bipolar disorder type II), including changes in sleep, appetite and psychomotor activity.[1–3] Owing to its severity, chronicity and early age of onset, bipolar disorder is considered the fifth leading cause of disability among mental health and substance-use disorders.[4] Bipolar disorder also carries a significantly elevated risk of suicide and psychiatric comorbidity, which further contribute to its illness burden.[5] Cognitive impairment and emotional lability are common clinical features of bipolar disorder, and they are present not only in acute mood episodes, but also in periods of clinical remission (euthymia).[6] Recent advancements in neuroimaging techniques have led to an increase in the use of functional magnetic resonance imaging (fMRI) in the study of brain activation and connectivity patterns in bipolar disorder.[7,8] To a large degree, resting state functional connectivity (rsFC) and task-based fMRI studies of patients with bipolar disorder during acute mood episodes have consistently found abnormal activity in brain regions that are implicated in cognitive and emotional processing. However, research in the euthymic phase has been less consistent.[7,8] Based on neuroimaging and postmortem research, a number of neurobiological models of bipolar disorder have been proposed, the majority of which suggest that bipolar disorder is associated with dysfunction in the dorsal and ventral neural streams.[1,9,10] The dorsal network plays an integral role in mediating cognitive processing and executive functioning; it typically consists of the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), dorsal anterior cingulate cortex and hippocampus. The insula, amygdala, ventral striatum, ventral anterior cingulate cortex (vACC) and ventromedial prefrontal cortex are involved in implicit aspects of emotional regulation and encompass the ventral neural stream.[1,9,10]

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Resting-state functional connectivity measures alterations in the blood oxygen level–dependent (BOLD) signal across the brain in the absence of specific engagement in cognitive or emotional tasks.[11] Participants commonly gaze at a fixation point or lie with their eyes closed for the duration of the scan. In this way, rsFC provides an indirect measure of neuronal activation patterns that occur without the influence of task or emotional or cognitive processing. The study of rsFC during periods of euthymia may be particularly useful to the understanding of compensatory brain mechanisms that interact to maintain clinical remission, as well as in understanding the neurobiology behind subclinical symptoms.

Resting-state functional connectivity is commonly explored using independent component analysis (ICA) or seed-based analysis (SBA) and by investigating localized properties of spontaneous activity, such as amplitude of low-frequency fluctuation (ALFF), fractional ALFF (fALFF), and regional homogeneity (ReHo). Independent component analysis is an exploratory, data-driven approach that maximizes statistical independence by deconstructing spatial maps of BOLD signal time-courses that are independent of one another.[12] Seed-based analysis is a hypothesis-driven approach that correlates the BOLD activation in a predefined "seed" region with activation at the same time in other brain regions.[13] Regional homogeneity measures the functional connectivity of a given voxel in the brain and its neighbourhood voxels,[14] and ALFF/fALFF are used to detect regional changes in spontaneous brain activity by measuring the amplitude of low-frequency fluctuations in BOLD signals.[15,16] While these techniques assume that functional connectivity remains static throughout the resting-state scan, dynamic functional connectivity is based on the principle that dynamic changes in rsFC occur over the course of a resting-state fMRI scan.[17] The diversity in these different methods used to analyze brain activation at rest often makes it difficult to establish consensus among related studies. A systematic review of the breadth of findings would help in determining consistent patterns of brain connectivity reported in individuals with bipolar disorder at rest, identify the inconsistencies and the main gaps in the literature and ultimately guide future research. Thus, the aim of this review was to systematically review the current literature about rsFC in people with bipolar disorder during clinical remission (euthymia); provide a critical appraisal of the literature in this field, including the research gaps; and propose directions for future research.

Methods

This systematic review was formulated in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Eligibility criteria

This systematic review included original studies with the principal objective of investigating rsFC in people with bipolar disorder during euthymia, as well as rsFC studies that reported subanalyses containing a well-defined population with bipolar disorder during euthymia. Studies were included if participants had a clearly defined diagnosis of bipolar disorder, according to validated diagnostic tools; at least a subset of the rsFC results were solely in reference to a population in euthymia; a healthy control group with no lifetime psychiatric history was included; at least 1 of the following techniques was used: SBA, ICA, ReHo, ALFF, fALFF or dynamic functional connectivity; the cluster size was over 50 voxels for significant results;[19] appropriate control was used for multiple comparisons and/or statistical thresholds; and the study was in participants aged 18 years or older. Pediatric studies were excluded from this review. The study participants should also have been free of neurological disorders or learning disabilities.

Information sources

We identified relevant studies published in English from PubMed/MEDLINE, Embase, PsycINFO and grey literature, with no time restriction. We conducted the search again before submission for publication to ensure that the final publication encompassed all current and relevant literature. To maximize literature retrieved, we used the search terms "bipolar disorder," "bipolar affective disorder," "bipolar I disorder," "bipolar II disorder," "cyclothymia/cyclothymic disorder," "rapid-cycling bipolar disorder," "bipolar depression" and "bipolar mania" with the Boolean operator OR. Further, we joined the terms "resting state functional connectivity," "functional connectivity," "resting state network" and "functional magnetic resonance imaging" with the Boolean operator OR and connected them to the search terms above using the Boolean operator AND.

Since many publications on rsFC in people with bipolar disorder contain a subanalysis of a euthymic population, we did not use "euthymic," "euthymia," "remission" or "inter-critical" as search terms to avoid unnecessarily excluding literature with subanalyses. The coauthors and a librarian reviewed the search strategies. We included only original articles; reviews, case reports and conference abstracts were excluded. Repeated articles and duplicate searches were removed.

Data screening and collection

Two reviewers (S.S. and M.S.) independently reviewed and selected papers based on titles and abstracts. Data were then extracted into a predetermined data extraction form. Reviewers recorded the following information: study characteristics (first author, year of publication and journal); demographic information (sample size, measures used to confirm diagnosis and clinical definition of remission/euthymia); neuroimaging information (scanner model and type, technique used, and preprocessing and analysis programs used); and a description of results, with Montreal Neurological Institute or Talairach coordinates, cluster size and probability values ($t/p/z$ values) where applicable. Further, studies that investigate the neural correlates of psychosis often use a sample of people with bipolar disorder that includes those with and without psychosis and schizophrenia. Because of the scope of this review, we made comparisons only between people with bipolar disorder and healthy controls. In case of discordance between the 2 reviewers, a third reviewer (L.M.) was consulted.

Results

Study selection

Our initial search identified 2125 possible research studies. After we had screened the titles and removed duplicates, 86 studies remained. We then screened the abstracts of these remaining studies, yielding 59 full-text papers, which we screened further for inclusion in the study. Finally, we extracted data from 23 papers. The primary reasons for exclusion of identified literature were the absence of a euthymic sample or subsample and the use of task-based fMRI or an analysis method other than rsFC.

Sample population

Of the 23 studies included, only 8 had a primary objective of studying rsFC in bipolar euthymia compared with controls (Table 1). The remaining 15 used an additional comparative group, which included 9 with schizophrenia or schizoaffective disorder, 1 with borderline personality disorder, 2 with mixed mood states, 2 with bipolar mania and 1 with bipolar depression. Each of these 15 studies contained a subanalysis from which we extracted results for this review.

Cumulatively, 897 patients with bipolar disorder and 1030 controls were analyzed in the 23 included studies. Two of the studies assessed a sample of women only, of which only 1 controlled for menstrual phase by scanning people in the mid-follicular phase, when hormonal fluctuations are least likely to influence mood. The mean age of people with bipolar disorder was 34 ± 5.26 years. All studies confirmed a diagnosis of bipolar disorder using validated diagnostic tools such as the Structured Clinical Diagnostic Interview for DSM-IV (SCID)[42] or the Mini International Neuropsychiatric Interview (MINI).[43] Only 3 studies imposed a maximum cutoff score on the Young Mania Rating Scale[44] and Hamilton Depression Rating Scale[45] or Montgomery–Åsberg Depression Rating Scale[46] in addition to using the SCID or MINI. Additionally, 3 studies used the Beck Depression Inventory[47] and the Bech–Rafaelsen Mania Scale[48] with clinically meaningful cutoffs of 18 and 7, respectively. Most studies reported inclusion and exclusion criteria and confirmed euthymia using well-validated measures. Criteria for inclusion in the bipolar disorder or control groups were similar across studies. People with bipolar disorder were stable for a minimum of 2 weeks to 2 months before scanning, adding some element of heterogeneity to the study sample. However, as mentioned previously, euthymia was confirmed in all cases using well-validated measures, such as the SCID[42] or MINI.[43] Two studies[20,37] neglected to report detailed inclusion or exclusion criteria for people with bipolar disorder.

The available literature consisted largely of studies of people with bipolar disorder type I; 3 studies used a mixed sample, and 1 used a sample of people with bipolar disorder type II. Psychosis history has been found to alter rsFC in people with bipolar disorder, and should be reported in the demographics section of articles. Of our included studies, 13 did not report participants' history of psychosis; 6 reported that all patients (bipolar disorder type I) had lifetime history of psychotic symptoms; 4 contained participants with a partial history of psychosis; and studies by Anticevic and colleagues compared patients with and without a history of psychosis.[28–30]

Little is known about the influence of psychotropic medications on rsFC. Therefore, a subanalysis reporting the effects of psychotropic medications on rsFC findings in patients with bipolar disorder in euthymia would be an important tool for highlighting medication effects. Of the 23 studies included in this review, 12 contained subanalyses reporting the effects of psychotropic medications on rsFC. This was most commonly done by converting psychotropic medications to chlorpromazine equivalent doses and/or using the method of Hassel and colleagues.[49] Although 11 studies found no influence of medication on rsFC, 1 found minimal effects of antipsychotics on ALFF/fALFF in the slow-4 bandwidth, resulting in reduced ALFF in the lingual/precuneus region (Table 2).[41] Three studies did not contain a subanalysis and did not report participant medication history.[20,23,26]

Independent component analysis

Eight of the 23 studies used ICA to investigate differences in rsFC between people with bipolar disorder and controls (Table 2 and Table 3). Among them, 17 networks of interest were identified. The default mode network (DMN), frontoparietal networks (FPNs) and salience networks (SNs) were the most commonly studied and yielded largely consistent results. In 6 of 8 studies,[21,22,25–27,38] no differences in rsFC of the DMN between individuals with bipolar disorder and controls were found. Two studies[24,50] reported hypoconnectivity in participants with bipolar disorder relative to controls: Brady and colleagues[50] reported hypoconnectivity in the anterior aspect of the DMN, largely concentrated in dorsal frontal regions, while Khadka and colleagues[24] reported it in the posterior DMN, with the left and right cingulate gyrus and left and right precuneus showing the greatest hypoconnectivity relative to controls. It is important to note that these 2 studies were the only ones to include solely bipolar disorder type I participants with a positive history of psychosis.

Because subthreshold symptoms and minor cognitive impairment may be hallmarks of bipolar euthymia,[6,51] the FPN is often investigated at rest. Although previous studies using SBA have found differences in the functional connectivity of the dlPFC at rest, studies using ICA to investigate rsFC of the entire FPN found no differences between patients with bipolar disorder and controls.[20,22,25–27,38] This result supports the notion that resting-state network (RSN) stability, seen through ICA, may be a hallmark of bipolar euthymia. In other words, the brain correlates of a euthymic, stable mood state may be reflected through brain-wide RSN stability. A similar pattern was seen with the SN, which was investigated in 3 studies and consistently showed no differences between people with bipolar disorder and controls.[22,25,26] The mesoparalimbic network (MPN) and the temporoinsular network (TIN) were investigated in 4 studies.[24,25,27,38] Two of those studies did not find differences in rsFC between people with bipolar disorder and controls,[25,38] but Khadka and colleagues[24] reported increased activation in the

left uncus in patients with bipolar disorder compared with controls. Yip and colleagues[27] investigated the TIN in a medication-naive sample of patients with bipolar disorder type II and found increased engagement of the right caudate, left precentral gyrus, left postcentral gyrus, left inferior frontal gyrus, left supplementary motor area, bilateral putamen and bilateral insula in individuals with bipolar disorder compared with controls. However, these results should be interpreted with caution, because although the sample had been euthymic according to study criteria, the lack of treatment with mood stabilizers or antipsychotics suggests that this population may have had a less severe course of illness and, therefore, may not be comparable to the majority of other study populations.

Less frequently studied networks included the cerebellum/midbrain network, frontotemporal paralimbic network, precuneus network, ventromedial prefrontal cortex network, motor network, visual processing network and executive control network, all of which have been associated with no significant differences in rsFC between people with bipolar disorder and controls.[22,24,26,27] Moreover, single studies have found that the dorsal attention network, cingulo-opercular network, fronto-thalamic basal ganglia network and fronto-occipital network were associated with hypoconnectivity between brain regions, as outlined in Table 2.[24,26,50] Since only 1 study reported on each of these networks, we are unable to speculate whether abnormal connectivity in these networks is a true reflection of the trait-based pathology of bipolar disorder. More studies investigating these networks in euthymic individuals with bipolar disorder are needed. The same is true for the single sensorimotor network reporting hyperconnectivity between the superior frontal gyrus and medial frontal gyrus in people with bipolar disorder relative to controls.[24]

As shown above, although between-group differences in RSN functional connectivity are typically negative, abnormal patterns of functional connectivity between RSNs (intra-network connectivity) have been reported to a greater degree between patients with bipolar disorder and controls. For instance, Das and colleagues[22] reported that coupling between the DMN–precuneus and social salience–ventromedial prefrontal cortex networks was increased in patients with bipolar disorder compared with controls, although differences did not withstand multiple comparison correction. Lois and colleagues[25] found increased functional connectivity between the meso/paralimbic and the right frontoparietal network in bipolar disorder ($p_{FDR} < 0.001$). Mamah and colleagues[26] reported less connectivity between the cingulo-opercular and cerebellum/midbrain network and the cingulo-opercular and salience network in bipolar disorder relative to controls ($p < 0.01$). Thus, the 3 studies that investigated intra-network rsFC between people with bipolar disorder and controls reported differences in functional connectivity.

Dynamic causal modelling was used by 1 study: Rashid and colleagues[20] investigated the static and dynamic functional connectivity of RSN. Although they found no differences in the functional connectivity of the DMN, visual processing network, sensorimotor network, cerebellum/midbrain network or subcortical regions between groups, results from dynamic causal modelling analysis revealed less connectivity between 2 parietal components — the paracentral and superior parietal lobule (dynamic state 4) — in people with bipolar disorder compared with controls. Moreover, they found greater connectivity in people with bipolar disorder relative to controls between the temporal component (bilateral fusiform gyrus) and a parietal component (left supramarginal gyrus; dynamic state 4). They found no differences in functional connectivity between controls and people with bipolar disorder in any other dynamic states.[20]

Du and colleagues[23] used the novel method of guided independent component analysis to identify patterns of functional connectivity at rest that were unique to a particular psychiatric illness and could be used to discriminate between patients with bipolar disorder and other illnesses. Guided independent component analysis involves the estimation of resting-state components using an algorithm that increases the correspondence of intrinsic components between subject groups and the independence of intrinsic networks specific to each participant. This study found that the insular cortex was a discriminatory region between euthymic patients with bipolar disorder and controls.[23]

Seed-based analysis

Seed-based analysis correlates the BOLD signal of an a priori chosen "seed" region with other temporally significant changes in BOLD signals throughout the brain.[13] Thirteen studies used SBA to investigate differences in rsFC in people with bipolar disorder compared to controls, 3 of which included subanalysis to explore differences in functional connectivity based on a history of psychosis.[28–30] Overall, the results from SBA were largely heterogeneous and lacked the consistency and generalizability of results obtained from ICA because a wide variety of seed regions were chosen for analysis. All regions of interest (ROIs) selected in individual studies are described in Table 2, and the seed regions most commonly studied are described in greater detail below.

Bilateral and left and right amygdala

It has been well established that the amygdala plays a role in emotional regulation and the trait-based pathology of bipolar disorder. The left and right amygdala were used as a priori seed regions in 5 of the 13 SBA studies.[21,28,37–39] No differences in the rsFC of the amygdala were found between people with bipolar disorder and controls.[37,38] However, 2 studies[21,28] found decreased connectivity between the amygdala and other regions of the brain in people with bipolar disorder relative to controls. More specifically, decreased connectivity was found between the bilateral amygdala and right BA5, left supplemental motor area, right supplemental motor area and left BA5;[21,28] between the right amygdala and right BA5 and right supplemental motor area;[21] and between the amygdala and the dlPFC.[28] On the other hand, increased connectivity between the amygdala and the medial prefrontal cortex (mPFC) was reported in the same population[28] and between the right amygdala and right vlPFC.[28] Interestingly, amygdala hyperconnectivity has been frequently reported in bipolar mania and to a lesser degree in bipolar depression;[7] thus, the absence of hyperconnectivity may reflect a state of functional connectivity adopted in euthymia.[7]

Medial prefrontal cortex

The mPFC is a central node of the DMN and has been postulated to play a role in emotional regulation by generating anticipatory responses preceding emotional events.[52] Aberrant connectivity of the DMN has been reported in bipolar and unipolar depression; coupled with the role of the mPFC in emotional regulation and the DMN, the mPFC is a logical a priori ROI to study in the pathophysiology of bipolar disorder.[8,53]

Two studies used the mPFC as an ROI through SBA: 1 study found differences in functional connectivity of the mPFC,[31] while 1 did not.[37] Favre and colleagues[31] found that mPFC activity was significantly correlated with the right amygdala in people with bipolar disorder, but not in controls. Moreover, in people with bipolar disorder, the mean duration of illness and mPFC–right amygdala functional connectivity were significantly correlated. Additionally, in people with bipolar disorder, increased functional connectivity between the mPFC and the right dlPFC was reported relative to controls. Anticorrelation between the mPFC and right dlPFC was seen in controls, but was not significant in people with bipolar disorder. Rey and colleagues[37] also investigated the rsFC of the mPFC, but did not find differences in functional connectivity between controls and people with bipolar disorder.

Dorsolateral prefrontal cortex

The dlPFC is central to high-order cognitive abilities and higher-order thinking. Owing to its large role in central executive and frontoparietal RSNs, the dlPFC has been explored as an ROI through SBA. While the studies mentioned in the section above have described aberrant connectivity between the mPFC and dlPFC and between the amygdala and dlPFC, none of them used the dlPFC as a primary ROI. Our group did use the dlPFC as a primary ROI in an SBA, and we found increased rsFC between the dlPFC and the brainstem (p_{FDR} = 0.03).[38] We postulated that this pattern of functional connectivity might reflect heightened activity of top–down and/or bottom–up processes between cortical regions and primitive neural regions involved in autonomic nervous and neurotransmitter system modulation. Further, it has been widely shown that cognitive difficulties, particularly in executive functioning and verbal memory, often persist between acute episodes in people with bipolar disorder.[51,54] Thus, it is conceivable that abnormal patterns of functional connectivity between the dlPFC and other brain regions may reflect some neural component of these persistent cognitive difficulties.

Ventrolateral prefrontal cortex/inferior frontal gyrus

The vlPFC/inferior frontal gyrus was one of the most commonly studied ROIs in the reviewed SBA literature and was investigated in 4 studies, with mixed results. Torrisi and colleagues[39] found increased connectivity between the right amygdala and the right vlPFC. This pattern of connectivity was not correlated with any clinical variable tested: illness duration, number of depressive or manic episodes or Hamilton Depression Rating Scale/Young Mania Rating Scale scores. Rey and colleagues[37] found decreased connectivity between the subgenual anterior cingulate cortex (sgACC) and vlPFC, as discussed below. Brady and colleagues[21] found no differences in rsFC of the right or left vlPFC. Moreover, Oertel-Knöchel and colleagues[35] found decreased functional connectivity of the left inferior frontal gyrus and the left hippocampus ($p < 0.001$, cluster-level correction).

Orbitofrontal cortex

The orbitofrontal cortex plays a well-established role in emotional regulation and impulsivity and has been widely implicated in the neurobiology of bipolar disorder.[55,56] The only study that tested the orbitofrontal cortex as a primary ROI in rsFC found no differences in connectivity between people with euthymic bipolar disorder and controls.[21]

Cingulate cortex

Subdivisions of the cingulate cortex were investigated in 5 studies,[21,30,34,37,38] each making a unique contribution to the knowledge on the trait-based pathophysiology of bipolar disorder. Anticevic and colleagues[30] explored the rsFC of the vACC between people with bipolar disorder (with and without a history of psychosis) and controls. They found decreased connectivity between the mPFC and the vACC in people with bipolar disorder and lifetime psychosis relative to controls, and increased connectivity between the mPFC and the vACC in people with bipolar disorder and without psychosis relative to controls. Our group studied rsFC through the DMN using both ICA and SBA, and found increased coupling between the posterior cingulate cortex (PCC) and angular gyrus relative to controls.[38] However, as mentioned above, we observed no differences in the functional connectivity of the DMN using ICA. In a recent study by Rey and colleagues,[37] increased coupling between the left sgACC and PCC and between the left and right sgACC were found in people with bipolar disorder compared to controls; however in the same population, decoupling was found between the right sgACC and right vlPFC (d' = 0.58, p = 0.04). Also worth mentioning is that the pattern of coupling between the right amygdala and right vlPFC reported by Torrisi and colleagues[39] was mediated by the anterior cingulate cortex (ACC). Further, 2 studies reported no difference in ACC connectivity between patients with bipolar disorder and controls.[21,34]

Amplitude of low-frequency fluctuations

Two studies investigated rsFC using ALFF. Meda and colleagues[41] found that people with bipolar disorder displayed decreased power in the medial frontal gyrus and ACC relative to controls in the slow-5 frequency bandwidth (0.01–0.027 Hz). In the same study, people with bipolar disorder displayed increased power in the inferior/middle temporal gyrus, uncus and parahippocampus relative to controls in the slow-4 frequency bandwidth (0.027–0.073 Hz).[41] Similarly, another study found decreased ALFF in the left orbitofrontal cortex and left ACC in patients with bipolar disorder relative to controls.[40] Increased functional connectivity was also found in people with bipolar disorder relative to controls between the right thalamus and left insula; left pre- and postcentral gyri and the right superior frontal gyrus; right thalamus and bilateral cuneus; and left ACC and left precuneus.[40]

Table 1: Demographic characteristics of the study samples

	Bipolar disorder							
Study	Sample, n	Subtype	Psychosis history	Sex, M/F	Age, yr, mean ± SD	Years of education, mean ± SD	Controls, n	Other comparative groups
Dynamic causal modelling/independent component analysis								
Rashid et al.[20]	38	NA	NA	18/20	38.96 ± 10.9	NA	61	SCZ or SAD (*n* = 60)
Independent component analysis								
Brady et al.[21]	24	BD-I	Yes (*n* = 24)	16/8	30.9 ± 11.9	NA	23	BD mania (*n* = 28)
Das et al.[22]	16	NA	NA	0/16	35.6 ± 10.71	15.87 ± 1.51	13	BPD (*n* = 14)
Du et al.[23]	20	NA	Yes (*n* = 20)	8/12	31.2 ± 9.5	NA	20	SCZ (*n* = 20), SADM (*n* = 20), SADD (*n* = 13)
Khadka et al.[24]	64	BD-I	Yes (*n* = 64)	35/29	35.1 ± 11.2	NA	118	SCZ (*n* = 70)
Lois et al.[25]	30	BD-I	Yes (*n* = 13)	13/17	40.8 ± 9.43	14.97 ± 2.58	35	—
Mamah et al.[26]	35	NA	NA	16/19	24.9 ± 3.75	14.1 ± 2.4	33	SCZ (*n* = 25)
Yip et al.[27]	15	BD-II	NA	7/8	23.1 ± 3.7	NA	20	—
Seed-based analysis								
Anticevic et al.[28]	68	BD-I	Yes (*n* = 34) No (*n* = 34)	PHx 13/21 No PHx 8/26	PHx 34.0 ± 10.8 No PHx 29.9 ± 11.9	PHx 13.9 ± 1.6 No PHx 14.4 ± 2.0	51	—
Anticevic et al.[29]	73	BD-I	Yes (*n* = 33) No (*n* = 40)	PHx 12/21 No PHx 8/32	PHx 34.2 ± 10.9 No PHx 30.2 ± 11.5	PHx 13.9 ± 1.6 No PHx 14.4 ± 2.1	56	SCZ (*n* = 73)
Anticevic et al.[30]	73	BD-I	Yes (*n* = 33) No (*n* = 40)	PHx 12/21 No PHx 8/32	PHx 34.2 ± 10.9 No PHx 30.2 ± 11.5	PHx 13.9 ± 1.6 PHx 14.4 ± 2.1	56	SCZ (*n* = 73)
Brady et al.[21]	24	BD-I	Yes (*n* = 24)	16/8	30.9 ± 11.9	NA	23	BD mania (*n* = 23)
Favre et al.[31]	20	Mixed (BD-I *n* = 13; BD-II *n* = 5; BD-NOS *n* = 2)	NA	9/11	42 ± 10.7	NA	20	—
Knöchel et al.[32]	21	BD-I	NA	12/9	35.7 ± 10.7	14.7 ± 2.4	21	SCZ (*n* = 21)
Lv et al.[33]	19	NA	NA	10/9	27.8 ± 6.7	13.3 ± 2.7	28	BD depression (*n* = 23)
Magioncalda et al.[34]	11	NA	NA	NA	NA	NA	40	BD depression (*n* = 11), mania (*n* = 11), mixed (*n* = 7)
Oertel-Knöchel et al.[35]	21	BD-I	NA	12/9	35.7 ± 10.7	14.7 ± 2.4	20	—
Reinke et al.[36]	21	BD-I	NA	12/9	35.7 ± 10.7	NA	20	—
Rey et al.[37]	15	BD-I (*n* = 7), BD-II (*n* = 3), BD-NOS (*n* = 3), BD rapid cycling (*n* = 1)	NA	6/9	41.4 ± 9.6	NA	15	BD non-euthymic (*n* = 12)
Syan et al.[38]	32	BD-I (*n* = 18), BD-II (*n* = 14)	NA	0/32	29 ± 8.07	15.6 ± 2.6	36	—
Torrisi et al.[39]	20	BD-I	NA	10/10	42.1 ± 11.4	14.1 ± 1.9	20	—
Absolute and fractional amplitude of low-frequency fluctuations								
Lui et al.[40]	57	BD-I	Yes (*n* = 57)	18/39	34 ± 13	14 ± 3	59	SCZ (*n* = 37), SCZR (*n* = 38), BDR (*n* = 28)
Meda et al.[41]	180	BD-I	Yes (*n* = 180)	58/122	36.94 ± 13.0	NA	242	SCZ (*n* = 220), SAD (*n* = 147), BDR (*n* = 134), SCZR (*n* = 150), SADR (*n* = 126)

BD = bipolar disorder; BDR = healthy relative of bipolar proband; BPD = borderline personality disorder; NA = not available; NOS = not otherwise specified; PHx = psychosis history; SAD = schizoaffective disorder; SADD = schizoaffective disorder, depressed subtype; SADM = schizoaffective disorder, manic subtype; SADR = healthy relative of schizoaffective proband; SCZ = schizophrenia; SCZR = healthy relative of schizophrenia proband; SD = standard deviation.

Table 2: Summary of neuroimaging findings (part 1 of 8)

	Methodology				
Study	Diagnosis of BD	Inclusion criteria	Medication information	ROI/network	Results
Dynamic causal modelling/independent component analysis					
Rashid et al.[20]	Chart review and SCID	NA; no patients acutely ill at time of scanning	NA	VSN, CC, AUD, SMN, DMN, CER, subcortical network/regions	No differences in static functional connectivity between BD and controls in VSN, SMN, DMN, CER or subcortical regions BD < controls: lower connectivity in BD between 2 parietal components, paracentral and superior parietal lobule (dynamic state 4) BD > controls: greater connectivity between the temporal component (bilateral fusiform gyrus) and a parietal component (left supramarginal gyrus; dynamic state 4) in BD No differences in functional connectivity between controls and BD in any other dynamic states, and symptomatology and functional connectivity were not correlated
Independent component analysis					
Brady et al.[21]	SCID	BD: 18–65 years of age; no history of neurologic illness; not currently pregnant or lactating; no electroconvulsive therapy within 3 mo of study enrolment; no history of head trauma resulting in a loss of consciousness for greater than a few min; no MRI contraindication Controls: no current or lifetime history of any axis I psychiatric disorder	Anticonvulsants 9; antipsychotics 15; benzodiazepenes 4; lithium 16; antidepressants 1 Subanalysis revealed no significant effect of medication on rsFC analysis ($p_{FDR} < 0.05$)	Exploratory whole-brain analysis Results found in DAN and DMN	BD < controls: hypoconnectivity in the DAN in BD relative to controls BD < controls: dorsal frontal hypoconnectivity in the DMN in BD relative to controls Additional uncorrected ROI–ROI results between BD and controls are described
Das et al.[22]	SCID	BD: euthymic state; no current hospitalization; no substance abuse; no history of traumatic head injury; no neurologic illness; no learning or developmental disorders or poor English proficiency Controls: no history of psychiatric illness	Unmedicated 3; antidepressants 7; antipsychotics 6; mood stabilizers 3; lithium 5 No medication subanalysis reported	FPN (R/L) precuneus, DMN, SS, vmPFC	No differences in network connectivity (FPN [R/L], precuneus, DMN, SS, vmPFC) between BD and controls BD > controls: inter-network differences — coupling between the DMN–precuneus and SS–vmPFC networks was increased in BD v. controls. Differences did not withstand multiple comparison correction Increased coupling in BD between the SS–vmPFC networks was positively correlated with lack of emotional clarity ($r = 0.605$, $p = 0.029$) Increased coupling in BD between the DM–precuneus was negatively correlated with lack of emotional awareness scores ($r = -0.574$, $p = 0.040$) Items 2 and 4 refer to correlations with subscores from the DERS
Du et al.[23]	DSM-IV-TR	BD: stable and consistent medication dose for 4 wk or longer	NA	FPN (R/L), DMN (1,2,3), SN, PN, ARN, VRN, VSN, CER, SMN	Insular cortex identified as a discriminatory region between controls and BD using guided ICA technique

Table 2: Summary of neuroimaging findings (part 2 of 8)

Study	Methodology				Results
	Diagnosis of BD	Inclusion criteria	Medication information	ROI/network	
Independent component analysis (continued)					
Khadka et al.[24]	SCID	BD: met criteria for BD-I with psychosis; clinically stable with consistent medication for at least 4 weeks before study enrolment	Mood stabilizer 44; typical antipsychotics 2; atypical antipsychotics 36; benzodiazepines 11; anticholinergics 4; SSRIs 16; tricyclics/ MAOs 13; psychostimulants 4 No medication subanalysis could be completed	FON, CER BGN, MPN pDMN, PLN, SMN	BD < controls: decreased functional connectivity in FON (left cuneus, left lingual gyrus), BGN (right thalamus), and pDMN (left and right cingulate gyrus, left and right precuneus) in BD v. controls HD > controls: BD greater connectivity than controls in MPN (left uncus) and SMN (right SFG, right MFG) No differences in connectivity of the CER or PLN between BD and controls
Lois et al.[25]	SCID axis I disorders	All: > 18 years of age; no history of neurologic disorder or head trauma with a loss of consciousness; did not meet common MRI exclusion criteria BD: did not meet criteria for another axis-I mental disorder within the last 6 mo; if they had lifetime diagnosis of rapid cycling, schizoaffective disorder or schizophrenia Controls; no current or lifetime history of any axis-I psychiatric illness or psychotropic medication	Mean ± SD medication load for BD-I patients: 3.1 ± 2.35 No correlation between functional connectivity and medication load	aDMN, pDMN, FPN (L/R), SN MPN	No differences in functional connectivity between BD and controls in any of the networks of interest BD > controls: increased functional connectivity between the meso/paralimbic and the right frontoparietal network in BD Abnormal connectivity pattern in BD patients did not correlate with variables related to the clinical course of the disease
Mamah et al.[26]	SCID axis I disorders	All: did not meet DSM-IV criteria for substance dependence or severe/moderate abuse during 6 mo preceding study enrolment; had no clinically unstable or severe general medical disorder; no history of head injury with documented neurologic sequelae or less of consciousness; met DSM-IV criteria for mental retardation BD: clinically stable for at least 2 weeks Controls: no current or lifetime history of psychotic or mood disorder, or first-degree family members with a psychotic disorder	NA	DMN, FPN CO, CER SN	BD < controls: BD had lower within-network connectivity of the CO than controls BD < controls: connectivity between the CO–CER and CO–SN was lower in BD than in controls

Table 2: Summary of neuroimaging findings (part 3 of 8)

Study	Methodology				Results
	Diagnosis of BD	Inclusion criteria	Medication information	ROI/network	
Independent component analysis (continued)					
Yip et al.[27]	MINI	All: no history of head injury, neurologic condition or MRI contraindication Controls: no history of psychotropic medication use; no history of hypomanic experiences as defined by the MDQ; no current or past psychiatric disorder BD: no current major depressive, manic or hypomanic episodes at the time of scanning; no use of any current psychotropic medication or exposure to antipsychotic agents or mood stabilizers; no other psychiatric disorder (excluding BD and anxiety disorders)	Entire sample was naive to antipsychotic or mood-stabilizing medication and unmedicated at the time of scanning	DMN, VPN (1,2), TIN, MN, ECN, FPN (R/L)	BD > controls: BD had increased engagement of the regions of the TIN v. controls: right caudate, left precentral gyrus, left postcentral gyrus, left inferior frontal gyrus, left supplementary motor area, bilateral putamen and bilateral insula No significant differences between BD and controls in any of the other networks of interest
Seed-based analysis					
Anticevic et al.[28]	SCID	All: no history of a major medical or neurologic conditions (e.g., epilepsy, migraines, head injury with loss of consciousness); IQ > 80 on WAIS BD: BD-I diagnosed using SCID by MA- or PhD-level research clinicians; comorbid axis I disorders and substance use disorders in remission for at least 6 mo were allowed Controls: no axis I diagnoses in lifetime as per SCID-NP; no history of mood or psychotic symptoms in first-degree relatives	Mood stabilizers 53%; antidepressants 43%; atypical antipsychotics 34%; anxiolytics 35%; lithium 16%; unmedicated 16% Medication type did not alter results when used as a covariate	Seed-based amygdala was correlated with all PFC voxels using a global brain connectivity method, restricted to PFC (rGBC)	BD < controls: decreased connectivity between mPFC and rGBC in BD v. controls BD > controls increased connectivity between amygdala and mPFC in BD v. controls BD < controls decreased connectivity between amygdala and dlPFC in BD v. controls.
Anticevic et al.[29]	SCID	All: no history of a major medical or neurologic condition (e.g., epilepsy, migraines, head injury with loss of consciousness); IQ > 80 on WAIS BD: BD-I diagnosed using SCID by MA- or PhD-level research clinicians; comorbid axis I disorders and substance use disorders in remission for at least 6 mo were allowed Controls: no axis I diagnoses in lifetime as per SCID-NP; no history of mood or psychotic symptoms in first-degree relatives	BD with psychosis: mood stabilizers 15%; antidepressants 33%; atypical antipsychotics 45%; lithium 24%; typical antipsychotic 2%; unmedicated 15% BD without psychosis: mood stabilizers 18%; antidepressants 50%; atypical antipsychotics 25%; lithium 12%; typical antipsychotic 0%; unmedicated 18% Medication subanalysis results: no effect of medication on rsFC results	vACC	BD < controls: decreased connectivity between mPFC and vACC in BD patients with psychosis history relative to controls BD > controls: increased connectivity in BD patients without psychosis between mPFC and vACC relative to controls

Table 2: Summary of neuroimaging findings (part 4 of 8)

Study	Methodology				Results
	Diagnosis of BD	Inclusion criteria	Medication information	ROI/network	
Seed-based analysis (continued)					
Anticevic et al.[30]	SCID	All: no history of a major medical or neurologic condition (e.g., epilepsy, migraines, head injury with loss of consciousness); IQ > 80 on WAIS BD: BD-I diagnosed using SCID by MA- or PhD-level research clinicians; comorbid axis I disorders and substance use disorders in remission for at least 6 mo were allowed Controls: no axis I diagnoses in lifetime as per SCID-NP; no history of mood or psychotic symptoms in first-degree relatives	BD with psychosis: mood stabilizers 15%; antidepressants 33%; atypical antipsychotics 45%; lithium 24%; typical antipsychotic 2%; unmedicated 15% BD without psychosis: mood stabilizers 18%; antidepressants 50%; atypical antipsychotics 25%; lithium 12%; typical antipsychotic 0%; unmedicated 18% No subanalysis in BD reported	Thalamic nuclei: MD nucleus and lateral geniculate nucleus	Bipolar with psychosis v. controls BD with psychosis > controls: coupling between the MD thalamic nucleus and the right superior temporal gyrus (BA22), left superior temporal gyrus (BA41), left insular cortex (BA13) and left precentral gyrus (BA4) in BD with psychosis relative to controls BD with psychosis < controls: decoupling between the MD thalamic nucleus and precuneus BD with psychosis > controls: coupling between the right superior temporal gyrus (BA22), right superior temporal gyrus (BA41), right precentral gyrus (BA6) BD with psychosis < controls: decoupling between the LGN and the right thalamus, and anterior cingulate (BA32) Bipolar without psychosis v. controls BD without psychosis > controls: coupling between the MD thalamic nucleus and the insular cortex (BA13), anterior insular cortex (BA13) and right precentral gyrus (BA4) BD without psychosis < controls: decoupling between the MD thalamic nucleus and the precuneus (BA7) BD without psychosis < controls: decoupling between the LGN and the right thalamus, right anterior cingulate cortex BD without psychosis > controls: coupling between the LGN and the right superior temporal gyrus (BA41), right precentral gyrus (BA6)
Brady et al.[21]	SCID	BD: 18–65 years of age; no history of neurologic illness; not currently pregnant or lactating; no electroconvulsive therapy within 3 mo of study enrolment; no history of head trauma resulting in a loss of consciousness for greater than a few min; no MRI contraindication Controls: no current or lifetime history of any axis I psychiatric disorder	Anticonvulsants 9; antipsychotics 15; benzodiazepenes 4; lithium 16; antidepressants 1 Subanalysis revealed no significant effect of medication on rsFC analysis ($p_{FDR} < 0.05$)	Bilateral amygdala (and included individual L/R seeds), bilateral OFC, bilateral ventral striatum, vlPFC (L/R) and ACC	BD < controls: decreased connectivity between the bilateral amygdala and right BA5, left SMA, right SMA, left BA5; cluster size p-value < 0.001 BD < controls: decreased connectivity between the right amygdala and right BA5, right SMA; cluster size p-value < 0.001

Table 2: Summary of neuroimaging findings (part 5 of 8)

Study	Methodology				Results
	Diagnosis of BD	Inclusion criteria	Medication information	ROI/network	
Seed-based analysis (continued)					
Favre et al.[31]	SCID	All: no history of alcohol or drug abuse; no current or past neurologic or medical diseases that affect cognition; no history of head trauma with a loss of consciousness; no MRI contraindications BD: euthymic for at least 1 mo before scanning and MADRS < 15 and YMRS < 7; no other axis I psychiatric disorder or electroconvulsive therapy during the previous year Controls: no current or lifetime history of psychiatric disorder; no family history of psychiatric disorders; no medical treatment affecting cerebral activity	Lithium 80%; anticonvulsants 60%; antidepressants 35%; atypical antipsychotics 5% No subanalysis reported	mPFC and mPFC–amygdala connectivity	BD > controls: increased functional connectivity between the mPFC and right dlPFC ($p_{FWE} < 0.05$, cluster-level correction) in BD v. controls. Anti-correlation between the mPFC and right dlPFC in controls (mean $r = -0.25$, $p < 0.001$), but not significant in BD mPFC activity significantly correlated to the right amygdala in BD ($r = 0.08$, $p = 0.002$) but not controls ($r = 0.01$, $p = 0.48$) In BD, mean duration of disorder and mPFC-right amygdala functional connectivity was significantly correlated ($r = 0.46$; $p = 0.04$)
Knöchel et al.[32]	SCID (SCID-I and SCID-II; German version)	BD: no comorbid axis I or II disorders; BDI-II < 18 and BRMAS < 7; stable mood state; no changes in medication within the month preceding study enrolment Controls: no current drug-abuse history of neurologic disease; no history of axis I or II disorders; ability to provide consent; family history of affective or psychotic disorders	Mood stabilizers 21; antidepressants 2 Mean duration of medication: 6.26 yr No subanalysis reported for effect of medication on rsFC	Hippocampus	BD < controls: decreased functional connectivity between the hippocampus and the left frontal lobe in BD v. controls
Lv et al.[33]	SCID	All: age 18–45 years; completed 9 or more years of education; right-handed; no history of neurologic disease or other physical illness; no history of electroconvulsive therapy; no history of drug or alcohol abuse; no psychiatric comorbidities: schizoaffective disorder, personality disorders, and mental retardation; no contraindications for MRI BD: does not meet criteria for current manic, hypomanic, or depressive mood according to SCID; HAM-D score of ≤ 8 and YMRS ≤ 6 within 6 mo preceding study enrolment Controls: no current or lifetime history for any psychiatric disorder	Increased connectivity strength between the right middle cingulate gyrus and the right supramarginal gyrus in BD was positively correlated with lithium doses No other significant interaction was found between dosage of other psychotropics and functional connectivity strength	Whole-brain analysis Broca's area (IFG: pars opercularis and pars triangularis) and Wernicke's area (LSTG, LMTG and LANG)	No significant differences in functional connectivity between BD and controls in any of the seed points studied: IFG (pars opercularis, pars triangularis) LSTG, LMTG and LANG BD > controls: increased connectivity between the left insula and LANG ($p < 0.001$, uncorrected)

Table 2: Summary of neuroimaging findings (part 6 of 8)

Study	Methodology				Results
	Diagnosis of BD	Inclusion criteria	Medication information	ROI/network	
Seed-based analysis (continued)					
Magioncalda et al.[34]	MINI SCID axis II personality disorders Structured Interview for Mood Disorders, revised	All: age 18–60; no history of schizophrenia, mental retardation, dementia, other cognitive disorders; no history of severe or decompensated somatic diseases or neurologic diseases; no history of head injury with loss of consciousness > 5 min; no current alcohol or substance abuse; no history of alcohol or substance dependence; no history of abuse of synthetic drug/new drug abuse; not pregnant or lactating; right-handed; no MRI contraindications; no previous treatment with electroconvulsive therapy, chemotherapy or brain radiotherapy BD: HAM-D score of < 8, YMRS score of < 8 Controls: no current or lifetime psychiatric history	Mood stabilizers 35; antidepressants 11; antipsychotics 24; benzodiazepines 12; unmedicated 1 No medication subanalysis for BD reported	dACC	Subgroup analysis yielded no significant results between euthymic BD and controls
Oertel-Knöchel et al.[35]	SCID (SCID-I and SCID-II; German version)	BD: no comorbid axis-I or II disorders; BDI-II < 18 and BRMAS < 7; stable mood state; no changes in medication within the month preceding study enrolment Controls: no current drug-abuse history of neurologic disease; no history of axis I or II disorders; ability to provide consent and a family history of affective or psychotic disorders	Mood stabilizers 21; antidepressants: 3 Mean duration of medication: 6.26 yr No effect of medication on rsFC	Left middle/ superior frontal gyrus, left IFG	BD < controls: decreased functional connectivity of the left middle/superior frontal gyrus and the bilateral medial frontal gyrus and the left and right superior and middle temporal gyrus ($p < 0.001$, cluster-level correction) in BD v. controls BD > controls: increased functional connectivity of the left middle/superior frontal gyrus and the bilateral dorsal cingulate cortex ($p < 0.001$, cluster-level correction) in BD v. controls BD < controls: decreased functional connectivity of the left IFG and the left hippocampus ($p < 0.001$, cluster-level correction)
Reinke et al.[36]	SCID axis I disorders	BD: no comorbid axis-I or II disorders; BDI-II < 18 and BRMAS < 7; stable mood state; no changes in medication within the month preceding study enrolment Controls: no current drug-abuse history or neurologic disease; no history of axis I or II disorders; ability to provide consent and a family history of affective or psychotic disorders	Specific medication history not reported in paper No significant relationships between indices of medication and results in resting state neuronal activation	Auditory cortex: Heschl's gyrus, planum temporale	BD < controls: decreased functional connectivity between bilateral Heschl's gyrus and the left middle temporal gyrus (BA 22) in BD relative to controls BD < controls: decreased functional connectivity between the bilateral PT and the right superior and middle temporal gyrus in BD relative to controls BD > controls: ncreased functional connectivity between the PT and right inferior frontal/precentral gyrus and the insula in BD relative to controls
Rey et al.[37]	DSM-IV TR criteria and MINI	Controls: no history of neurologic illness; no history of axis I psychiatric disorders as assessed by the MINI; not taking any drug	Mood stabilizers 9; antipsychotics 7; antidepressants 6; benzodiazepines 4; psychostimulants 1 No medication subanalysis reported	Amygdala (L/R), sgACC (L/R), PCC, mPFC, vlPFC (L/R)	BD < controls: decreased functional connectivity between the left sgACC and PCC BD < controls: decreased functional connectivity between the right sgACC and right vlPFC BD > controls: increased functional connectivity between the left and right sgACC in BD relative to controls

Table 2: Summary of neuroimaging findings (part 7 of 8)

Study	Methodology				Results
	Diagnosis of BD	Inclusion criteria	Medication information	ROI/network	
Seed-based analysis (continued)					
Syan et al.[38]	SCID axis I disorders	All: no use of systemic hormonal treatment within 3 mo of study enrolment; not currently pregnant; no contraindication for MRI; no history of head trauma resulting in a loss of consciousness; no neurologic disorders affecting cognition; no current or recent (6 mo) alcohol drug abuse or dependence; no unstable medical conditions BD: no current depressive, manic or hypomanic episode; no changes in psychotropic medications or mood state within 2 mo before enrolment Controls: no current or lifetime history of psychiatric disorder	Lithium 3; anticonvulsants 15; anxiolytics 6; antipsychotics 16; antidepressants 12; sleep aids 2; unmedicated 7 Subanalysis found no effect of medication load on rsFC analysis	ICA: DMN, FPN, MPN SBA: PCC, dlPFC (R/L, BA 46), amygdala (R/L)	BD > controls: increased functional connectivity between the PCC and AG in BD v. controls BD > controls: increased functional connectivity between the right dlPFC and brainstem in BD v. controls No differences in functional connectivity between groups within networks using ICA In the BD group only, PCC–AG coupling was positively correlated with state anxiety ($r = 0.39$; $p = 0.028$)
Torrisi et al.[39]	SCID	All: right-handedness; no neurologic illness; no metal implants; no history of skull fracture or head trauma with loss of consciousness > 5 min BD: no other current axis I psychiatric disorder Controls: current or lifetime history of psychiatric disorders (including substance abuse); not taking medications for any medical reasons	Antipsychotics 15%; antidepressants 75%; anticonvulsants (valproic acid 25%, lamotrigine 20%) Medication subanalysis reported no significant effect of medication on observed results	Amygdala (L/R), vlPFC (L/R)	BD > controls: increased connectivity between the right amygdala and right vlPFC in BD v. controls; this pattern of connectivity was not correlated with any clinical variables: illness duration, number of depressive or manic episodes or HAM-D/YMRS scores No differences in whole-brain connectivity between BD and controls in the primary somatosensory cortex (BA 1), auditory cortex (BA 41,42) or primary visual cortex (BA17) ACC mediated the effect in (Sobel test, $z = 7.88$)

Table 2: Summary of neuroimaging findings (part 8 of 8)

Study	Methodology				Results
	Diagnosis of BD	Inclusion criteria	Medication information	ROI/network	
Absolute and fractional amplitude of low-frequency fluctuations					
Lui et al.[40]	SCID	All: no history of significant neurologic or systemic illness; negative urine drug screen for common drugs of abuse on the day of testing; no diagnosis of substance abuse in the prior 30 d, or substance dependence in the prior 6 mo; not currently pregnant; no head translation or rotation movement during scanning > 1.5 mm Controls: free of axis I psychiatric disorders and not taking psychoactive medications BD: clinically stable for 1 mo before study participation; stable medication for treatment for 1 mo before testing	Mood stabilizers 38; mean ± SD chlorpromazine equivalent daily dose 236 ± 249 Correlational analysis of MRI data and medication was not significant	Regions displaying differences in ALFF were used as seed points in a whole-brain functional connectivity analysis	BD < controls: decrease ALFF in the left OFC and left ACC in BD relative to controls BD > controls: increased functional connectivity between the right thalamus and the left insula, left pre- and postcentral gyri and right SFG; the right thalamus and the bilateral cuneus; the left ACC and left precuneus ($p < 0.05$, AlphaSim to correct for multiple comparisons) in BD v.controls
Meda et al.[41]	Chart review and SCID (SCID I/P)	BD: all participants were stable for at least 1 mo before scanning and on stable medications	Unknown medication history 4; medication-naive 8; not medicated 14; antipsychotics 124; mood stabilizer 122; antidepressant 82; anxiolytic 55; anticholinergic 15; stimulants 18; miscellaneous 5 Medication subanalysis results: no significant effects of chlorpromazine equivalents were noted in ALFF/fALFF; no effect of medication doses for slow-5 and slow-4; minimal effects were present with antipsychotics on slow-4 (reduced ALFF in the lingual/precuneus region)	NA	BD < controls: BD displayed decreased power in the medial frontal gyrus and ACC (slow-5) BD > controls: BD displayed increased power in the inferior/middle temporal gyrus, uncus and parahippocampus relative to controls (slow-4) BD < controls: reduced power was seen in the pre- and post- central gyri in BD v. controls

aDMN = anterior default mode network; ACC = anterior cingulate cortex; AG = angular gyrus; ALFF = amplitude of low-frequency fluctuations; ARN = auditory-related network; AUD = auditory network; BD = bipolar disorder; BDI-II = Beck Depression Inventory-II; BGN = frontothalamic/basal ganglia network; BRMAS = Bech–Rafaelsen Mania Scale; CC = cognitive control network; CER = cerebellum/midbrain network; CO = cingulo-opercular network; dACC = dorsal anterior cingulate cortex; DAN = dorsal attention network; DERS = Difficulty in Emotional Regulation Scale; dlPFC = dorsolateral prefrontal cortex; DMN = default mode network; DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders,* text revision; ECN = executive control network; fALFF = fractional amplitude of low-frequency fluctuations; FDR = false discovery rate; FON = fronto-occipital network; FPN = frontoparietal network; FWE = family-wise error; HAM-D = Hamilton Depression Rating Scale; ICA = independent component analysis; IFG = inferior frontal gyrus; IQ = intelligence quotient; L = left; LANG = left angular gyrus; LGN = lateral genicuate nucleus; LMTG = left middle temporal gyrus; LSTG = left superior temporal gyrus; MADRS = Montgomery–Åsberg Depression Rating Scale; MAO = monoamine oxidase; MD = mediodorsal; MDQ = Mood Disorders Questionnaire; MFG = middle frontal gyrus; MINI = Mini International Neuropsychiatric Interview; MN = motor network; mPFC = medial prefrontal cortex; MPN = mesoparalimbic network; MRI = magnetic resonance imaging; NA = not available; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; pDMN = posterior default mode network; PFC = prefrontal cortex; PLN = frontotemporal/paralimbic network; PN = parietal network; PT = planum temporale; R = right; rGBC = restricted global brain connectivity; ROI = region of interest; rsFC = resting-state functional connectivity; SCID = Structured Clinical Interview for DSM-IV; SCID-NP = Structured Clinical Interview for DSM-IV, non-patient version; SD = standard deviation; SFG = superior frontal gyrus; sgACC = subgenual anterior cingulate cortex; SMN = sensorimotor network; SN = salience network; SS = social salience network; TIN = temporo-insular network; vACC = ventral anterior cingulate cortex; vlPFC = ventrolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex; VPN = visual processing network; VRN = vision-related network; VSN = visospatial network; WAIS = Wechsler Abbreviated Intelligence Scale; YMRS = Young Mania Rating Scale.

Table 3: Summary of independent component analysis study findings between individuals with bipolar disorder and controls

Study	DMN	FPN	SN	MPN	TIN	CO	CER	DAN	BGN	SMN	PLN	FON	Prec.	vmPFC	VPN	MN	ECN
Brady et al.[21]	Hypo	—	—	—	—	—	—	Hypo	—	—	—	—	—	—	—	—	—
Das et al.[22]	NS	NS	NS	—	—	—	—	—	—	—	—	—	NS	NS	—	—	—
Khadka et al.[24]	Hypo	—	—	Hyper	—	—	NS	—	Hypo	Hyper	NS	Hypo	—	—	—	—	—
Lois et al.[25]	NS	NS	NS	NS	—	—	—	—	—	—	—	—	—	—	—	—	—
Mamah et al.[26]	NS	NS	NS	—	—	Hypo	NS	—	—	—	—	—	—	—	—	—	—
Rashid et al.[20]	NS	NS	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Syan et al.[38]	NS	NS	—	NS	—	—	—	—	—	—	—	—	—	—	—	—	—
Yip et al.[27]	NS	NS	NS	—	Hyper	—	—	—	—	—	—	—	—	—	NS	NS	NS
Du et al.[23]	Used GIG-ICA																

BGN = frontothalamic/basal ganglia network; CER = cerebellum/midbrain network; CO = cingulo-opercular; DAN = dorsal attention network; DMN = default mode network; ECN = executive network; FON = fronto-occipital network; FPN = frontoparietal network; GIG-ICA = guided independent component analysis; hyper = hyperconnectivity; hypo = hypoconnectivity; MN = motor network; MPN = mesoparalimbic network; NS = not significant; PLN = frontotemporal/paralimbic network; prec = precuneus network; SMN = sensorimotor network; SN = salience network; TIN = temporoinsular network; vmPFC = ventromedial prefrontal cortex network; VPN = visual processing network.

Discussion

Investigating rsFC during interepisodic periods of bipolar disorder may contribute to our understanding of the neurobiology of bipolar disorder; common patterns of rsFC may highlight regions implicated in its pathophysiology, and/or markers of bipolar euthymia. In this systematic review of the literature, we found that studies using ICA to examine the functional connectivity of the DMN, FPN and SN largely showed that patterns of functional connectivity were not distinguishable between patients with bipolar disorder and controls. Notably, the 2 studies[24,50] (of the 8 investigated) that reported hypoconnectivity between nodes of the DMN in patients with bipolar disorder relative to controls included only people with a positive history of psychosis. Therefore, the reported hypoconnectivity of the DMN may reflect a positive history of psychosis. Aberrant patterns of DMN connectivity are well-documented in bipolar mania and in schizophrenia during task-based and resting-state fMRI,[57] and in acute mood states of bipolar disorder (for review[8]). Modulation of DMN connectivity with antipsychotic medication has also been reported.[58] The DMN is central to spontaneous cognition, self-referential processing and emotional regulation.[11,59] The absence of aberrant connectivity in DMN functional connectivity found in most studies of euthymic participants with bipolar disorder may reflect a normalization of DMN activity between acute mood episodes. Psychotic symptoms may alter the integrity of the DMN and lead to persistent hypoactivation, even during periods of euthymia. Despite the common presence of subjective cognitive impairment in people with bipolar disorder, our review suggests that FPN and SN functional connectivity are largely similar between people with bipolar disorder and controls. Therefore, stability of the DMN, FPN and SN shown in ICA may reflect stabilization of the RSN and a state of remission in bipolar disorder.

Contrary to the results from ICA, studies that used SBA found hyper-/hypoactivation of important regions of the DMN and FPN such as the mPFC, PCC and dlPFC. These regions are central to emotional regulation, self-referential processing and executive functioning,[11,59] deficits in all of which are reported during euthymic periods of bipolar disorder.[6] Because SBA largely investigates functional connectivity between distinct regions of the brain (seed points) and other voxels in the brain (seed–voxel) or other brain regions (ROI–ROI), this technique may be more useful at capturing smaller-scale changes in rsFC, such as those between brain regions. Smaller-scale/seed-based changes in rsFC may also be more susceptible to the influence of patient characteristics. In this respect, heterogeneity in the patient populations may contribute to the differences in functional connectivity reported with SBA. Although each patient group included in this review comprised euthymic samples, differences in psychotropic medication use, illness duration, history of psychiatric comorbidities and severity of subthreshold symptoms might have influenced the results. These factors should be carefully considered when interpreting functional connectivity results both from individual studies and in the framework of this review. With respect to SBA, we postulate that aberrant patterns of DMN functional connectivity may reflect a neural correlate of subthreshold symptoms or differences in psychiatric comorbidities or medication use; sustained patterns of rsFC present in bipolar euthymia that may contribute to its trait-based pathology; and/or a compensatory mechanism to maintain a state of euthymia.

The MPN and its primary seed point, the amygdala, play an important role in emotional regulation,[7] and this network has largely been implicated in the pathophysiology of bipolar disorder.[1,7,9] However, results from ICA studies in bipolar disorder euthymia are conflicting: 2 of 4 studies reported no difference in rsFC of the MPN,[25,38] and 2 studies reported hyperconnectivity of nodes of the MPN/TIN

(1 study in an antipsychotic-naive population[27] and the other in people with a positive history of psychosis[24]). The functional connectivity of the amygdala, a central node of the limbic network, was explored in 5 studies using SBA,[21,28,37–39] also yielding mixed results, with 2 reporting no differences between patients with bipolar disorder and controls and 3 reporting hyperconnectivity between the amygdala and the vlPFC, mPFC and somatosensory association cortex and decoupling with the dlPFC. As mentioned above, heterogeneity in variables associated with the patient population (illness history, number of episodes, psychotropic medication use) may help to explain these differences in functional connectivity.

Numerous studies have investigated the role of the cingulate cortex in emotional regulation and in both dorsal and ventral streams of cognition.[3,9,52,60] The cingulate cortex is split into many anatomic and functional regions, each of which makes a unique contribution to emotional regulation, cognition and the trait-based pathology of various psychiatric illnesses.[3,9,52,60] Studies included in this review highlighted patterns of altered functional connectivity in 5 key subregions of the cingulate cortex: the PCC, sgACC, vACC, pACC and in 1 instance the entire ACC. Studies using ALFF further highlight aberrance in rsFC in the left ACC in people with bipolar disorder.[40,41] Functional coupling of specific nodes of the cingulate cortex in people with bipolar disorder relative to controls may reflect trait-based pathology of bipolar disorder that highlights compensatory neural activity responsible for maintaining a state of remission and/or an increased vulnerability to acute mood states associated with bipolar disorder.

Limitations

An important limitation of these findings is related to certain aspects inherent in the rsFC technique. First, rsFC provides an indirect measure of neuronal activity at an ultralow frequency, typically ranging from 0.01 to 0.10 Hz.[61] Therefore, findings from rsFC studies must be interpreted within this framework. Moreover, commonly used rsFC techniques (SBA, ICA, ALFF, ReHo) rely on the oversimplification that BOLD activation is static through the scanning paradigm.[62,63] An exception to this is a dynamic causal modelling or sliding-window approach.[17] Further, participants are told at the beginning of many resting-state scanning paradigms to keep their eyes open, fixed on a fixation cross/point, and to try not to think of anything in particular. However, many studies do not use objective measures such as simultaneous electroencephalograms or eye tracking to confirm this.[62,63] Also, although participants are often advised to keep a "clear mind" throughout the session, we do not know if they are able to do this. Additionally, it is important to consider that SBAs are limited by the location and size of the ROI used across participants. Although most studies included preprocessing steps such as normalization and segmentation to mitigate these effects, they should still be carefully considered as a potential limitation of SBA studies.[23]

To achieve a sustained period of clinical stability, most people with bipolar disorder need to be managed pharmacologically on a mood-stabilizing regimen, so studies involving euthymic participants typically recruit people on medications.[9] Psychotropic medications may, indeed, exert an influence on brain regions involved in the pathophysiology of bipolar disorder and, in turn, influence functional connectivity. In this capacity, the effects of psychotropic medications, beyond their role in contributing to a state of euthymia, are still a common limitation of neuroimaging research on bipolar euthymia. Many studies investigating rsFC in bipolar disorder, including our previous work, have tried to assess this effect and have ruled out the influence of medication.[21,25,28,30,33,35,36,38,39,50,64] Unfortunately, previous studies have not been designed — nor were they likely powered — to test the real influence of psychotropics on rsFC in people with bipolar disorder. We encourage authors to report complete medication histories and conduct subanalyses of the effect of medication on rsFC, so that we can better understand the effects of psychotropic medication on rsFC. More importantly, we also encourage future studies that are specifically designed to investigate the potential effects of psychotropic medications on rsFC.

Patient characteristics such as body mass index (BMI), subthreshold mood/anxiety symptoms and lifetime history of psychosis may also be associated with certain discrepancies between available studies.[30,65,66] Many studies did not report psychosis history, nor did they conduct subanalyses to assess the potential influence of psychosis on rsFC in their sample. Notably, BMI is known to affect brain structure in people with bipolar disorder,[65] but the effect of BMI on rsFC in bipolar disorder is largely unknown; future studies are warranted. Another important knowledge gap is the degree to which the presence of subclinical/subthreshold symptoms may affect rsFC.[6] We encourage future studies to provide a detailed report on the scores of clinical measures to allow findings to be interpreted in the framework of clinical characteristics experienced by the specific study populations.

This systematic review also highlighted the lack of rsFC research on sex, menstrual cycle phase or menstrual cycle disorders in studies that investigated women of reproductive age. This may be important for numerous reasons: the clinical course of bipolar disorder has been shown to progress differently in men and women,[67] with women reporting greater symptoms of depression and more lability in mood resulting from hormonal fluctuations;[68,69] and an increasing body of literature that has found women with bipolar disorder report higher rates of premenstrual syndrome and premenstrual dysphoric disorder (PMDD) than controls.[70–73] Further, these differences also extend to brain structure and function: a recently published study found differences in cortical thickness, rsFC and the volume of the caudate nucleus in women with bipolar disorder and comorbid PMDD compared with women who have bipolar disorder without a comorbid diagnosis of PMDD.[74] We encourage researchers to explore these themes, because it would help to create a more diverse body of literature on rsFC in patients with bipolar disorder. Moreover, we encourage researchers to control for or at least include the presence of PMDD in women with bipolar disorder in their analysis models. This can be accomplished by conducting

scans in the mid-follicular menstrual phase (days 5–10 of the menstrual cycle) to ensure that patterns of functional connectivity associated with bipolar disorder are not confounded by those associated with the PMDD symptoms that occur in the symptomatic late luteal phase. This is especially important given the high prevalence of PMDD in women with bipolar disorder, as well as differences in brain structure and function observed in euthymic women with bipolar disorder and comorbid PMDD relative to those without PMDD.[74]

This study provided a concise review of the rsFC literature in bipolar euthymia, but it is not without limitations. A major limitation was the considerable heterogeneity in analytical approaches used in the included studies. In studies using SBA in particular, the ROIs used were quite diverse, making it difficult to compare results between studies. Further, the size and location of ROIs also varied among studies and may have contributed to the diversity of the results. For this reason, we were unable to conduct a meta-analysis. These challenges will likely be mitigated as research in the field increases; with the accumulation of more RSN studies using an ICA approach, meta-analyses will become possible. With reference to ROI-based analysis, we encourage future studies to investigate the rsFC in bipolar disorder using well-established and validated neuroimaging atlases, such as those available with the FreeSurfer Toolbox. If researchers are manually creating their ROIs, we encourage them to always share the brain imaging coordinates and granular methodological details of their creation of ROIs. Finally, we excluded studies on pediatric bipolar disorder. As a result, this review encapsulates the literature on a distinct phase of bipolar disorder in adults and although it contributes to providing an overview of bipolar remission, it cannot be generalized to younger populations.

Conclusion

Neuroimaging studies may help to inform neurobiological models of bipolar disorder by highlighting aberrant functional networks associated with its pathophysiology. Current models of bipolar disorder postulate that its pathophysiology is more likely associated with larger-scale changes in structural and functional networks, rather than with abnormalities in the structure or function of individual brain areas.[1,9,55,75] In bipolar disorder, aberrant structural and functional connectivity in pathways involved in emotional and cognitive processing are hypothesized to arise from a loss of top-down prefrontal modulation of limbic circuitry and the dysregulation of at least 2 interdependent networks responsible for mediating emotional regulation: the lateral prefrontal cortical system (originating in the vlPFC, including the dlPFC, dorsal anterior cingulate cortex and hippocampus); and the medial prefrontal cortical system (originating in the vmPFC, including the insula, amygdala, ventral striatum and vACC). It has been hypothesized that an imbalance between these 2 neural streams may lead to the onset of affective episodes and clinical symptoms experienced in bipolar disorder.[1,9,55,75]

Stability of the DMN, FPN and SN was a consistent finding in ICA studies, with the exception of studies whose entire sample endorsed a positive history of psychosis, which may reflect patterns of connectivity similar to those seen during bipolar mania or schizophrenia. We postulate that the stability of resting-state networks may be a neural correlate of a state of clinical remission in bipolar disorder, whereas history of psychosis may be reflected in instability of the DMN, which seems to persist in remission. Results from SBA studies were significantly more diverse, owing at least in part to heterogeneity in patient populations and localization of ROIs. Changes in rsFC between neural regions central to the pathophysiology of bipolar disorder such as the amygdala, prefrontal cortex and cingulate cortex may reflect a neural correlate of subthreshold symptoms experienced during bipolar disorder euthymia; a compensatory mechanism of neural activity that is underlying the stability of RSN using ICA; and/or a reflection of the trait-based pathophysiology of bipolar disorder.

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