The activity and connectivity of the facial emotion processing neural circuitry in bipolar disorder: a systematic review

Lisa S Furlong[a], Susan L Rossell[b,c], Georgia F Caruana[a], Vanessa L Cropley[a,b], Matthew Hughes[b], Tamsyn E Van Rheenen[a,b*]

[a] Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Australia
[b] Centre for Mental Health, Faculty of Health, Arts and Design, School of Health Sciences, Swinburne University, Melbourne, Australia
[c] St Vincent's Mental Health, St Vincent's Hospital, VIC, Australia

Address correspondence to: Dr Tamsyn Van Rheenen, Melbourne Neuropsychiatry Centre, Level 3, Alan Gilbert Building, 161 Barry St, Carlton, Vic 3053, Australia, tamsyn.van@unimelb.edu.au

Abstract

Background: Facial emotion processing abnormalities may be a trait feature of bipolar disorder (BD). These social cognitive impairments may be due to abnormalities in the neural processing of facial affective information in visual ("core"), and limbic and prefrontal ("extended") networks, however, the precise underlying neurobiological mechanism(s) underlying this symptom are unclear.

Methods: We conducted a systematic review to appraise the literature on the activity and connectivity of the facial emotion processing neural circuitry in BD. Two reviewers undertook a search of the electronic databases PubMed, Scopus and PsycINFO, to identify relevant literature published since inception up until September 2019. Study eligibility criteria included; BD participants, neuroimaging, and facial emotion processing tasks.

Results: Out of an initial yield of 6121 articles, 66 were eligible for inclusion in this review. We identified differences in neural activity and connectivity within and between occipitotemporal, limbic, and prefrontal regions, in response to facial affective stimuli, in BD compared to healthy controls.

Limitations: The methodologies used across studies varied considerably.

Conclusions: The findings from this review suggest abnormalities in both the activity and connectivity of facial emotion processing neural circuitry in BD. It is recommended that future research aims to further define the connectivity and spatiotemporal course of neural events within and between occipitotemporal, limbic, and prefrontal regions.

Keywords: Bipolar disorder; facial emotion processing; fMRI; EEG; MEG; systematic review

Title: The activity and connectivity of the facial emotion processing neural circuitry in bipolar disorder: a systematic review

1. Introduction

Subtle social cognitive symptoms related to altered perception of, and responsiveness to, social information have been increasingly recognised as features of bipolar disorder (BD) (Van Rheenen et al., 2019; Van Rheenen and Rossell, 2013). The presence of these symptoms during euthymic periods of the illness suggest that they may be trait-like in nature (Samame et al., 2015; Van Rheenen and Rossell, 2014). Within the social cognitive profile of BD, one of the most consistently noted behavioural deficits is in the domain of emotion processing (Miskowiak et al., 2019), which describes the perception, identification and interpretation of salient affective stimuli, and the subsequent regulation and modulation of emotional arousal (Phillips et al., 2003). The neural circuitry implicated in emotion processing has been studied extensively in healthy samples, and models of this circuitry have been proposed and evaluated in several meta-analyses (Fusar-Poli et al., 2009; Murphy et al., 2003; Vytal and Hamann, 2010). Neuroimaging techniques in conjunction with tasks containing visual or auditory affective stimuli have been primarily used to probe this circuitry. Visual affective stimuli used are typically in the form of emotionally-laden images; with facial expressions being the most common. These expressions provide important social cues regarding another person's emotional state; the perception of which may influence the viewer's own emotions (Haxby et al., 2002). Faces convey information that is important for social communication, and abnormalities in the processing of this information represents an impairment in social cognition that may impact an individual's interpersonal and social well-being (Kanwisher and Yovel, 2006).

Findings from behavioural research suggest that compared to healthy controls, individuals with BD are impaired in their ability to label and discriminate facial emotions in

terms of both accuracy and speed (Bozikas et al., 2006; Van Rheenen and Rossell, 2014). While case-control effect sizes for emotion recognition deficits are small, they are significant and generally consistent across studies, particularly in relation to the processing of faces expressing fear (Samame et al., 2015). Increasingly, research has indicated a role for abnormal brain function and connectivity in limbic and prefrontal regions in BD, although the brain correlates of facial emotion recognition in BD remain to be fully understood. A thorough characterisation of facial emotion processing neural networks involved in emotion processing deficits in BD may lead to a more complete understanding of its pathophysiology.

An understanding of the neural circuitry implicated in facial emotion processing in healthy individuals is required to interpret abnormalities in BD. Research has revealed widespread cortical and subcortical brain regions involved in facial emotion processing. These regions form a distributed network that include *core* and *extended* components, first described by Haxby and colleagues (Haxby et al., 2000). The *core* network, which includes the inferior occipital gyrus (IOG), fusiform gyrus (FG), and superior temporal sulcus (STS), is primarily involved in face processing. It has been suggested that within the core network, visual information is projected bi-directionally via the ventral stream from the IOG to the STS and FG (Haxby et al., 2000). The IOG plays a role in the very early perception of static facial features (Rossion et al., 2003), while the FG, particularly the 'fusiform face area', is primarily involved in the processing of facial features (Weiner and Zilles, 2016), their spatial configuration (Zhao et al., 2014) and identity (Hoffman and Haxby, 2000). Finally, the STS is involved in processing the changeable aspects of faces such as eye gaze and lip movement (Haxby et al., 2002; Hoffman and Haxby, 2000).

In contrast, the *extended* network for facial emotion processing includes the amygdala (AMG), and components of the prefrontal cortex (PFC) (Haxby et al., 2000, 2002), including the ventral PFC (vPFC) and orbitofrontal cortex (OFC) (Adolphs, 2002; Fairhall and Ishai,

2007). It should be noted that in this literature, the vPFC, the inferior frontal gyrus, and the ventrolateral PFC (vlPFC), have been referred to interchangeably in the context of the extended network. Other limbic, temporal, parietal, and auditory cortical regions are also involved in the network (Haxby et al., 2000, 2002), with putative roles in affective and cognitive processing of complex information related to others' mood, direction of attention, and interest (Haxby et al., 2000). Specifically, the AMG is involved in the processing of information about emotion and emotional arousal (Rasia-Filho et al., 2000). The OFC is involved in modulating affective behaviour (Drevets, 2000), and the vlPFC has roles in cognitive functions such as decision making (Grabenhorst and Rolls, 2011) and the appraisal of emotional stimuli (Goldin et al., 2008). Importantly, in healthy individuals these regions are implicated in the inhibition of AMG activity (Hariri et al., 2000), a mechanism by which PFC function may regulate emotion and emotional arousal.

Connectivity between the core and extended systems has been described in healthy individuals. The original model by Bruce and Young (Bruce and Young, 1986), and elaborated upon by Haxby and colleagues (Haxby et al., 2000), proposed a hierarchical sequence of information processing from core to extended face processing areas, in which visual information is transmitted from early visual areas, through the core network, to the extended network, in a feed-forward fashion. More recent evidence suggests there may be multiple parallel pathways between nodes linking the core and extended networks, modulated by facial emotion stimuli (Dima et al., 2011; Pyles et al., 2013). Together, these findings suggest a complex interaction between visual-face and cognition-emotion processing systems in the brain. Though the activity and connectivity of and between these networks have been characterised in healthy individuals, they are currently not completely understood in BD. Indeed, previous facial emotion processing research has focused on limbic abnormalities in the disorder, but the broader context of how these abnormalities relate to other brain areas

remains unknown. The aim of this systematic review is to appraise the literature pertaining to the neural circuitry underlying facial emotion processing in BD, and thereby contribute to a broader understanding of brain network pathophysiology in BD.

2. Methods

2.1 Search strategy

Articles were screened and selected in accordance with the PRISMA guidelines (Moher et al., 2009) (Supplementary material 1). PubMed, Scopus and PsycINFO electronic databases, in addition to manual searches through reference lists, were used to identify relevant literature published up until September 2019 (see Supplementary material 2 for the search strategy used).

2.2 Study selection and eligibility criteria

Titles, abstracts and key words were screened by two reviewers (LF and GC). Articles were included if they met the following eligibility criteria: (1) The text was published in the English language; (2) was empirical in nature; (3) contained a sample of only human participants; (4) included adult participants diagnosed with BD (type 1 or 2) in any mood state; (5) included a healthy comparison group; (6) used neuroimaging methodologies to examine brain activity and/or connectivity in the context of facial emotion processing; and (7) included a task designed to examine facial emotion processing. Articles were excluded if they: (1) were a case report; (2) were a narrative, systematic or meta-analytic review; (3) contained a sample of paediatric BD participants only; (4) used a task that examined emotion regulation (i.e., tasks that require participants to consciously alter their emotional response to a stimulus); (5) used a task that examined attention (i.e., emotional Stroop task); (6) used only a facial affective processing task that probed multiple sensory modalities (i.e., auditory

tasks combined with visual emotion processing tasks); or (7) did not run the facial emotion processing task during neuroimaging (i.e., correlated behavioural facial emotion processing data with brain volumetric data).

2.3 Quality assessment of individual studies

An adapted version of the National Institute of Health (NIH) study quality assessment tool, consisting of ten questions, was used for quality assurance purposes for all eligible studies (Supplementary material 3). Briefly, the questions in this tool focused on factors such as whether study-specific research questions had been reported, task design features had been described at a level of detail to ensure replication, participant characteristics etc. In line with the NIH tool, each study was given an overall quality rating of 'good', 'fair' or 'poor'.

2.4 Data extraction

Data extraction focused on three main topics; sample characteristics, methodologies, and key findings, as described below.

2.4.1 Sample characteristics

The BD sample characteristics included; sample size, mean and standard deviation values for age, mood state, and BD type. The healthy control sample characteristics included; sample size, and mean and standard deviation values for age.

2.4.2 Methodologies

The extracted methodology-related data included; neuroimaging technique used, criteria to determine mood state, facial emotion processing task type, emotional expressions examined, neuroimaging analysis type (ROI, whole-brain analysis, psychophysiological

interaction [PPI] and DCM), face-relevant event-related potentials in studies using encephalographic techniques, confounding variables, and brain regions investigated.

2.4.3 Key findings

Between-group (BD compared to healthy controls) data was extracted from all eligible studies, including; alterations in brain activity, alterations in brain connectivity, location(s) of altered brain activity, locations of altered brain connectivity, altered brain activity in response to particular emotional expressions and their location(s), altered brain connectivity in response to particular emotional expressions and their locations. For the purpose of this review, the most recent descriptions of the core (FG, STS, IOG) and extended (AMG, OFC, vlPFC) networks (Dima et al., 2011; Fairhall and Ishai, 2007) were used to present our findings. Given the importance of these networks in the neurobiology of emotion processing, the activity and connectivity of these networks were investigated together. To ensure we captured the activity and connectivity of all brain regions, we then present findings from brain regions outside of the core and extended networks as defined here.

3. Results

3.1 Study selection

The study selection process is illustrated in Figure 1. A total number of 6121 records were yielded, and after duplicate removal, there were 4735 records. Following independent title, abstract and keyword screening by LF and GC, articles were excluded if they did not meet at least one of the eligibility criteria. A total number of 116 articles were eligible for full-text review, and a final number of 66 were selected for inclusion in this systematic review. These articles were published between the years of 2000 and 2019. Results from the data collection process were synthesized into a systematic narrative to aid with interpretation.

3.2 Quality assessment of individual studies

Overall, the majority of included studies were assessed as being 'good' in quality (see Supplementary material 3), and all studies passed the quality assessment. The diagnostic subtype of BD was not reported in 12 studies (Adleman et al., 2013; Burger et al., 2017; Fournier et al., 2013; Fournier et al., 2016; Killgore et al., 2008; Liu et al., 2012; Liu et al., 2014; Mukherjee et al., 2016; Shah et al., 2009; Van der Schot et al., 2010; Wang et al., 2009; Yurgelun-Todd et al., 2000). As BD type 1 is clinically distinct from BD type 2, this feature of the study population should be reported. In addition, 3 studies did not report on mood-related characteristics of the study sample, such as the criteria used for the assessment of mood state, or clinical scale score information (Blumberg et al., 2005; Mukherjee et al., 2016; Yurgelun-Todd et al., 2000).

3.3 Methodologies used to examine facial emotion processing circuitry in BD

To probe the facial emotion processing circuitries in BD, functional MRI (fMRI) and encephalographic techniques, such as electroencephalography (EEG) and magnetoencephalography (MEG), have been used in conjunction with emotion processing tasks that involve the labelling, recognition, and/or discrimination of various facial emotions presented either in an explicit or implicit manner. fMRI is a technique that enables investigation of activity in the brain by identifying localised areas of altered haemodynamic responses using the blood-oxygen-level depended (BOLD) signal (Glover, 2011). In contrast, EEG is a technique used to measure the synchronous electrical activity of neuronal populations using scalp electrodes (Light et al., 2010), while MEG measures the magnetic fields generated by the brain electrical activity, using an array of magnetic sensors placed around the head (Singh, 2014). Finally, implicit tasks generally involve the direction of attention towards non-affective cues, such as facial features or gender (Critchley et al., 2000).

Consequently, the processing of facial affect likely occurs outside the individual's awareness. In contrast, explicit tasks involve the conscious labelling of facial affect, where the focus of attention is on the facial affective stimuli itself (Critchley et al., 2000). Other facial emotion processing tasks used included emotional go/no-go tasks and emotional gaze discrimination tasks.

3.4 Functional activity of facial emotion processing structures in BD

In this section, we first present findings from the extended network, as the majority of research has focussed on these brain regions. We then present findings from the core network, followed by findings from other brain regions.

3.4.1 Functional activity of the extended network – fMRI findings

Of the 66 studies included in this review, a total of 46 used fMRI in conjunction with facial emotion processing tasks to investigate the functional activity of brain regions in BD (Table 1). The extended network, including the AMG and other limbic regions, and prefrontal regions, was investigated thoroughly; in 37 studies, out of the 46. The majority of these studies focused on AMG activation, investigated *a priori* through ROI analysis. Specifically, in BD compared to healthy controls, results demonstrated AMG activity was increased in response to facial affect (Almeida et al., 2010; Altshuler et al., 2005; Blumberg et al., 2005; Brotman et al., 2014; Chen et al., 2006; Chen et al., 2010; Foland et al., 2008; Hulvershorn et al., 2012; Keener et al., 2012; Lawrence et al., 2004; Perlman et al., 2012; Rosenfeld et al., 2014; Sagar et al., 2013; Surguladze et al., 2010; Yurgelun-Todd et al., 2000), AMG activity was reduced in response to facial affect (Blumberg et al., 2005; Chen et al., 2006; Grotegerd et al., 2014; Korgaonkar et al., 2019; Lennox et al., 2004; Van der Schot et al., 2010; Vizueta et al., 2012), and there was no difference in AMG activity in response to

facial affect (Almeida et al., 2010; Altshuler et al., 2008; Burger et al., 2017; Deveney et al., 2014; Foland-Ross et al., 2012; Fournier et al., 2016; Fournier et al., 2013; Grotegerd et al., 2014; Hassel et al., 2009; Hassel et al., 2008; Killgore et al., 2008; Kim et al., 2012; Korgaonkar et al., 2019; Li et al., 2019; Liu et al., 2012a; Marchand et al., 2011; Perlman et al., 2012; Radaelli et al., 2012; Robinson et al., 2008; Shah et al., 2009; Tesli et al., 2015; Tesli et al., 2013) (Table 1). Both hyper- and hypoactivation of the AMG occurred across all BD mood states. Hyperactivation of the AMG generally occurred in response to fearful, happy, and sad facial affect, and in response to both explicit and implicit tasks, while hypoactivation of the AMG occurred in response to a mix of facial emotional stimuli. Most of the studies that found AMG hypoactivation did not use implicit tasks. It is unclear whether abnormal AMG activation in BD relates to inefficient processing of socially salient stimuli, or dysregulation of emotional responses.

Functional neural abnormalities in other components of the extended network were also evident in individuals with BD during facial emotion processing. Indeed, findings from a number of studies suggested that there is hypoactivation of vlPFC during euthymic (Dima et al., 2013; Foland-Ross et al., 2012), depressed (Vizueta et al., 2012), and manic (Foland et al., 2008) mood states in BD, in response to facial affect. This result has also been found in a mixed BD cohort of multiple mood states (Brotman et al., 2014). Similarly, hypoactivation of the OFC has been consistently demonstrated during facial emotion processing in BD across mood states (Altshuler et al., 2005; Hulvershorn et al., 2012; Liu et al., 2012a; Van der Schot et al., 2010; Vizueta et al., 2012), though hyperactivation of the OFC (Chen et al., 2010; Wessa et al., 2007) and vPFC (Chen et al., 2006; Lawrence et al., 2004; Robinson et al., 2008), has also been reported. One study found hyperactivation in the left lateral OFC and hypoactivation in the right lateral OFC, in depressed BD compared to healthy controls

during emotion processing (Altshuler et al., 2008). Overall, prefrontal hypoactivation during emotion processing may be a trait feature in BD that occurs across mood states.

Fearful facial affect most frequently elicited prefrontal hypoactivation, compared to other facial affective stimuli, in BD compared to healthy controls. Across studies, fearful affect was also the most commonly used stimulus in emotion processing tasks. Angry affect also frequently elicited prefrontal hypoactivation, though was used less commonly in task design. Happy, neutral, sad, scared, and disgusted facial stimuli were also associated with prefrontal hypoactivation, though demonstrated in fewer studies.

In sum, though there were some inconsistent results, these fMRI findings generally demonstrated reduced PFC activity and increased AMG activity in response to facial affect in BD relative to healthy controls. This suggests that altered prefrontal function disinhibits limbic circuitry during the processing of facial affect in BD.

3.4.2 Functional activity of the core network – fMRI findings

Relative to brain regions within the extended facial emotion processing network, regions in the core network have received little research attention in fMRI studies of BD using ROI approaches (Table 1). Findings from fMRI studies primarily taking a whole-brain analysis approach, however, provide preliminary evidence that regions within this network may function abnormally in BD. Several studies have demonstrated altered FG activity across BD mood states in response to facial affective stimuli. FG activity has been found to be attenuated in euthymic (Dima et al., 2013; Malhi et al., 2007), and depressed (Fournier et al., 2013) mood states, and also in a BD cohort containing participants in euthymic, manic and mixed mood states (Adleman et al., 2013). Conflicting results from one other study suggest FG hyperactivation in manic BD (Chen et al., 2006), though this study had a relatively smaller sample size. Finally, one study found FG activity comparable to that of

healthy controls (Blumberg et al., 2005). This study also had a relatively small sample size, and the BD group was comprised of different mood states, including euthymic, depressed, hypomanic, manic and mixed. Across these studies, altered FG activation primarily occurred in response to negative facial emotions, such as fearful, sad, angry, and disgusted.

There is also evidence of hyperactivity in temporal structures in response to facial affective stimuli in BD. Using whole-brain analyses, these studies found hyperactivation of the superior temporal gyrus (Fournier et al., 2013; Malhi et al., 2007; Wessa et al., 2007) and middle temporal gyrus (Chen et al., 2006; Fournier et al., 2013; Wessa et al., 2007) in BD compared to healthy controls, though one study found hypoactivation of the superior temporal gyrus in depressed BD compared to HC (Vizueta et al., 2012). To our knowledge, functional activity of the STS has not been specifically examined in response to facial affective stimuli in BD.

Finally, only one fMRI study investigated functional activity of the IOG using an ROI approach. This study found IOG hypoactivation in response to facial affect in euthymic BD compared to healthy controls (Dima et al., 2013). Though this finding needs to be replicated, it is supported by other studies that have demonstrated functional abnormalities in other visual areas more broadly (Chen et al., 2006; Dima et al., 2013; Fournier et al., 2013; Malhi et al., 2007). Taken together, these findings suggest that there may be early deficits in the visual affective processing circuitry in BD.

3.4.3 Functional activity of other brain regions – fMRI findings

Other brain regions have also shown altered activity in response to facial affective stimuli in BD (Table 1). The anterior cingulate cortex (ACC), in particular, has consistently exhibited altered functioning. ACC activity has been found to be both increased (Brotman et al., 2014; Chen et al., 2006; Hulvershorn et al., 2012; Powell et al., 2019; Radaelli et al.,

2012; Rosenfeld et al., 2014; Sagar et al., 2013; Wessa et al., 2007), and reduced (Blumberg et al., 2005; Brotman et al., 2014; Chen et al., 2006; Foland et al., 2008; Jogia et al., 2008; Lagopoulos and Malhi, 2011; Lennox et al., 2004; Liu et al., 2012a; Marchand et al., 2011; Shah et al., 2009; Vizueta et al., 2012) in BD compared to healthy controls. These findings occurred across all mood states in BD, and in response to both positive and negative facial affect. In addition, the insula has also shown altered activity in response to facial affect in BD, with both increased (Chen et al., 2010; Hulvershorn et al., 2012; Lennox et al., 2004; Malhi et al., 2007; Rosenfeld et al., 2014) and reduced (Foland-Ross et al., 2012; Fournier et al., 2016; Vizueta et al., 2012; Wessa et al., 2007), activity found across all BD mood states.

In regards to the dorsolateral PFC (dlPFC), and similar to other prefrontal regions, most studies reported reduced activity in response to facial affective stimuli in BD compared to healthy controls (Almeida et al., 2009a; Altshuler et al., 2008; Hassel et al., 2008; Radaelli et al., 2012; Van der Schot et al., 2010; Yurgelun-Todd et al., 2000); though one study found increased right but reduced left dlPFC activity (Sagar et al., 2013). Another study found dlPFC hyperactivation, though only in manic, but not depressed or euthymic, BD compared to healthy controls (Hulvershorn et al., 2012).

Other affected frontotemporal areas in BD include; medial prefrontal areas (Keener et al., 2012; Lagopoulos and Malhi, 2011), hippocampal structures (Almeida et al., 2009a; Chen et al., 2006; Chen et al., 2010; Jogia et al., 2008; Lagopoulos and Malhi, 2011; Malhi et al., 2007; Radaelli et al., 2012; Vizueta et al., 2012), superior and middle frontal gyri (Chen et al., 2006; Marchand et al., 2011), precentral gyrus (Chen et al., 2006; Jogia et al., 2008; Malhi et al., 2007; Vizueta et al., 2012), claustrum (Malhi et al., 2007), temporal pole (Van der Schot et al., 2010), and inferior temporal gyrus (Wessa et al., 2007).

Using primarily whole-brain approaches, other brain regions have demonstrated altered activity, with mixed directionality. These brain regions include; the thalamus and

basal ganglia (Brotman et al., 2014; Chen et al., 2006; Chen et al., 2010; Foland-Ross et al., 2012; Fournier et al., 2016; Hassel et al., 2008; Hulvershorn et al., 2012; Lagopoulos and Malhi, 2011; Lawrence et al., 2004; Surguladze et al., 2010; Vizueta et al., 2012; Wessa et al., 2007), parietal areas (Fournier et al., 2013; Malhi et al., 2007; Vizueta et al., 2012), and occipital areas (Fournier et al., 2013; Malhi et al., 2007; Marchand et al., 2011; Tesli et al., 2015; Wessa et al., 2007). It is possible that the mixed findings in relation to these brain areas relate to differences in the stringency of whole-brain analysis corrections; these findings could be further clarified using ROI approaches.

3.4.4 Functional activity - EEG and MEG findings

Findings from studies using encephalographic techniques such as EEG and MEG also suggest functional activation abnormalities in components of the core and extended face processing network in BD, though there has not been much research using these techniques (Table 2). These techniques are critical as they exhibit millisecond temporal resolution, enabling an understanding of the sequence of affective network activation. These studies generally examined different components of face-relevant event-related potential (ERP) waveforms, including the P80, P100, N120, N170, N250, P200/vertex positive potential (VPP), P3a, and P3b. The P100 is a positive going wave that peaks approximately 100ms after stimulus onset that is generated in occipital areas, and is associated with early visual processing (Degabriele et al., 2011). The N170 is a later negative peak that is generated at occipitotemporal sites such as the FG (Sadeh et al., 2010) and STS (Itier and Taylor, 2004), and generally is associated with the configuration of facial features (Batty et al., 2014; Hinojosa et al., 2015). The N250 is a negative going potential that is maximal at frontal sites (Wynn et al., 2013). It is associated with the decoding of facial features, including features of the face that are related to particular emotions (Streit et al., 1999). The P3a and P3b,

subcomponents of the P300, are long-latency positive going potentials generated at frontal (Knight et al., 1995) and temporal-parietal (Verleger et al., 1994) areas respectively. The P3a and P3b are associated with attention, and the P3b is also associated with working memory processing (Polich, 2007). Finally, less is known about the P80 and VPP in relation to facial emotion processing, but it has been suggested that these ERPs represent components of early visual response, are relevant in the processing of facial affective stimuli, and are distinct from other early potentials (Ashley et al., 2004; Williams et al., 2006). Similarly, MEG captures event-related fields, which are comparable to ERPs for EEG.

Abnormalities in ERPs involved in visual processing have been demonstrated in BD. Degabriele and colleagues (Degabriele et al., 2011) used EEG in conjunction with an explicit emotional go/no-go inhibition task using happy and sad face stimuli. The authors found that BD was associated with increased P100 amplitudes in response to happy, compared to sad, facial affect (Degabriele et al., 2011), corroborating findings of differential neural activation to particular emotions from fMRI studies (Blumberg et al., 2005; Chen et al., 2006; Lawrence et al., 2004; Sagar et al., 2013), and implicating occipital and temporal cortical regions. Another study also found evidence of altered VPP and P80 latencies in BD (Degabriele and Lagopoulos, 2012), adding further support to the notion that early visual processing regions are implicated in BD.

Research investigating a later ERP, the N170, as an index of configural face processing, found altered amplitudes in BD in response to facial affective stimuli (Degabriele et al., 2011; Howells et al., 2014; Ibanez et al., 2014; Sokhadze et al., 2011; Tso et al., 2017). One study found no difference in N170 amplitude in response to happy and angry affective stimuli in BD compared to healthy controls, where there were emotion-specific N170 differences (Ibanez et al., 2012). This suggests that in BD, the N170 - and possibly by

association, the FG - are involved in the abnormal processing of facial emotions, not just faces themselves.

In relation to later facial processing, one study compared the N250, as a measure of facial feature decoding, between BD and healthy control groups (Wynn et al., 2013). Results indicated reduced amplitudes and increased latencies of the N250 waveform in response to facial affect in BD compared to healthy controls (Wynn et al., 2013). Altered P3b waveforms have also been found in BD; in response to sad facial affect, BD has been associated with increased P3b amplitudes and latencies, compared to healthy controls (Zhang et al., 2018). These findings suggest altered facial emotion processing in frontal and temporal-parietal regions in BD.

MEG has also been used to examine the temporal dynamics of facial emotion processing in BD. One study found increased alpha oscillatory activity in the right middle occipital gyrus, right inferior parietal gyrus, and the right inferior and middle frontal gyrus in response to angry affect in BD, regions relevant to the core and extended networks (Lee et al., 2010). Another study also found increased gamma oscillatory activity in right middle and occipital cortices, and the right middle temporal cortex, at the early 80-120s timepoint, in response to angry but not sad facial affect in BD (Liu et al., 2014). Finally, another study found reduced mean frontal and prefrontal gamma activity in early (50-150ms) and late (200-300ms) time-windows respectively, as well as increased gamma activity in parieto-temporal regions in an early time window, in BD (Liu et al., 2012b). As early gamma oscillations are thought to represent a key mechanism for perceptual binding of object features (Tseng et al., 2016), the latter results were taken as suggesting hypersensitivity to facial information in BD.

In combination, the results of encephalographic studies generally support the fMRI data by demonstrating abnormal neural activity in regions implicated in the core and extended facial processing networks in BD, and provide important information about the time

course of neural activity in facial emotion processing. Furthermore, these findings add to the literature by demonstrating that in addition to evidence for abnormal AMG and *top-down* processing (indexed by abnormal frontal activity) in facial emotion processing in BD, there may be other abnormalities in the *bottom-up* processing of visual and configural facial information.

3.5 Functional connectivity of facial emotion processing circuitry in BD

3.5.1 Functional connectivity - fMRI findings

Functional connectivity refers to the statistical correlation between functional brain activity signals between two or more brain regions. Functional connectivity analyses are used to understand the integration of nodes (brain regions) within distributed brain networks (Friston, 2011). In healthy individuals, it has been demonstrated that there is negative functional connectivity between the AMG and vlPFC during explicit evaluation (labelling) of facial affect (Foland et al., 2008; Hariri et al., 2000); that is, the vlPFC is negatively correlated with AMG activation during such tasks. This is thought to reflect an inhibitory influence of the vlPFC upon the AMG, though the directionality cannot be determined from fMRI functional connectivity analyses alone.

There have been relatively few studies that have used fMRI to explicitly probe functional connectivity associated with facial emotion processing in BD, especially in relation to core face processing structures (Table 3). These studies primarily used psychophysiological interaction analysis (PPI) (Friston et al., 1997), and found reduced or absent negative functional connectivity between AMG and PFC structures during facial emotion processing in euthymic, manic, or depressed BD patients. Specifically, reduced AMG-vlPFC functional connectivity (Foland et al., 2008), and reduced AMG-OFC functional connectivity (Tseng et al., 2016; Versace et al., 2010b; Vizueta et al., 2012) were

found in BD compared to HC, suggesting altered connectivity of the extended facial emotion processing network. In addition, one study found reduced AMG-dlPFC negative functional connectivity (Vizueta et al., 2012). However, there have been some inconsistent findings, with absent or increased functional connectivity between AMG and medial OFC (Korgaonkar et al., 2019), AMG and vlPFC (Versace et al., 2010b; Vizueta et al., 2012), and AMG and middle frontal gyrus (Foland et al., 2008), in BD compared to HC. These mixed findings, showing both a reduction in negative PFC-AMG functional connectivity during facial emotion processing in BD, and an increase in PFC-AMG connectivity in other studies, are consistent with a previous systematic review (Chase and Phillips, 2016), which attributed the inconsistency in findings to differences in task methodology. More sophisticated statistical techniques are required to determine the directionality of abnormalities in functional connectivity findings.

Functional connectivity findings between the AMG and other limbic structures are somewhat inconsistent. Findings suggest increased AMG-ACC negative functional connectivity (Foland et al., 2008) and increased AMG-hippocampus positive functional connectivity (Vizueta et al., 2012), while other studies found reduced functional connectivity between the AMG and the hippocampus and insula (Korgaonkar et al., 2019), reduced functional connectivity between the AMG and perigenual ACC (Wang et al., 2009), and no significant between-group differences in AMG-ACC functional connectivity (Mukherjee et al., 2016). These mixed findings suggest that connectivity between limbic structures in BD, in response to emotion processing, are complex, and require further investigation.

Functional connectivity between the AMG and putamen has also been examined with mixed results; one study found increased AMG-putamen positive functional connectivity (Vizueta et al., 2012), and another study found reduced AMG-putamen functional connectivity (Korgaonkar et al., 2019). In addition, one study found increased positive

functional connectivity between AMG and the superior temporal gyrus in BD compared to HC (Vizueta et al., 2012), suggesting abnormal connectivity between early face processing and limbic regions.

3.5.2 Functional connectivity – EEG and MEG findings

EEG and MEG techniques allow for the examination of functional connectivity at a faster time resolution compared to that observed with fMRI. Though EEG has been used to investigate functional connectivity in BD broadly (Chase and Phillips, 2016), no EEG study has specifically investigated functional connectivity of the facial emotion processing circuitry using facial affective tasks. To our knowledge, only one MEG study has investigated functional connectivity of the emotion processing circuitry in BD, using an implicit facial emotion processing paradigm. Liu and colleagues (Liu et al., 2012b) found *increased* negative functional connectivity between frontal and parietal-occipital regions occurring in the early time window of 50-150ms, in the gamma oscillatory range, in BD compared to HC. It is unclear how to interpret this finding in the context of the fMRI functional connectivity literature, however it provides evidence of altered long-range integration between visual face-processing and downstream emotion-cognitive brain areas.

3.6 Effective connectivity of facial emotion processing circuitry in BD

Effective connectivity analyses augment findings from functional connectivity studies by using statistical techniques to infer causality and directionality of correlations in activity between brain regions (Friston et al., 2003). DCM has been the primary technique used to examine effective connectivity of brain networks by using probabilistic Bayesian modelling applied to brain networks (Friston et al., 2003; Penny et al., 2004). DCM enables the exploration of the dynamics between neural systems, and how one neural system may exert

an effect on another. In addition to modelling the strength of effective connectivity between ROIs, DCM can also model how this connectivity may be modulated by an external variable, such as a facial processing task, or the activity of another brain area. DCM may be applied to both fMRI and encephalographic data, though the majority of research uses DCM in conjunction with fMRI (Friston et al., 2003).

Effective connectivity of facial emotion processing circuitry in BD has received little research attention to date (Table 4). A study by Dima and colleagues (Dima et al., 2013) investigated the influence of the BD risk alleles *CACNA1C* and *ANK3* on the activity and effective connectivity of the core (IOG and FG) and extended (AMG and vPFC) facial emotion processing networks in euthymic BD and healthy controls. They found that facial affective stimuli increased the feed-forward effective connectivity from the IOG to the vPFC in healthy controls, and this effective connectivity was further increased in healthy controls who had the risk alleles of the genes of interest. In contrast, individuals with BD were found to have reduced effective connectivity in the visual-prefrontal (IOG-vPFC) pathway, and this connectivity was further reduced in BD individuals who had the risk alleles. Additionally, the AMG-vPFC feed-forward pathway was modulated by facial affect in BD, but not in healthy controls, suggesting that this localised extended pathway may exhibit neural over-responsiveness to facial affective stimuli in BD. In another study that used an explicit facial affective stimuli task, these same authors showed that first degree relatives of BD individuals as well as individuals with BD themselves, had increased effective connectivity between the AMG and vPFC (Dima et al., 2016). However, additional increased connectivity between the IOG and FG to the vPFC was found in the first-degree relatives, suggesting that AMG-vPFC connectivity may be a connectomic marker of shared genetic risk; and that hyperconnectivity in the ventral visual stream may be an adaptive, protective response to genetic vulnerability.

Another study that investigated the effective connectivity between AMG and orbitomedial PFC in depressed BD patients during an explicit facial emotion processing task (Almeida et al., 2009b) indicated that individuals with BD had less 'top-down' effective connectivity from the left orbitomedial PFC to the left AMG during processing of both happy and sad facial affect. Further, there was greater negative effective connectivity from the 'bottom-up' right AMG to right orbitomedial PFC pathway during the processing of happy facial affect. These findings contrast with those of another study, which found greater 'top-down' PFC-AMG effective connectivity in response to happy affect, and greater 'bottom-up' AMG-PFC effective connectivity in response to fearful affect, in euthymic and depressed BD compared to healthy controls (Perlman et al., 2012). Other studies have found reduced effective connectivity from the dlPFC to the AMG (Radaelli et al., 2015), and increased effective connectivity from the medial frontal gyrus to the putamen (Radua et al., 2013). The results from these studies are difficult to compare directly, due to multiple methodological differences; for example, in explicit vs. implicit task design, in the facial emotional stimuli used, and in the prefrontal areas investigated.

Finally, altered effective connectivity has also been found between components of the limbic system. Specifically, one study found increased effective connectivity from right parahippocampal gyrus to right subgenual cingulate gyrus in euthymic BD compared to healthy controls (Almeida et al., 2009a).

Together, these findings provide preliminary evidence for network abnormalities in facial emotion processing circuitry in BD, and partially validate functional connectivity findings. However, further effective connectivity studies are needed, particularly to clarify the inter-regional connectivity between core and extended networks.

4. Anatomical architecture of facial emotion processing circuitry in BD

Brain function and connectivity cannot be understood in isolation as they are constrained, in part, by their underlying structural architecture. As such, it is necessary to also discuss the morphological structure and connectivity of the facial emotion processing system. It should be noted that anatomical architecture of the facial emotion processing circuitry in BD *was not systematically reviewed* as it was beyond the scope of this paper. A narrative synthesis of the primary findings in this area are included below to assist with interpretation of the functional and effective connectivity findings.

Volumetric findings from structural MRI studies suggest grey matter morphological abnormalities in fronto-limbic and subcortical structures may be implicated in facial emotion processing in BD. Indeed, there are several studies using both ROI and whole-brain analysis methods that have demonstrated volumetric abnormalities in regions of the extended network, including the vlPFC (Adler et al., 2005; Lu et al., 2019), AMG (Hibar et al., 2016; Strakowski et al., 1999), and OFC (Lu et al., 2019), though there appears to be some across-study heterogeneity (McDonald et al., 2004). Regions of the core network have been examined to a lesser degree, with some evidence for volumetric differences in the FG (Adler et al., 2005) and the superior temporal gyrus (Lu et al., 2019) in BD. A recent, large multi-centre study using ROI volumetric analysis of structural MRI data from 2,447 individuals with BD corroborated the above findings, by demonstrating that the vlPFC, AMG, and FG are associated with cortical thinning (Hibar et al., 2018). These findings provide strong evidence that regions of the core and extended networks show structural alterations, which may underlie functional emotion processing abnormalities in BD.

Altered structural connectivity of prefrontal, limbic and other subcortical regions, including components of the core and extended circuitry have been consistently reported in BD. For example, findings show reduced fractional anisotropy (FA) - a measure of white matter integrity believed to be modulated by various neuronal properties including axonal

membrane thickness and diameter (Basser and Pierpaoli, 1996) - in the corpus callosum in BD patients, particularly in the anterior horn (Benedetti et al., 2011; Versace et al., 2014). This suggests dysconnectivity between inter-hemispheric prefrontal and limbic structures. Other areas affected include the anterior cingulum bundle (Versace et al., 2014) - which connects areas of the frontal, temporal and subcortical structures; uncinate fasciculus (Versace et al., 2014) which connects the OFC and the anterior temporal lobes; and the superior longitudinal fasciculus (Benedetti et al., 2011) - which connects occipital, parietal, frontal and temporal areas. Furthermore, there may be localised white matter abnormalities in specific regions, including the OFC (Beyer et al., 2005) and other prefrontal areas (Adler et al., 2004), as well as frontotemporal and occipitotemporal regions (Versace et al., 2010a). This provides further evidence for potentially reduced connectivity among a wide range of cognitive and emotional structures in BD relevant to facial emotion processing.

Taken together, findings in this area generally indicate that there may be abnormal structural connectivity in prefrontal and limbic structures in BD, areas that are implicated in the core and extended face processing networks. However, at this stage, little is known specifically about the structural connectivity *between* these networks. It will be necessary to examine this to move forward in our understanding of the neurobiology of BD.

5. Discussion and future directions

This systematic and narrative review examined the facial emotion processing neural circuitry of BD. Overall, the findings from this review suggest altered occipitotemporal, limbic and prefrontal activity and connectivity in BD, in response to facial affect. In particular, there appears to be increased AMG activity and reduced prefrontal activity in BD, with abnormalities occurring across BD mood states including euthymia. Furthermore, the

findings from whole brain fMRI research, and encephalographic evidence, suggest that there are abnormalities in early visual processing areas in BD, in response to facial affect.

These important findings warrant further discussion. Firstly, it clear that the traditional focus of research in this population so far has been on identifying abnormalities in the functional activity of segregated brain regions of this circuitry. There are multiple lines of evidence suggesting the presence of abnormalities both within the more comprehensively studied extended network, and in the relatively less studied core network. For example, the fMRI findings from this review suggest that FG activity is attenuated across mood states in BD, and EEG findings suggest that this abnormality is specific to the processing of facial affective information, not just faces themselves. Early occipitotemporal components of the facial emotion processing pathways need to be more systematically explored to develop a broader understanding of the network-level and inter-regional properties of these circuits.

Secondly, little is currently known about the connectivity between brain regions involved in facial emotion processing in BD. It is clear that there have only been a small number of studies that have examined functional connectivity in response to facial affective stimuli. Furthermore, the focus of this small number of studies has primarily been on understanding the functional connectivity between the AMG and PFC. These studies have generally indicated altered AMG-PFC connectivity, and effective connectivity studies corroborate these findings and help characterise the directionality of connectivity abnormalities in BD. These results, taken together, suggest reduced 'top-down' prefrontal control of the AMG in response to facial affective stimuli, though more research is needed. The few studies that have investigated connectivity between the core and extended networks in BD have demonstrated reduced effective connectivity (Dima et al., 2013) and increased negative functional connectivity (Liu et al., 2012b) between visual-prefrontal areas, but this inter-regional connectedness is poorly characterized and requires further study. To

incorporate a systems-level neuroscience approach to understand the integrated function of distributed networks in the brain, the *extended* network in BD cannot be viewed as an isolated system.

Thirdly, there appears to be an amygdalocentric model of emotion processing which has been a longstanding paradigm in BD studies (Delvecchio et al., 2012). The majority of studies investigating the activity and connectivity of facial emotion processing circuitry in BD have focussed on the AMG. While it is well established that the AMG plays a role in facial emotion processing, an amygdalocentric model ignores the relative contributions of other key components of the facial emotion circuitry, particularly the earlier face processing structures (i.e., IOG, FG, STS), and other important limbic structures, such as the ACC, which consistently demonstrate abnormal activation during emotion processing in BD.

Fourthly, there has been scant encephalographic research investigating facial emotion processing in BD. It is important to understand the temporal and neuronal oscillatory properties of facial emotion processing in BD, which can only be achieved using techniques such as EEG and MEG. Although both techniques capitalize on waveforms generated by electro-chemical transmission in neuronal assemblies, MEG enables researchers to better localise brain activity as the neuromagnetic signal recorded by MEG is less distorted by the scalp compared to the electrical signal recorded by EEG (Singh, 2014). With the advent of techniques such as Beamforming (Hillebrand et al., 2005) that allow for source localisation from deep structures including the AMG, MEG may allow for more direct probing of emotion processing neural circuitry. Moving forward in this area of research, it will be important to clarify the sequence of neural activation across brain structures within the core and extended networks in BD. In healthy individuals, it has been previously demonstrated that facial affect increases connectivity to the PFC from not only limbic regions, but also early face processing structures such as the FG and IOG (Dima et al., 2011). It appears that

this information is then transmitted back to the AMG and FG. This raises the question as to whether the FG and IOG can really be considered 'early' structures in the context of this sequence of neural events; top-down influence may occur almost as early as bottom-up processes. Understanding the temporal ordering of neural events in BD, using MEG, may help to explain whether facial emotion processing deficits are driven by bottom-up or top-down processes.

There are multiple factors that contribute to the heterogeneity of findings between studies, which makes comparison across studies difficult and may account for some of the inconsistent findings. The statistical methods employed across studies to interpret neuroimaging data are also not necessarily homogenous. For example, DCM can be applied to both fMRI and encephalographic data, while Granger modelling is better suited to the analysis of encephalographic data (Seth et al., 2015). Other methodological differences also complicate comparisons across studies. For example, studies used ROI or whole-brain analysis, explicit or implicit tasks, and different facial emotions as stimuli. A limitation of this systematic review was that not all studies reported these methodological variables consistently. For example, the criteria required to define a particular BD mood state for participants varied, and was not reported in a few studies. Furthermore, many of the studies included in this review had a modest sample size, possibly limiting their power. Given the heterogeneity of BD illness variables, such as mood state and severity of symptoms, this is a significant limitation of this area of research. In contrast, most of the studies in this review controlled for age and sex. As such, it is likely that facial emotion processing abnormalities in BD are independent of these demographic factors. Some studies did not control for the potential effect of the racial and ethnic composition of participants on study outcomes (Blumberg et al., 2005; Foland et al., 2008; Killgore et al., 2008). This is potentially problematic as many tasks contain stimuli of only Caucasian actors, such as the Pictures of

Facial Affect (Ekman and Friesen, 1976). Considering evidence has suggested that the recognition of other-race faces is poorer than own-race faces (Meissner, 2001), this may lead to biased results and is a limitation of the facial emotion recognition research more broadly. Lastly, the findings of this review may not be generalisable to paediatric BD, as this population were excluded from this review to factor out the potentially confounding effect of developmental brain changes that occur during childhood and adolescence.

One other major methodological issue across studies relates to the control stimuli used in facial emotion processing tasks. The control stimuli (or baseline condition) differed across studies, with some studies using shapes or other non-facial, non-emotional stimuli, and others commonly using neutral faces. The use of neutral faces as a baseline could be problematic, as some studies found that neutral faces evoked differences in neural activation between BD and control groups (Almeida et al., 2009a; Almeida et al., 2010; Brotman et al., 2014; Liu et al., 2012a; Sokhadze et al., 2011). As such, the appropriateness of using neutral faces as a baseline stimulus needs to be re-evaluated and future research should investigate the behavioural and neural responses to neutral faces in BD in more detail. Further, recent evidence raises the possibility that within-group scores generated by contrasting the experimental and baseline conditions of an imaging task may be unreliable as a measure of between-group differences (Infantolino et al., 2018). Hence, it will be important for future studies on this topic to more carefully consider the specific baseline condition and/or measure of between group comparison.

In relation to facial affective stimuli, predominantly negative facial affect (fearful, sad, angry, disgust) was associated with altered neural responses. As such, future research should further characterise the effect of specific emotional stimuli on emotion processing in BD. Non-facial affective stimuli, such as that used in the International Affective Picture System (Lang, 1997), have also been used to investigate the neural circuitry of emotion

processing. While there is overlap between the neural networks activated by facial affective stimuli and non-facial affective stimuli, such as the limbic system (Chen et al., 2011), it is possible that these two types of stimuli differentially activate early visual processing areas. As such, the findings from this review are only partially generalisable to emotion processing of non-facial affective stimuli, and future research should aim to directly compare the neural circuitry of facial and non-facial emotion processing.

Individual imaging modalities have been useful in elucidating the activity and connectivity of facial emotion processing circuitry. Yet in isolation these modalities are constrained by limitations including the low temporal resolution of fMRI and the 'inverse problem' for MEG/EEG, since the location of intracranial electrical activity must be deduced by extracranial electrical potentials and magnetic fields (Michel and Brunet, 2019). Source localisation techniques exist, but their utility is limited in the absence of cross-validation with fMRI data. This could be overcome using a multimodal approach to determine spatial agreement between encephalographic techniques in combination with fMRI (Brookes et al., 2011), which is critical for more precisely understanding the integration of top-down and bottom-up cognitive processes (Bar et al., 2006).

Beyond the complementary information that might be derived from examining the same brain network, investigating covariation in functional connectivity measures derived from fMRI and oscillatory connectivity at different frequency bands also has potential to enable the identification of brain networks that are spatially distinct. For example, Brookes and colleagues (Brookes et al., 2011) showed an absence of overlap in MEG-derived theta connectivity and fMRI-derived functional connectivity despite seeing overlap in the alpha, beta and gamma bands. Identification of electroencephalographic oscillatory networks involved in facial emotion processing that do not map to spatially-localised fMRI signals

would still be valuable given different frequency bands map onto different cellular and neurochemical mechanisms.

Combining structural neuroimaging with functional techniques would also enable an improved characterisation of structure-function relationships and spatiotemporal qualities of brain network activity by overcoming the individual limitations of singular techniques (Liu et al., 2015). In the context of facial emotion processing in BD, the integration of structural and functional modalities would enable a more precise understanding of this circuitry, for example, by using diffusion imaging in combination with fMRI to test whether alterations in connectivity in BD arise from structural white matter abnormalities in implicated tracts (Wang et al., 2009).

Taken together, it is evident that there are abnormalities in the functional activity, and functional and effective connectivity, of the facial emotion processing neural circuitry in BD. It is possible that these neural alterations underlie the social cognitive deficits in BD. The connectivity between components of the core and the extended networks, and the spatiotemporal course of neural events between these networks, requires further investigation using structural, functional and multimodal neuroimaging techniques. This will allow for an understanding of the neural correlates of cognition and emotion processing in BD, and the development of a comprehensive model that considers the spatiotemporal course of neural activity between core and extended networks. Examining the mechanisms of emotion processing impairments in BD from a network-level perspective is crucial to understanding the pathophysiology of this condition, and may lead to the development of novel targeted treatments.

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Table 1. Summary of studies investigating functional activity using fMRI and facial emotion processing tasks in bipolar disorder

Study	Participants (*n*) Mean (SD) age (years)	Clinical state of BD participants / criteria for mood state	Facial emotion processing task (implicit/explicit)	Control/ baseline condition	Emotions examined	Confound control	Brain regions investigated (if ROI-analysis)	Main findings
Adleman et al., 2013^	BD (*n* = 22), type not specified Mean (SD) age: 41.3 (9.9) HC (*n* = 35) Mean (SD) age: 36.2 (10.4)	Euthymic, manic, mixed Mean (SD) YMRS score: 4.7 (5.5); Mean (SD) SIGH-SAD score: 16.5 (9.8) Criteria for mood state not explicitly stated	Implicit and explicit	Fixation	Happy Angry Fear Neutral	Age, sex, other	NA – whole-brain	Different pattern of FG activity in hypomanic and mixed BD compared to HC No difference in FG activity between BD subjects across different medications
Almeida et al., 2009a¶	BD type 1 euthymic (*n* = 21) Mean (SD) age: 31.9 (8.5) HC (*n* = 25) Mean (SD) age: 28.84 (9.63)	Euthymic Mean (SD) YMRS score: 1.6 (2.6); Mean (SD) HAM-D score: 2.63 (3.64) Criteria for euthymia: HAM-D score < 7; YMRS score < 10	Explicit	Fixation cross	Happy (displayed at mild and intense intensities) Neutral	Age, sex, mood state/symptoms*	dlPFC Cingulate gyri vmPFC Insula Parahippocampal gyrus Inferior frontal gyrus Caudate ROI- and whole-brain analyses used	↓ right dlPFC activity in response to mild and intense happy facial affect, and neutral faces, in euthymic BD compared to HC ↓ right parahippocampal gyrus activity in response to mild and intense happy facial affect, but not neutral faces, in euthymic BD compared to HC
Almeida et al., 2010^	BD type 1 euthymic (*n* = 15) Mean (SD) age: 33.28 (7.83) BD type 1 depressed (*n* = 15) Mean (SD) age: 36.56 (11.88) HC (*n* = 15) Mean (SD) age: 32.69 (8.00)	*BD euthymic group:* Mean (SD) HAM-D score: 1.47 (1.13) *BD depressed group:* Mean (SD) HAM-D score: 21.53 (6.40) Cut-off scores for mood states not specified	Explicit	Fixation cross	Fear Happy Sad All emotions displayed at mild (50%) and intense (100%) intensities Neutral	Age, sex, mood symptoms*	AMG	↑ left AMG activity in response to mild sad facial affect, and neutral faces, in euthymic and depressed BD compared to HC No significant between-group differences in AMG activation in response to happy or fearful facial affect
Altshuler et al., 2005	BD type 1 manic (*n* = 9) Mean (SD) age: 34.6 (8.0) HC (*n* = 9) Mean (SD) age: 30.4 (7.6)	Manic Mean (SD) YMRS score: 15.1 (3.7) Manic BD diagnosed according to SCID	Explicit	Shapes	Fear Angry	Age, sex	AMG OFC	↑ left AMG activity in response to fearful and angry facial affect, in manic BD compared to HC ↓ bilateral lateral OFC activity in in response to fearful and angry facial affect, in manic BD compared to HC
Altshuler et al., 2008	BD type 1 (*n* = 11) Mean (SD) age: 32 (7.3) HC (*n* = 17) Mean (SD) age: 29.5 (6.6)	Depressed Criteria for depression: SCID diagnosis and HAM-D score ≥ 18	Explicit	Shapes	Fearful Angry Neutral	Age, sex	NA – whole-brain	↓ right lateral OFC, left OFC, and right dlPFC activity in response to fearful and angry facial affect, in BD compared to HC ↑ left lateral OFC activity in response to fearful and angry facial affect, in BD compared to HC

								No significant differences in AMG activity between BD and HC
Blumberg et al., 2005	BD type 1 unmedicated (*n* = 5) Mean (SD) age: 40.0 (12.3) BD type 1 medicated (*n* = 12) Mean (SD) age: 45.8 (9.4) HC (*n* = 17) Mean (SD) age: 33.2 (10.8)	Euthymic, depressed, manic, mixed, hypomanic CARS-M and HAM-D used, cut-offs not specified	Passive viewing	Fixation point	Fear Happy Sad Neutral	Age, sex, mood state/symptoms, other	AMG vPFC FG (used as comparison ROI)	↑ AMG activity in response to happy facial affect, in unmedicated BD compared to HC ↓ AMG activity in response to happy facial affect, in medicated BD compared to HC ↓ rostral anterior cingulate activity in unmedicated BD compared to HC No significant between-group differences in rostral anterior cingulate activation in medicated BD compared to HC No significant between-group differences in regional activation of FG
Brotman et al., 2014^	BD type 1 and 2 (*n* = 26) Mean (SD) age: 41.7 (10.3) HC (*n* = 62) Mean (SD) age: 34.24 (9.54)	Euthymic, depressed, hypomanic, manic, mixed Mean (SD) YMRS score for BD adults: 4.92 (5.19); Mean (SD) SIGH-SAD score for BD adults: 16.79 (10.91) Criteria for euthymia, depression, hypomania, mania and mixed episode not explicitly stated	Implicit, explicit, and passive viewing	Fixation	Fear Angry Happy Neutral	Age, sex, mood state/symptoms*, other	AMG ACC Inferior frontal gyrus Putamen	↑ AMG activity in adult BD compared to adult HC in response to fearful facial affect (explicit processing), and angry and neutral faces (passive viewing/processing) ↓ ACC activity in BD compared to HC in response to angry (explicit and implicit processing), happy (implicit processing), and neutral faces (implicit processing) ↑ ACC activity in BD compared to HC in response to angry facial affect (passive viewing) ↓ inferior frontal gyrus activity in BD compared to HC in response to happy and neutral faces (implicit processing) ↑ putamen activity in BD compared to HC in response to angry and neutral faces (passive viewing) ↓ putamen activity in BD compared to HC in response to hostile facial affect (explicit processing)
Burger et al., 2017^	BD, type not specified (*n* = 36) Mean (SD) age: 38.56 (12.30) HC (*n* = 36) Mean (SD) age: 41.33 (6.05)	Depressed Mean (SD) HAM-D score: 22.25 (5.19); Mean (SD) BDI score: 25.52 (7.65); Mean (SD) MADRS score: 24.11 (6.38); Mean (SD) YMRS score: 2.14 (2.38) Criteria for depression not explicitly stated	Implicit	Shapes	Fear Angry Happy	Age, sex, other	AMG Anterior cingulate gyrus ROI- and whole-brain analyses used	No significant differences in AMG activity in response to facial affect in depressed BD compared to HC
Chen et al., 2006	BD type 1 manic (*n* = 8) Mean (SD) age: 39 (13.44) BD type 1 depressed (*n* =8) Mean (SD) age: 41.88 (12.09)	*Manic BD group:* Mean (SD) YMRS: 24.13 (8.27) *Depressed BD group:* Mean (SD) HAM-D: 18.38 (6.44)	Implicit and explicit	Neutral faces	Fear Happy Sad	Not reported+	NA – whole-brain	↑ middle temporal gyrus, postcentral gyri, parahippocampal gyrus, striatum, thalamus, and brainstem activity in response to fearful facial affect, in manic and depressed BD compared to HC

	HC (n = 8) Mean (SD) age: 38.75 (12.5)	YMRS and HAM-D cut-offs not specified			Neutral All expressions shown in low, medium and high intensities			No significant difference in middle temporal gyrus, postcentral gyri, parahippocampal gyrus, striatum, thalamus, and brainstem activity in response to fearful facial affect between manic and depressed BD ↑ left FG activity in response to sad faces, in manic BD, compared to depressed BD and HC ↑ vPFC, superior frontal gyrus, precentral cortex, striatum, thalamus, cingulate gyrus, middle temporal gyrus, and visual cortex activity in response to happy faces, in depressed BD compared to HC and manic BD ↑ AMG, hippocampus, lateral temporal cortex, medial superior frontal cortex, and ACC activity in manic BD compared to depressed BD and HC when sad faces were implicitly recognised ↓ AMG, hippocampus, lateral temporal cortex, medial superior frontal cortex, and ACC activity in manic BD compared to depressed BD and HC when sad faces were explicitly recognised
Chen et al., 2010	BD type 1 (n = 12; 9 were re-scanned at timepoint 2) Mean (SD) age for manic: 37.92 (13.4) Mean (SD) age for euthymic: 37.99 (14.27) HC (n = 12; 9 were scanned at timepoint 2) Mean (SD) age for timepoint 1: 38.00 (12.04) Mean (SD) age for timepoint 2: 42.00 (11.07)	*Euthymic BD group:* Mean (SD) YMRS: 0.44 (0.88) Mean (SD) HAM-D: 3.11 (2.09) *Manic BD group:* Mean (SD) YMRS: 29.17 (8.13) Mean (SD) HAM-D: 0.67 (0.78) Criteria for euthymia: YMRS score <2 and HAM-D score <4 for at least a 4 week period	Explicit	Neutral faces	Fear Happy Sad Angry Disgust Surprise Neutral	Not reported[+]	AMG OFC Hippocampus Striatum Cingulate cortex Insula	↑ right OFC and left caudate activity in response to facial affect, in manic BD compared to HC at timepoint 1 ↑ right AMG, hippocampus, insula and OFC in response to facial affect, in euthymic BD compared to HC ↑ right activity OFC in response to facial affect in BD, regardless of mood state, compared to HC ↓ posterior cingulate cortex activity in response to facial affect, in BD compared to HC ↓ left AMG and hippocampus activity in response to facial affect, in manic BD compared to euthymic BD
Deveney et al., 2014[^]	BD type 1 and 2 (n = 22) Mean (SD) age: 35.54 (11.2) HC (n = 19) Mean (SD) age: 32.8 (11.4)	Euthymic, depressed, hypomanic, manic, mixed Mean (SD) YMRS score in adult BD: 3.4 (3.2); Mean (SD) SIGH-SAD score in adult BD: 14.7 (13.3) Criteria for euthymia: YMRS ≤ 12 and SIGH-SAD ≤ 20 Criteria for depression: YMRS ≤ 12 and SIGH-SAD > 20 Criteria for hypomania/mania: YMRS > 12 and SIGH-SAD ≤ 20 Criteria for mixed state: YMRS > 12 and SIGH-SAD > 20	Implicit and explicit	Fixation cross	Angry Happy Neutral	Age, sex, other	AMG vPFC ROI- and whole-brain analyses used	No significant differences in AMG activity in response to happy facial affect in adult BD compared to adult HC Less activation of AMG in response to increasing angry facial affect in BD compared to HC BD showed an increased negative correlation between subgenual ACC activation and intensity of angry facial affective stimuli, compared to HC

Dima et al., 2013¶	BD type 1 (*n* = 49) Mean (SD) age: 44.3 (11.9) HC (*n* = 40) Mean (SD) age: 40.2 (13.2)	Euthymic Mean (SD) YMRS score: 1.4 (3.0); Mean (SD) HAM-D score: 4.8 (5.3) Cut-off score for euthymia not specified, but YMRS and HAM-D scores provided	Explicit	Neutral faces	Fear Sad Angry All facial expressions displayed at 150% intensity Neutral	Age, sex, race, mood state/symptoms, other	IOG FG AMG vPFC ROI- and whole-brain analyses used	↓ IOG, FG and VPFC activity in response to facial affect, in BD compared to HC
Foland et al., 2008§	BD type 1 (*n* = 9) Mean (SD) age: 34.6 (8.0) HC (*n* = 9) Mean (SD) age: 30.4 (7.6)	Manic, hypomanic Mean (SD) YMRS score: 15.1 (3.7); Mean (SD) HAM-D score: 9.1 (5.3)	Explicit	Shapes	Fear Angry	Age*, sex	AMG PFC ROI- and whole-brain analyses used	↑ left AMG activity in response to fearful and angry facial affect, in BD compared to HC ↓ vlPFC activity in response to fearful and angry facial affect, in BD compared to HC ↓ ventral ACC activity in BD compared to HC in response to negative emotions
Foland-Ross et al., 2012	BD type 1 (*n* = 24) Mean (SD) age: 38.8 (12.8) HC (*n* = 26) Mean (SD) age: 37.9 (13.4)	Euthymic Mean (SD) YMRS: 1.5 (1.9); Mean (SD) HAM-D: 4.6 (2.1) Criteria for euthymia: lack of meeting criteria for a current manic, hypomanic or depressed episode, as assessed by the SCID, YMRS score ≤ 7, HAM-D score ≤ 7	Implicit and explicit	Shapes	Fear Angry	Age, sex, race, other	AMG vlPFC ROI- and whole-brain analyses used	No significant difference in AMG activity between groups ↓ right vlPFC, right insula, putamen, thalamus, and lingual gyrus activity in BD compared to HC
Fournier et al., 2013	BD, type not specified (*n* = 22) Mean (SD) age: 34.0 (8.2) HC (*n* = 29) Mean (SD) age: 32.5 (6.3)	Depressed Mean (SD) YMRS score for BD group: 4.0 (2.6); Mean (SD) HAM-D score for BD group: 19.7 (6.1) Criteria for depression not explicitly stated	Implicit	Shapes	Fear Angry Sad Happy Neutral	Age, sex, other	AMG ROI- and whole-brain analyses used	No significant differences in AMG activity in response to angry facial affect in BD compared to HC ↑ right ACC activity in response to sad facial affect, in BD compared to HC ↑ left middle temporal and superior temporal activity in response to sad facial affect, in BD compared to HC ↓ right temporal-parietal regional activity in response to angry facial affect, in BD compared to HC ↓ right occipital activity in response to fearful facial affect, in BD compared to HC ↓ left FG activity in response to sad facial affect, in BD compared to HC
Fournier et al., 2016^	BD, type not specified (*n* = 16) Mean (SD) age: 35.22 (8.91) HC (*n* =19) Mean (SD) age: 32.17 (6.28)	Depressed Mean (SD) YMRS score: 3.94 (2.57) Participants screened using the SCID, and depressive symptoms assessed using HAM-D and YMRS, but exact cut-offs not stated	Implicit	Shapes	Fear Angry Sad Happy	Age, sex, mood state/symptoms*, other	AMG	↓ left striatum activity in response to facial affect, in depressed BD compared to HC ↓ left thalamus activity in response to facial affect, in depressed BD compared to HC ↓ left insula activity in response to facial affect, in depressed BD compared to HC

								No significant differences in AMG activity in response to facial affect in depressed BD compared to HC
Grotegerd et al., 2014^	BD depressed type 1 (n = 22) Mean (SD) age: 42.0 (11.0) HC (n = 22) Mean (SD) age: 41.1 (10.9)	Depressed Mean (SD) YMRS score: 2.1 (1.7); Mean (SD) HAM-D score: 23.3 (4.6) Participants assessed on the SCID, and HAM-D and YMRS used, however cut-offs for depression not specified	Implicit	Neutral faces	Sad Happy Neutral	Age, sex, other	AMG	↓ AMG activity in response to sad facial affect, in depressed BD compared to HC No significant differences between depressed BD and HC in AMG activity in response to happy facial affect
Hassel et al., 2008	BD type 1 (*n* = 19) Mean (SD) age: 32.47 (8.8) HC (*n* = 24) Mean (SD) age: 27.78 (8.7)	Euthymic Mean (SD) YMRS: 1.37 (2.67); Mean (SD) HAM-D: 1.94 (2.59) Criteria for euthymia: in remission for at least 2 months as assessed by the SCID and clinical interview	Implicit	Fixation cross	Fear Happy Neutral Fear and happy expressions shown in mild and intense intensities	Age, sex, mood state/symptoms*, other	NA – whole-brain	No significant difference in AMG activity between groups in response to fearful and happy facial affect ↑ left striatum activity in response to happy facial affect, in BD compared to HC ↓ dlPFC activity in response to happy and fearful facial affect, in BD compared to HC
Hassel et al., 2009	BD type 1 (*n* = 14) Mean (SD) age: 32.64 (9.92) HC (*n* = 16) Mean (SD) age: 28.50 (9.28)	Euthymic Mean (SD) YMRS score: 1.54 (2.60); Mean (SD) HAM-D score: 3.0 (4.84) Euthymia defined as: "having been in remission for at least 2 months as assessed by SCID and clinical interview".	Implicit	Fixation cross	Fear Happy Both emotions viewed at mild and intense intensities Neutral	Age, sex, other*	Prefrontal regions	No significant differences in AMG activity in response to happy or fearful facial affect, in BD compared to HC ↓ right dPFC activity in response to happy facial affect, in BD compared to HC
Hulvershorn et al., 2012	BD depressed (*n* = 30) Mean (SD) age: 35.0 (11.0) BD hypomanic/manic (*n* = 30) Mean (SD) age: 34.0 (11.0) BD euthymic (*n* = 15) Mean (SD) age: 31.0 (11.0) BD participants were type 1 and 2 HC (*n* = 30) Mean (SD) age: 32.0 (10.0)	Depressed, hypomanic/manic, euthymic Mean (SD) YMRS for depressed, euthymic, and manic BD respectively: 3 (3); 2(3); 16(3) Mean (SD) HAM-D for depressed, euthymic, and manic BD respectively: 20 (4); 7(4); 6(3) Criteria for depression: HAM-D score >15; YMRS <12 Criteria for hypomania/mania: YMRS > 10, and HAM-D < 18 Criteria for euthymia: YMRS < 10 and HAM-D < 10	Explicit	Shapes	Angry Scared	Age, sex, ethnicity	AMG and other limbic regions OFC ROI- and whole-brain analyses used	↑ AMG activity in response to angry and scared facial affect, in depressed and euthymic BD (but not manic BD) compared to HC ↑ right putamen activity in response to negative facial affect in depressed, euthymic, and manic BD, compared to HC ↑ insula activity in response to negative facial affect, in manic and euthymic BD compared to HC ↑ dorsal ACC activity in response to negative facial affect, in manic BD compared to HC ↑ dlPFC activity in response to negative facial affect, in manic BD compared to HC ↓ left OFC activity in response to angry and scared facial affect in manic BD, compared to HC and euthymic BD
Jogia et al., 2008	BD type 1 (*n* = 12) Mean (SD) age: 42.1 (11.8) HC (*n* = 12) Mean (SD) age: 41.8 (10.9)	"stable" Mean (SD) YMRS score: 1.0 (1.3); Mean (SD) HAM-D score: 13.75 (2.43)	Explicit	Neutral faces	Sad displayed at 150% intensity Neutral	Age, sex	NA – whole-brain	↓ superior, inferior and middle frontal gyrus activity in response to sad facial affect, in BD compared to HC ↑ parahippocampal gyrus activity in response to sad facial affect, in BD compared to HC

		BD patients needed to to have HAM-D scores < 14, and YMRS scores < 7 to participate						↓ cingulate and precentral gyri activity in response to sad facial affect, in BD compared to HC
Keener et al., 2012	BD type 1 (*n* = 27) Mean (SD) age: 32.4 (6.52) HC (*n* = 27) Mean (SD) age: 31.7 (8.47	Euthymic Criteria for euthymia: In remission for at least 2 months, HAM-D ≤ 7 and YMRS ≤ 10 Mean (SD) YMRS: 2.15 (2.41); Mean (SD) HAM-D: 6.04 (4.5)	Implicit	Shapes	Fear Happy Angry Sad Neutral	Age, sex	AMG ROI- and whole-brain analyses used	↑ AMG activity in response to happy facial affect, in euthymic BD compared to HC ↑ mPFC activity in response to happy facial affect, in euthymic BD compared to HC
Killgore et al., 2008	BD, type not specified (*n* = 14) Mean (SD) age: 28.1 (11.2) HC (*n* = 13) Mean (SD) age: 25.5 (4.7)	Mood state of BD participants not reported Mean (SD) YMRS score: 14.3 (8.9); Mean (SD) HAM-D score: 15.6 (9.9)	Passive viewing	Fixation	Fear	Age	AMG Basal ganglia	No significant difference in AMG activity in response to passive viewing of fearful facial affect between BD and HC No significant whole-brain analysis differences between groups after correction for multiple comparisons
Kim et al., 2012^	BD type not specified (*n* = 17) Mean (SD) age: 40.04 (10.06) HC (*n* = 22) Mean (SD) age: 34.91 (12.27)	Euthymic Depressed Hypomanic Mean (SD) YMRS score: 3.77(4.55); Mean (SD) SIGH-SAD score: 17.47 (15.59) Cut-offs for mood: YMRS ≤ 12 and SIGH-SAD ≤ 20 for euthymia; YMRS ≤ 12 and SIGH-SAD > 20 for depression; YMRS > 12 and SIGH-SAD ≤ 20 for hypomania/mania; YMRS > 12 and SIGH-SAD > 20 for mixed state	Implicit	Fixation cross	Fear Angry Neutral	Age, sex, other	AMG ROI- and whole-brain analyses used	No significant difference in AMG activation between BD and HC, in response to facial affect
Korgaonkar et al., 2019^	BD type 1 (*n* = 23) Mean (SD) age: Mean (SD) age: HC (*n* = 25) Mean (SD) age: 34.29 (13.31)	Euthymic Mean (SD) YMRS score: 2.09 (2.58); Mean (SD) HAM-D score: 5.22 (6.11) Criteria for euthymia: 2 weeks of being asymptomatic, and HAM-D < 7 for at least 2 weeks	Passive viewing (supra- and sub-liminal exposure to stimuli)	Implicit baseline	Fear Angry Happy Sad Disgust Neutral	Age, sex, mood state/symptoms*	AMG ACC Hippocampus Insula mOFC Basal ganglia ROI- and whole-brain analyses used	No significant difference in AMG activity on supraliminal task, in BD compared to HC ↓ AMG activity in response to subliminal passive viewing across all emotions, in euthymic BD compared to HC
Lagopoulos et al., 2011	BD type 1 euthymic (n = 11); females only Mean (SD) age: 33.33 (9.23)	Euthymic	Explicit	Neutral faces	Disgust Neutral	Age, sex, other	NA – whole-brain	↑ bilateral caudate activity in response to disgust, in BD compared to HC

	HC (n = 11) Mean (SD) age: 33.56 (6.73)	Mean (SD) YMRS score: 0.89 (0.33); Mean (SD) HAM-D score: 4.33 (1.12) Criteria for euthymia: HAM-D scores ≤ 6 and YMRS scores ≤ 6						↑ left hippocampus activity in response to disgust, in BD compared to HC ↓ medial prefrontal gyrus activity in response to disgust, in BD compared to HC ↓ anterior cingulate gyrus activity in response to disgust, in BD compared to HC ↓ thalamus activity in response to disgust, in BD compared to HC
Lawrence et al., 2004^	BD type 1 (*n* = 12) HC (*n* = 11) Overall mean (SD) age: 41 (11)	Euthymic, depressed YMRS scores ranged from 2 to 7 in BD group (only ranges reported); Mean (SD) BDI score: 15.3 (9.2) Cut-offs for mood: YMRS ≤ 7, BDI < 9 for euthymia, BDI 10-19 for mild depression, BDI >20 for moderate-severe depression	Implicit	Neutral faces	Fear Happy Sad Neutral For all expressions, 'mild' (50%) and 'intense' (100%) intensities were used	Age, sex, other	AMG Striatum Thalamus Hippocampus Parahippocampal gyrus dPFC vPFC	↑ AMG, caudate and putamen activity in response to mild happy facial affect, in BD compared to HC ↑ right globus pallidus and thalamus activity in response to mild fearful affect, in BD compared to HC ↑ left AMG and vlPFC activity in response to intense fearful facial affect, in BD compared to HC ↑ vPFC activity in response to mild happy facial affect, and mild and intense sad facial affect, in BD compared to HC
Lennox et al., 2004	BD type 1 (*n* = 10) Mean (SD) age: 37.3 (12.8) HC (*n* = 12) Mean (SD) age: 32.6 (10.7)	Manic, determined by standardised clinical interview (unspecified) Mean (SD) YMRS score: 27.7 (7.9); Mean HAM-D score: 0.0	Explicit	Neutral faces	Happy Sad Both expressions were shown in the following intensities: 0%, 50%, 100%, 125%	Age, sex, other	AMG ROI- and whole-brain analyses used	↓ AMG and subgenual ACC activity in response to sad facial affect, in manic BD compared to HC ↑ posterior cingulate cortex and posterior insula activity in response to sad affect, in manic BD compared to HC No significant between-group differences in response to happy affect
Li et al., 2019	BD type 1 (*n* = 13) Mean (SD) age: 30.0 (9.0) HC (*n* = 16) Mean (SD) age: 29.0 (7.0)	Euthymic Criteria for euthymia: asymptomatic for the 2 months prior to scanning (assessed using the SCID); YMRS score < 6 and HAM-D score < 6 Mean (SD) YMRS score for BD on valproate and lithium respectively: 0.7 (0.95); 0.8 (1.09); Mean (SD) HAM-D score for BD on valproate and lithium respectively: 1.1 (1.26); 1.1 (1.61)	Explicit	Shapes	Angry Afraid	Age, sex, other	NA- whole-brain	No significant between-group differences observed (this null result included the AMG)
Liu et al., 2012a	BD euthymic (*n* = 39) Mean (SD) age: 32.1 (12.3) BD depressed (*n* = 19) Mean (SD) age: 34.2 (10.8) BD hypomanic/manic/mixed (*n* = 18) Mean (SD) age: 31.4 (12.5) BD type not specified	Euthymic, hypomanic/manic/mixed, depressed Mood states determined using SCID, but exact criteria for mood state not specified	Implicit	Fixation cross	Fear Happy Neutral	Age, sex	AMG Striatum PFC ROI- and whole-brain analyses used	↓ OFC, striatum, and ventral ACC activity in response to happy and neutral faces in BD compared to HC, with no effect of mood state (result found for depressed, euthymic, hypomanic/manic/mixed) ↓ right rostral PFC activity in response to fearful and neutral faces, in hypomanic/manic/mixed BD compared to HC No significant differences in AMG activity in response to facial affect, in BD compared to HC

Malhi et al., 2007	HC (*n* = 58) Mean (SD) age: 30.0 (9.9) BD type 1 (*n* = 10) Mean (SD) age: 33.5 (8.7) HC (*n* = 10) Mean (SD) age: 32.4 (6.4)	Euthymic Criteria for euthymia: HAM-D ≤ 6, YMRS ≤ 6	Explicit	Neutral faces	Fear Disgust Neutral	Age, sex, other	NA – whole-brain	↑ left middle occipital gyrus and bilateral lingual gyrus activity in response to disgust facial affect, in BD compared to HC ↑ left FG, cerebellum, and right insula activation, in response to disgust facial affect, in HC compared to BD ↑ left superior temporal gyri, inferior parietal lobe, claustrum, and hippocampus, bilateral parahippocampal gyrus, right lingual gyrus, and cerebellum activity in response to fearful facial affect, in BD compared to HC ↑ left precentral gyrus activity in response to fearful affect, in HC compared to BD
Marchand et al., 2011	BD type 2 (*n* = 16) Mean (SD) age: 32.9 (7.5) HC (*n* = 19) Mean (SD) age: 33.7 (12.5)	Depressed Mean (SD) YMRS score: 2.8 (1.6); Mean (SD) MADRS score: 27.5 (7.3) Criteria for depression: ≥ 2 week episode of depression, MADRS score ≥ 18, and YMRS score ≤ 6	Explicit	Neutral faces	Fear Happy Neutral	Age, sex, other	AMG ROI- and whole-brain analyses used	↓ left superior frontal gyrus, precuneus, and left cingulate activity, in response to happy facial affect in depressed BD compared to HC Within the BD group, happy facial affect was associated with less superior temporal gyrus activity than fearful facial affect (differential processing of positive and negative facial affect) No significant between-group differences in AMG activity in response to facial affect
Perlman et al., 2012¶	BD type 1 euthymic (*n* = 31) Mean (SD) age: 32.63 (8.21) BD type 1 depressed (*n* = 21) Mean (SD) age: 33.09 (8.38) HC (*n* = 25) Mean (SD) age: 31.75 (6.46)	Euthymic, depressed Mean (SD) YMRS scores in euthymic and depressed BD respectively: 2.39 (2.50); 4.00 (2.72) Mean (SD) HAM-D scores in euthymic and depressed BD respectively: 7.29 (5.53); 24.62 (8.20) Criteria for euthymia: in remission for at least 2 months, HAM-D ≤ 7 and YMRS ≤ 10 Criteria for depression: depressed mood for at least 2 weeks (current), based on SCID interview	Implicit	Shapes	Fear Happy Angry Sad Neutral	Age, mood symptoms*	AMG PFC ROI- and whole-brain analyses used	↑ AMG activity in response to fearful, sad, and angry facial affect, in euthymic BD compared to HC ↑ right AMG activity in response to fearful facial affect, in depressed BD compared to HC No significant differences between euthymic BD and depressed BD in AMG activity in response to facial affect
Powell et al., 2019^	BD type 1 euthymic (*n* = 41) Mean (SD) age: 44.04 (10.3) HC (*n* = 46) Mean (SD) age: 39.71 (14.82)	Euthymic Mean (SD) YMRS score: 1.4 (3.0); Mean (SD) HAM-D score: 4.8 (5.3) Criteria for euthymia: YMRS score < 7 and HAM-D score < 7	Explicit	Neutral faces	Fear Angry Sad (All emotions displayed at 150% intensity)	Age, sex, race, mood symptoms, other	IOG FG AMG PFC	↓ superior frontal gyrus activity in response to facial affect, in BD compared to HC ↑ right ventral ACC in response to facial affect, in BD compared to HC

Radaelli et al., 2012	BD type 1 depressed (*n* = 14) Mean (SD) age: 47.86 (8.19) BD type 1 depressed with comorbid borderline personality disorder (*n* = 14) Mean (SD) age: Mean (SD) age: HC (*n* = 17) Mean (SD) age: 45.41 (12.26)	Depressed Mean (SD) HAM-D score for BD depressed: 22.80 (4.18); Mean (SD) HAM-D score for BD depressed with borderline personality disorder: 23.71 (1.80) Criteria for depression: HAM-D score ≥ 18	Implicit	Shapes	Fear Angry	Age, sex	AMG ACC Hippocampus PFC	↑ cingulate cortex and hippocampus activity in depressed BD with borderline personality disorder, compared to HC, in response to facial affect ↓ dlPFC and hippocampus activity in depressed BD with borderline personality disorder, compared to HC, in response to facial affect
Robinson et al., 2008	BD type 1 (*n* = 15) Mean (SD) age: 38.53 (12.97) HC (*n* = 16) Mean (SD) age: 36.31 (10.53)	Euthymic Mean (SD) YMRS score: 1.80 (2.08); Mean (SD) HAM-D score: 4.07 (2.99) Exact criteria for euthymia not stated	Implicit and explicit	Shapes	Fear Angry Afraid	Age, sex, other	AMG Inferior frontal gyrus	No significant difference in AMG activity in response to facial affect, in euthymic BD compared to HC ↑ inferior prefrontal cortical activity in response to facial affect, in euthymic BD compared to HC
Rosenfeld et al., 2014	BD type 1 (*n* = 18) Mean (SD) age: 33.9 (11.0) HC (*n* = 22) Mean (SD) age: 35.9 (11.7)	Euthymic Mean (SD) YMRS score: 4.8 (4.8); Mean (SD) MADRS score: 4.9 (6.0) Criteria for euthymia: not meeting any current DSM-IV criteria for BD, and no hospitalisations in the month prior to testing	Implicit	Fixation cross	Happy Angry Neutral	Age, sex, ethnicity, mood symptoms*, other	AMG PFC regions Putamen	Prolonged neural response to facial affect in various prefrontal and limbic regions in BD compared to HC, including OFC, vlPFC, ACC, AMG, and insula No significant differences in the length of neural response in right AMG and left OFC in response to facial affect between groups
Sagar et al., 2013	BD type 1 (*n* = 23) Mean (SD) age: 26.65 (6.65) HC (*n* = 18) Mean (SD) age: 23.11 (3.15)	"Primarily euthymic" Euthymia determined by SCID Use of mood rating scales was not reported	Implicit	Neutral faces	Happy Fear Neutral	Age*, other	AMG Cingulate dlPFC	↑ AMG, ACC, and dlPFC activity in response to fearful facial affect, in BD compared to HC ↑ left AMG, subgenual ACC, and right dlPFC activity in response to happy facial affect, in BD compared to HC ↓ mid-cingulate cortex and left dlPFC activity in response to happy faces, in BD compared to HC
Shah et al., 2009	BD, type not specified (*n* = 30) Mean (SD) age: 31.9 (13.5) HC (*n* = 48) Mean (SD) age: 28.2 (10.0)	Euthymic Mean (SD) YMRS scores for BD long-long 5-HTTLPR homozygotes, and short allele carriers, respectively: 2.2 (2.8); 2.0 (3.3) Mean (SD) HAM-D scores for BD long-long 5-HTTLPR homozygotes, and short allele carriers, respectively: 11.1 (10.8); 7.8 (9.9) YMRS and HAM-D used, but cut-offs for euthymia not defined	Implicit	Fixation cross	Fear Happy Neutral	Age, sex, ethnicity	AMG Ventral ACC	No significant differences in AMG activity in response to facial affect, in BD compared to HC ↓ ventral ACC activity in response to fearful facial affect, in BD compared to HC
Surguladze et al., 2010^	BD type 1 (*n* = 20) Mean (SD) age: 42.7 (10.4) HC (*n* = 20)	Euthymic	Implicit	Fixation cross	Fear Happy	Age, sex, mood state/symptoms, other	AMG ROI- and whole-brain analyses used	↑ left AMG activity in response to happy facial affect, in euthymic BD compared to HC

	Mean (SD) age: 41.9 (11.6)	Mean (SD) Atman Self-Rating Mania Scale score: 3.39 (2.45); Mean (SD) BDI score: 7.26 (6.08) Criteria for euthymia not explicitly stated			Both emotions displayed at 50% and 100% intensities			↑ mPFC activity in response to fearful and happy facial affect in BD and FDR compared to HC ↑ putamen activity in response to fearful facial affect in euthymic BD compared to HC
Tesli et al., 2013^	BD type 1, type 2, and not otherwise specified (*n* = 66) Mean (SD) age: 34.8 (10.6) HC (*n* = 123) Mean (SD) age: 34.6 (9.0)	Mood state not explicitly stated, but participants were recruited from both inpatient and outpatient settings Mean (SD) YMRS score for BD group: 1.9 (3.5); Mean (SD) IDS score for BD group: 15.4 (13.1)	Implicit	Shapes	Fear Angry	Age, sex, ethnicity, other	AMG	No significant between-group differences in AMG activity in response to facial affect
Tesli et al., 2015	BD type 1 and 2 (*n* = 85) Mean (SD) age: 34.8 (11.2) HC (*n* = 121) Mean (SD) age: 35.0 (8.8)	Euthymic, depressed Mean (SD) YMRS score: 2.5 (3.5); Mean (SD) IDS score: 17.2 (13.6); Mean (SD) PANSS score: 10.4 (4.2) Criteria for euthymia and depression not stated	Implicit	Shapes	Fear Angry Happy	Age, sex, ethnicity, mood symptoms*	AMG ROI- and whole-brain analyses used	No significant between-group differences in AMG activity in response to facial affect ↓ precuneus/cuneus activity in response to negative facial affect, in BD compared to HC ↑ lateral occipital cortex activity in response to facial affect, in BD type 2 compared to HC
Van der Schot et al., 2010	BD euthymic (*n* = 18) Mean (SD) age: 36.0 (7.6) BD depressed (*n* = 12) Mean (SD) age: 43.0 (11.2) BD manic/hypomanic (*n* = 12) Mean (SD) age: 38.0 (14.0) BD type not specified HC (*n* = 18) Mean (SD) age: 33.6 (6.5)	Euthymic, depressed, manic/hypomanic Mean (SD) YMRS scores for euthymic, depressed, and (hypo)manic BD, respectively: 0.38 (0.50); 1.1 (0.79); 15.1 (8.8) Mean (SD) IDS scores for euthymic, depressed, and (hypo)manic BD, respectively: 9.6 (5.0); 44.3 (13.4); 16.7 (9.0) Criteria for euthymia: YMRS score < 3 and IDS score < 18 Criteria for depression: IDS score > 12 and YMRS score < 3 Criteria for hypomania/mania: YMRS > 3	Passive viewing	Fixation cross	Fear Happy Neutral	Age, sex, mood symptoms*, other	AMG OFC dlPFC Temporal pole	↓ OFC activity in response to facial affect, in euthymic, depressed and manic/hypomanic BD compared to HC ↓ AMG activity in response to facial affect, in euthymic and manic, but not depressed BD, compared to HC ↓ right dlPFC activity in response to facial affect, in manic BD compared to euthymic and depressed BD, and HC ↓ right temporal pole activity in response to facial affect, in manic and euthymic BD compared to HC
Vizueta et al., 2012§	BD type 2 (*n* = 21) Mean (SD) age: 38.4 (12.2) HC (*n* = 21) Mean (SD) age: 41.1 (10.9)	Depressed Mean (SD) YMRS score: 2.9 (2.2); Mean (SD) HAM-D score: 19.9 (3.8) Criteria for depression: ≥ 22 on the IDS	Explicit	Shapes	Fear Angry	Age, sex, race, mood state/symptoms*	AMG vlPFC OFC ROI- and whole-brain analyses used	↓ OFC activity in response to fearful and angry facial affect, in BD type 2 depressed compared to HC ↓ vlPFC activity in response to fearful and angry facial affect, in BD type 2 depressed compared to HC ↓ right AMG activity in response to fearful and angry facial affect, in BD type 2 depressed compared to HC ↓ inferior frontal gyri, insula, ACC, putamen, hippocampus, middle temporal gyrus, superior temporal gyrus, supramarginal gyrus, precentral gyrus, and inferior parietal lobule activity in response to facial affect, in BD type 2 depressed compared to HC

Wessa et al., 2007	BD type 1 and 2 (*n* = 17) Mean (SD) age: 44.94 (12.70) HC (*n* = 17) Mean (SD) age: 44.94 (11.36)	Euthymic Mean (SD) YMRS score: 0.65 (1.97); Mean (SD) HAM-D score: 1.35 (1.41) Criteria for euthymia: YMRS score < 8 and HAM-D score < 5 for at least 8 weeks	Explicit	Neutral faces	Fear Happy Neutral	Age, sex, other	NA – whole-brain	↑ inferior, middle, and superior temporal gyri activity in response to fearful and happy facial affect, in BD compared to HC ↑ OFC, ACC, precuneus, insula, and caudate activity in response to fearful and happy facial affect, in BD compared to HC
Yurgelun-Todd et al., 2000	Bipolar affective disorder (*n* = 14) Mean (SD) age: 31.6 (10.2) HC (*n* = 10) Mean (SD) age: not specified	'Stable outpatients' YMRS and HAM-D used but clinical state and cut-offs for euthymia otherwise not specified YMRS range: 2-29 HAM-D range: 4-24	Explicit	Fixation point	Fear Happy	Age*, mood state/symptoms*	AMG dlPFC	↑ left AMG activity in response to fearful facial affect, in BD compared to HC ↓ activation of right dlPFC in response to fearful affect, in BD compared to HC

Note. ACC, anterior cingulate cortex; AMG, amygdala; BD, bipolar disorder; BDI, Beck depression inventory; CARS-M, clinician-administered rating scale for mania; dPFC, dorsal prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; FG, fusiform gyrus; HAM-D, Hamilton depression rating scale; HC, healthy controls; IDS, Inventory for depressive symptoms; MDD, major depressive disorder; NA, not applicable; OFC, orbitofrontal cortex; ROI, region of interest; SCID, Structured clinical interview for DSM-5; SD, standard deviation; SIGH-SAD, Structured interview guide for the Hamilton depression rating scale; vPFC, ventral prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; YMRS, Young mania rating scale.
↓ indicates a reduction; ↑ indicates an increase.
§study also appears in Table 3 as it contains functional connectivity findings.
¶study also appears in Table 4 as it contains effective connectivity findings.
^study included groups other than those reported in this table, i.e., paediatric BD, schizophrenia, major depressive disorder, and first-degree relative groups. As the focus of this review is on adults with bipolar disorder, only bipolar disorder and healthy control group information is presented in this table.
*variable was correlated with the variable(s) of interest post-hoc and not statistically within the analysis, and this correlation was not statistically significant.
+Demographic variable means and standard deviations, but not between-group statistical comparisons, reported.
Explicit facial emotion processing tasks were defined as those involving the conscious labelling of facial affect, while implicit tasks were defined as those involving passive viewing of facial stimuli without direction of attention to any specific facial cue, or tasks in which attention was directed towards non-affective cues.
The 'confound control' column includes group-matched variables and/or covariates. Variables labelled 'other' may include factors such as IQ, level of education, etc.

Table 2. Summary of studies investigating functional activity using EEG/MEG and facial emotion processing tasks in bipolar disorder

Study	Participants (*n*) Mean (SD) age (years)	Clinical state of BD participants / criteria for mood state	Facial emotion processing task (implicit/explicit)	EEG / MEG	Emotions examined	Confound control	Brain regions investigated	Main findings
Degabriele et al., 2011	BD type 1 (*n* = 18) Mean (SD) age: 39.9 (11.0) HC (*n* = 18) Mean (SD) age: 39.9 (13.3)	Mood state not explicitly stated BDI Mean (SD) score: 14.1 (9.3)	Explicit	EEG	Happy Sad	Age, sex	Occipital regions	↑ P100 amplitude but not latency, in response to happy facial affect, compared to sad facial affect, in BD but not HC ↓ N170 amplitude but not latency, in response to facial affective stimuli, in BD compared to HC
Degabriele et al., 2012	BD type 1 (*n* = 18) Mean (SD) age: 39.9 (11.0) HC (*n* = 18) Mean (SD) age: 39.9 (13.3)	Stable Mean (SD) BDI score: 14.1 (9.3) Criteria for stable mood state not specified	Explicit	EEG	Happy Sad	Age, sex, race/ethnicity, mood state/symptoms*, other	Occipital and frontocentral regions	↓ VPP latencies in response to sad facial affect, compared to happy facial affect, in both BD and HC groups ↑ P80 and VPP latencies in response to facial affect (sad and happy analysed together), in BD compared to HC No significant between group differences in ERP (P80, N120, VPP) amplitudes in response to facial affect No significant between group differences in N120 latencies in response to facial affect
Howells et al., 2014	BD type 1 (*n* = 12) Mean (SD) age: 37 (7.3) HC (*n* = 9) Mean (SD) age: 29.0 (6.4)	Euthymic Mean (SD) YMRS score: 3.41 (3.02); Mean (SD) Hospital Depression score: 5.08 (2.93) YMRS and HADS used each testing day to confirm mood state, but explicit criteria for euthymia not stated	Explicit	EEG	Angry Happy Scared	Not reported[+]	Cortical regions	↑ N170 amplitude over frontal cortex in response to facial affect, in BD compared to HC
Ibanez et al., 2012	BD type 2 (*n* = 13) Mean (SD) age: 40.1 (2.5) HC (*n* = 13) Mean (SD) age: 39.3 (2.51)	Euthymic Mean (SD) YMRS score: 0.30 (0.85); Mean (SD) BDI score: 8.07 (7.06) Criteria for euthymia: MADRS scores ≤ 8 and YMRS ≤ 6	Explicit	EEG	Angry Happy	Age, sex, mood state/symptoms, other	Cortical regions	No significant difference in N170 amplitude when processing happy facial affect compared to angry facial affect in BD, whereas this difference was observed in HC
Ibanez e al., 2014[^]	BD type 2 (*n* = 14) Mean (SD) age: 40.4 (9.2) HC (*n* = 41) Mean (SD) age: 38.3 (11.4)	Euthymic Mean (SD) YMRS score: 0.1 (0.3); Mean (SD) BDI score: 5.2 (6.9) Criteria for euthymia: YMRS ≤ 6 and BDI ≤ 6	Explicit	EEG	Angry Happy	Age, sex, other	Cortical regions	↓ N170 amplitude in response to facial affect, in euthymic BD compared to HC
Lee et al., 2010[^]	BD type 1 and 2 (*n* = 20)	Euthymic, depressed	Implicit	MEG	Angry (happy, sad neutral also tested, but	Age, sex	Fronto-parietal-occipital regions	↑ right middle occipital gyrus alpha oscillatory activity in response to angry facial affect, in BD compared to HC

	Mean (SD) age: 32.1 (8.33) HC (*n* = 20) Mean (SD) age: 38.4 (12.06)	Mean (SD) YMRS score: 1.8 (2.16); Mean (SD) HAM-D score: 7 (3.97) Criteria for euthymia: HAM-D score < 8 Criteria for depression not explicitly stated			only results for angry facial affect reported			↑ right inferior/middle frontal gyrus alpha oscillatory activity in response to angry facial affect, in BD compared to HC ↑ right inferior parietal gyrus alpha oscillatory activity in response to angry facial affect, in BD compared to HC
Liu et al., 2012b§^	BD type 1 (*n* = 20) Mean (SD) age: 34.75 (11.04) HC (*n* = 20) Mean (SD) age: 34.05 (11.04)	13/20 BD participants were in remission Mean (SD) YMRS score: 1.6 (2.16); Mean (SD) HAM-D score: 6.7 (4.69)	Implicit	MEG	Angry Happy Sad Neutral	Age, sex, mood state/symptoms*, other	Frontal regions Temporal-parietal regions	↓ gamma activity in prefrontal regions ↑ gamma activity in temporal regions abnormal oscillatory activity in the gamma band (35-55 Hz) in right frontal and posterotemporal regions
Liu et al., 2014^	BD, type not specified (*n* = 25) Mean (SD) age: 36.80 (11.38) HC (*n* = 24) Mean (SD) age: 36.62 (11.36)	Mood state not reported Mean (SD) YMRS score: 1.44 (2.02); Mean (SD) HAM-D score 6.80 (5.29)	Implicit	MEG	Angry Happy Sad Neutral	Age, sex, mood state/symptoms*	Gamma band activation index (whole-brain)	↑ right middle and inferior occipital cortex gamma activity in response to angry facial affect, in BD compared to HC (at the "early" 80-120ms timepoint) ↑ right middle temporal cortex gamma activity in response to happy facial affect, in BD compared to HC (at the "early" 90-120ms timepoint) No significant differences between BD and HC in response to sad and neutral faces
Sokhadze et al., 2011	BD type 1 and 2 (*n* = 9) Mean (SD) age: 41.8 (15.9) HC (*n* = 9) Mean (SD) age: 31.4 (11.08)	Euthymic Criteria for euthymia: YMRS < 8; MADRS < 10; PSRS < 10; mean scores not reported	Implicit	EEG	Happy Sad Disgust Contempt Neutral	Age, sex, ethnicity, other	Cortical regions	↓ N170 amplitude and latency in response to facial affect, in BD compared to HC ↓ P3b amplitude in response to neutral faces, in BD compared to HC
Tso et al., 2017	BD type 1 (*n* = 42) Mean (SD) age: 41.6 (11) HC (*n* = 43) Mean (SD) age: 41.2 (12.9)	Mood state not explicitly stated Mean (SD) BDI score: 11.12 (9.27)	Implicit	EEG	Fear Neutral	Age, sex, mood state/symptoms*, other	Occipitotemporal regions	No significant difference in peak N170 latency in BD compared to HC ↑ N170 amplitude in left hemisphere in response to fearful facial affect compared to neutral faces, in BD compared to HC
Wynn et al., 2013^	BD (*n* = 57; 39 BD type 1; 19 BD type 2) Mean (SD) age: 44.9 (10.4) HC (*n* = 30) Mean (SD) age: 40.6 (10.1)	BD group were "outside of a mood episode" Mean (SD) YMRS score: 3.5 (3.9); Mean (SD) HAM-D score: 9.1 (7.5) Cut-off scores for mood state not reported	Implicit and explicit	EEG	Fear Happy Sad Shame Surprised Afraid	Age, sex, other	Occipitotemporal regions Frontal regions	↑ N170 latency in response to facial affect, in BD type 1 and type 2 compared to HC No significant differences in N170 amplitude in response to facial affect, in BD compared to HC ↓ N250 amplitude in response to facial affect,t in BD compared to HC

								↑ N250 latency in response to facial affect, in BD compared to HC
Zhang et al., 2018	BD type 1 (*n* = 39) Mean (*SD*) age: 20.36 (2.0) BD type 2 (*n* = 22) Mean (*SD*) age: 19.46 (1.74) HC (*n* = 54) Mean (*SD*) age: 20.68 (2.83)	Euthymic, depressed, manic, hypomanic Depressed BD type 1 - Mean (*SD*) PVP score: 12.36 (6.81) BD type 2 – Mean (*SD*) PVP score: 25.82 (8.53) Manic BD type 1- Mean (*SD*) MDQ score: 9.62 (1.07 Hypomanic BD type 1- Mean (*SD*) HCL-32 score: 22.79 (1.54) BD type 2- Mean (*SD*) HCL-32 score: 20.32 (1.94) Criteria for mood states not explicitly stated	Explicit	EEG	Happy Sad Angry Neutral	Age, sex, other	Occipitotemporal regions	↑ P3b amplitude and latency in response to sad facial affect, in BD type 1 compared to HC ↑ N170 latency in response to neutral and happy facial affect in BD type 2 ↓ P3b amplitude in response to sad facial affect in BD type 2 Right hemispheric dominance during facial emotion processing in BD type 1 and type 2

Note. BD, bipolar disorder; BDI, Beck depression inventory; EEG, electroencephalography; Hospital Anxiety and Depression Scale; HAM-D, Hamilton depression rating scale; HC, healthy controls; HCL-32, Hypomania checklist-32; MEG, magnetoencephalography; MDQ, mood disorder questionnaire; PSRS, psychiatric symptom rating scale; PVP, Plutchik–van Praag Depression Inventory (PVP); YMRS, Young mania rating scale.

↓ indicates a reduction; ↑ indicates an increase.

§study also appears in Table 3 as it contains functional connectivity findings.

^study included groups other than those reported in this table, i.e., paediatric BD, schizophrenia, ADHD, major depressive disorder, and first-degree relative groups. As the focus of this review is on adults with bipolar disorder, only bipolar disorder and healthy control group information is presented in this table.

[+]Demographic variable means and standard deviations, but not between-group statistical comparisons, reported.

Explicit facial emotion processing tasks were defined as those involving the conscious labelling of facial affect, while implicit tasks were defined as those involving passive viewing of facial stimuli without direction of attention to any specific facial cue, or tasks in which attention was directed towards non-affective cues.

The 'confound control' column includes group-matched variables and/or covariates. Variables labelled 'other' may include factors such as IQ, level of education, etc.

Table 3. Summary of studies investigating functional connectivity using fMRI and MEG and facial emotion processing tasks in bipolar disorder

Study	Participants (*n*) Mean (SD) age (years)	Clinical state of BD participants / definition of mood state	Facial emotion processing task (implicit/explicit)	Control/ baseline condition	Emotions examined	Confound control	Technique and analysis	Brain regions investigated	Main findings
Foland et al., 2008†	BD type 1 (*n* = 9) Mean (SD) age: 34.6 (8.0) HC (*n* = 9) Mean (SD) age: 30.4 (7.6)	Manic, hypomanic Mean (SD) YMRS score: 15.1 (3.7); Mean (SD) HAM-D score: 9.1 (5.3)	Explicit	Shapes	Angry Fear	Age*, sex	fMRI PPI	AMG PFC	↓ negative functional connectivity between left AMG and vlPFC, in BD compared to HC ↑ negative functional connectivity between left ACC and left AMG, in BD compared to HC ↑ negative functional connectivity between right middle frontal gyrus and left AMG, in BD compared to HC
Korgaonkar et al., 2019†^	BD type 1 (*n* = 23) Mean (SD) age: 33.48 (13.43) HC (*n* = 25) Mean (SD) age: 34.29 (13.31)	Euthymic Mean (SD) YMRS score: 2.09 (2.58); Mean (SD) HAM-D score: 5.22 (6.11) Criteria for euthymia: 2 weeks of being asymptomatic, and HAM-D < 7 for at least 2 weeks	Passive viewing; subliminal and supraliminal	Implicit baseline	Fear Angry Happy Sad Disgust Neutral	Age, sex, mood state/symptoms*	fMRI PPI	AMG PFC regions Limbic regions Striatum	No significant difference in AMG-medial OFC connectivity in BD compared to HC during either supraliminal or subliminal processing ↓ functional connectivity between AMG and hippocampus in response to supraliminal sad and neutral facial affect, in BD compared to HC ↓ functional connectivity between left and right AMG in response to supraliminal neutral facial affect, in BD compared to HC ↓ functional connectivity between AMG and putamen in response to supraliminal positive facial affect, in BD compared to HC ↓ functional connectivity between AMG and insula in response to negative facial affect, in BD compared to HC ↓ functional connectivity between AMG and hippocampus in response to negative facial affect, in BD compared to HC
Liu et al., 2012b‡^	BD type 1 (*n* = 20) Mean (SD) age: 34.75 (11.04) HC (*n* = 20) Mean (SD) age: 34.05 (11.04)	13/20 BD participants were in remission Mean (SD) YMRS score: 1.6 (2.16); Mean (SD) HAM-D score: 6.7 (4.69)	Implicit	n/a	Neutral Angry Sad Happy	Age, sex, mood state/symptoms*, other	MEG Time frequency analysis Gamma power bands	Prefrontal Temporal	↑ negative functional connectivity between right frontal and right parietal-occipital areas in BD
Mukherjee et al., 2016^	BD, type not stated (*n* = 15) Mean (SD) age: 42.93 (6.46) HC (*n* = 29) Mean (SD) age: 46.38 (7.27)	Psychotic Psychosis assessed via psychiatric review	Implicit	Neutral faces	Fear Angry Neutral	Age, sex, mood symptoms*	fMRI PPI	AMG mPFC ACC	No significant between-group differences in AMG-mPFC functional connectivity in response to facial affect No significant between-group differences in AMG-ACC functional connectivity in response to facial affect

Tseng et al., 2016	BD type 1 (*n* = 9) and 2 (*n* = 5) Mean (SD) age: 37.94 (9.98) HC (*n* = 14) Mean (SD) age: 31.34 (9.66)	Euthymic, depressed Mean (SD) YMRS score: 4 (3.19) Cut-offs for mood not stated	Implicit	Fixation	Angry Happy Neutral	Age, sex, mood state/symptoms*, other	fMRI PPI	AMG PFC	↓ functional connectivity between left AMG and left vmPFC irrespective of emotion type and conscious/unconscious processing in BD No significant alterations in right AMG-vmPFC functional connectivity in BD
Versace et al., 2010	BD type 1 (*n* = 31) Mean (SD) age: 37.94 (9.98) HC (*n* = 24) Mean (SD) age: 31.34 (9.66)	Euthymic (*n* = 17); HAM-D score ≤ 7 Depressed (*n* = 14); HAM-D score ≥ 13 All BD participants had YMRS score ≤ 10	Explicit	Fixation cross	Happy (intense and mild) Sad Neutral	Age, sex, mood state/symptoms*, other	fMRI PPI	AMG PFC	↑ functional connectivity between AMG and vlPFC in right hemisphere in response to sad facial affect in BD ↓ functional connectivity between AMG and OFC in depressed BD, but not euthymic BD or HC, in response to happy facial affect
Vizueta et al., 2012†	BD type 2 (*n* = 21) Mean (SD) age: 38.4 (12.2) HC (*n* = 21) Mean (SD) age: 41.1 (10.9)	Depressed Mean (SD) YMRS score: 2.9 (2.2); Mean (SD) HAM-D score: 19.9 (3.8) Criteria for depression: ≥ 22 on the IDS	Explicit	Shapes	Fear Angry	Age, sex, race, mood state/symptoms*	fMRI Seed-based analysis from AMG	AMG PFC	↓ negative functional connectivity between right AMG and right OFC in response to facial affect, in BD type 2 depressed compared to HC ↓ negative functional connectivity between right AMG and right dlPFC in response to facial affect, in BD type 2 depressed compared to HC ↑ positive functional connectivity between AMG and superior temporal gyrus in response to facial affect, in BD compared to HC ↑ positive functional connectivity between AMG and putamen in response to facial affect, in BD compared to HC ↑ positive functional connectivity between AMG and hippocampus in response to facial affect, in BD compared to HC No significant between-group differences in vlPFC-AMG negative functional connectivity in response to facial affect
Wang et al., 2009	BD, type not stated (*n* = 33) Mean (SD) age: 31.8 (9.6) HC (*n* = 31) Mean (SD) age: 30.4 (10.8)	Manic, hypomanic, mixed, depressed, euthymic, rapid cycling Mean (SD) HAM-D score: 10.8 (12.8); Mean (SD) clinician-administered rating scale for mania score: 4.9 (6.2) SCID used to determine mood state	Implicit	Fixation cross	Fear Happy Neutral	Age, sex, mood state*	fMRI Seed-based analysis from pACC	AMG pACC	↓ functional connectivity between pACC and AMG in response to fearful and happy facial affect, in BD compared to HC No significant between-group functional connectivity differences observed in response to neutral faces

Note. ACC, anterior cingulate cortex; AMG, amygdala; BD, bipolar disorder; dlPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; HAM-D, Hamilton depression rating scale; HC, healthy controls; MEG, magnetoencephalography; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; pACC, perigenual anterior cingulate cortex;

PPI; psychophysiological interaction analysis; SCID, structured clinical interview for DSM disorders; SD, standard deviation; vlPFC, ventrolateral prefrontal cortex; YMRS, Young mania rating scale.
↓ indicates a reduction; ↑ indicates an increase.
†study also appears in Table 1 as it contains fMRI functional activity findings.
‡study also appears in Table 2 as it contains MEG functional activity findings.
^study included groups other than those reported in this table, i.e., paediatric BD, schizophrenia, major depressive disorder, and first-degree relative groups. As the focus of this review is on adults with bipolar disorder, only bipolar disorder and healthy control group information is presented in this table.
*variable was correlated with the variable(s) of interest post-hoc and not statistically within the analysis, and this correlation was not statistically significant.
Explicit facial emotion processing tasks were defined as those involving the conscious labelling of facial affect, while implicit tasks were defined as those involving passive viewing of facial stimuli without direction of attention to any specific facial cue, or tasks in which attention was directed towards non-affective cues.
The 'confound control' column includes group-matched variables and/or covariates. Variables labelled 'other' may include factors such as IQ, level of education, etc.

Table 4. Summary of studies investigating effective connectivity using facial emotion processing tasks in bipolar disorder

Study	Participants (*n*) Mean (SD) age (years)	Clinical state of BD participants / definition of mood state	Facial emotion processing task (implicit/explicit)	Control/ baseline condition	Emotions examined	Confound control	Technique and analysis	Brain regions investigated	Main findings
Almeida et al., 2009a†	BD type 1 euthymic (*n* = 21) Mean (SD) age: 31.9 (8.5) HC (*n* = 25) Mean (SD) age: 28.84 (9.63)	Euthymic Mean (SD) YMRS score: 1.6 (2.6); Mean (SD) HAM-D score: 2.63 (3.64) Criteria for euthymia: HAM-D score < 7; YMRS score < 10	Explicit	Fixation cross	Happy (displayed at mild and intense intensities) Neutral	Age, sex, mood state/symptoms*	fMRI DCM	Ventromedial regions	↑ effective connectivity from right parahippocampal gyrus to right subgenual cingulate gyrus in response to happy and neutral facial affect, in euthymic BD compared to HC No significant between-group differences in right subgenual anterior cingulate to dlPFC effective connectivity, in euthymic BD compared to HC
Almeida et al., 2009b^	BD type 1 (*n* = 15) Mean (SD) age: 36.6 (11.9) HC (*n* = 16) Mean (SD) age: 28.3 (8.4)	Depressed Mean (SD) HAM-D score: 21.5 (6.4) Depression assessed using SCID, cut-offs not stated	Explicit	Neutral faces	Happy Sad Neutral	Age, sex, mood state/symptoms*, other	fMRI DCM	AMG omPFC	↓ effective connectivity from left omPFC to left AMG in in response to happy and sad facial affect, in BD compared to HC ↑ effective connectivity from right AMG to right omPFC in response to happy facial affect, in BD compared to HC
Dima et al., 2013†	BD type 1 (*n* = 49) Mean (SD) age: 44.3 (11.9) HC (*n* = 40) Mean (SD) age: 40.2 (13.2)	Euthymic Mean (SD) YMRS score: 1.4 (3.0); Mean (SD) HAM-D score: 4.8 (5.3) Cut-offs for euthymia not specified	Explicit	Neutral faces	Fear Sad Angry Neutral All facial expressions displayed at 150% intensity	Age, sex, race, mood state/symptoms, other	fMRI DCM	IOG FG AMG vPFC	↓ effective connectivity from IOG to vPFC in BD Facial affect modulated AMG-vPFC feed-forward pathway in BD, but not HC
Dima et al., 2016^	BD type 1 (*n* =41) Mean (SD) age: 44.3 (11.9)	Euthymic Mean (SD) YMRS score: 1.4 (3.0); Mean (SD) HAM-D score: 4.8 (5.3)	Explicit	Neutral faces	Fear Sad Angry	Age, sex, mood state/symptoms, other	fMRI DCM	IOG vPFC AMG	Facial affect ↑ strength of effective connectivity between AMG and vPFC, in BD compared to HC

	HC (*n* = 46) Mean (SD) age: 40.3 (13.2)	Criteria for euthymia: (HAM-D <7, YMRS <7)			Neutral All facial expressions displayed at 150% intensity			FG	Facial affect ↓ strength of effective connectivity between IOG and vPFC, in BD compared to HC
Perlman et al., 2012†	BD type 1 euthymic (*n* = 31) Mean (SD) age: 32.63 (8.21) BD type 1 depressed (*n* = 21) Mean (SD) age: 33.09 (8.38) HC (*n* = 25) Mean (SD) age: 31.75 (6.46)	Euthymic, depressed Mean (SD) YMRS scores in euthymic and depressed BD respectively: 2.39 (2.50); 4.00 (2.72) Mean (SD) HAM-D scores in euthymic and depressed BD respectively: 7.29 (5.53); 24.62 (8.20) Criteria for euthymia: in remission for at least 2 months, HAM-D ≤ 7 and YMRS ≤ 10 Criteria for depression: depressed mood for at least 2 weeks (current), based on SCID interview	Implicit	Shapes	Fear Angry Sad Happy Neutral	Age, mood symptoms*	fMRI Granger Causality Mapping for effective connectivity	AMG PFC	↑ bilateral PFC to AMG effective connectivity in response to happy facial affect in both euthymic and depressed BD compared to HC ↑ bilateral AMG to PFC effective connectivity in response to fearful facial affect in both euthymic and depressed BD compared to HC
Radaelli et al., 2015	BD type 1 (*n* = 52) Mean (SD) age: 47.59 (10.85) HC (*n* = 40) Mean (SD) age: 41.85 (14.51)	Depressed Mean (SD) HAM-D score: 22.68 (4.7) Cut-offs for depression not explicitly stated, but all patients were inpatients, and assessed on the BDI (in addition to the HAM-D)	Implicit	Shapes	Fear Angry	Age, sex	fMRI DCM	AMG ACC dlPFC	↓ effective connectivity from dlPFC to AMG in response to facial affect, in depressed BD compared to HC No significant between-group differences in AMG to ACC effective connectivity in depressed BD compared to HC No significant between-group differences in AMG to ACC effective connectivity in depressed BD compared to HC No significant between-group differences in dlPFC to ACC effective connectivity in depressed BD compared to HC
Radua et al., 2013^	BD type 1 (*n* = 20) Mean (SD) age: 42 (12) HC (*n* = 20) Mean (SD) age: 42 (14)	Euthymic Mean (SD) Atman Self-Rating Mania Scale score: 3.39 (2.45); Mean (SD) BDI score: 7.26 (6.08) Criteria for euthymia not explicitly stated	Implicit	Fixation cross	Fear	Not reported+	fMRI	AMG Putamen Medial frontal gyrus	↑ effective connectivity from medial frontal gyrus to left putamen in response to facial affect in BD ↑ effective connectivity from left AMG to left putamen in response to facial affect in BD

Note. ACC, anterior cingulate cortex; AMG, amygdala; BD, bipolar disorder; BDI, Beck depression inventory; DCM, dynamic causal modelling; dlPFC, dorsolateral prefrontal cortex; FG, fusiform gyrus; fMRI, functional magnetic resonance imaging; HAM-D, Hamilton depression rating scale; HC, healthy controls; IOG, inferior occipital gyrus; omPFC, orbitomedial prefrontal cortex; PFC, prefrontal cortex; SCID, Structured clinical interview for DSM-5; SD, standard deviation; vPFC, ventral prefrontal cortex; YMRS, Young mania rating scale.
↓ indicates a reduction; ↑ indicates an increase.

†study also appears in Table 1 as it contains fMRI functional activity findings.
^study included groups other than those reported in this table, i.e., paediatric BD, schizophrenia, major depressive disorder, and first-degree relative groups. As the focus of this review is on adults with bipolar disorder, only bipolar disorder and healthy control group information is presented in this table.
*variable was correlated with the variable(s) of interest post-hoc and not statistically within the analysis, and this correlation was not statistically significant.
+Demographic variable means and standard deviations, but not between-group statistical comparisons, reported.
Explicit facial emotion processing tasks were defined as those involving the conscious labelling of facial affect, while implicit tasks were defined as those involving passive viewing of facial stimuli without direction of attention to any specific facial cue, or tasks in which attention was directed towards non-affective cues.
The 'confound control' column includes group-matched variables and/or covariates. Variables labelled 'other' may include factors such as IQ, level of education, etc.

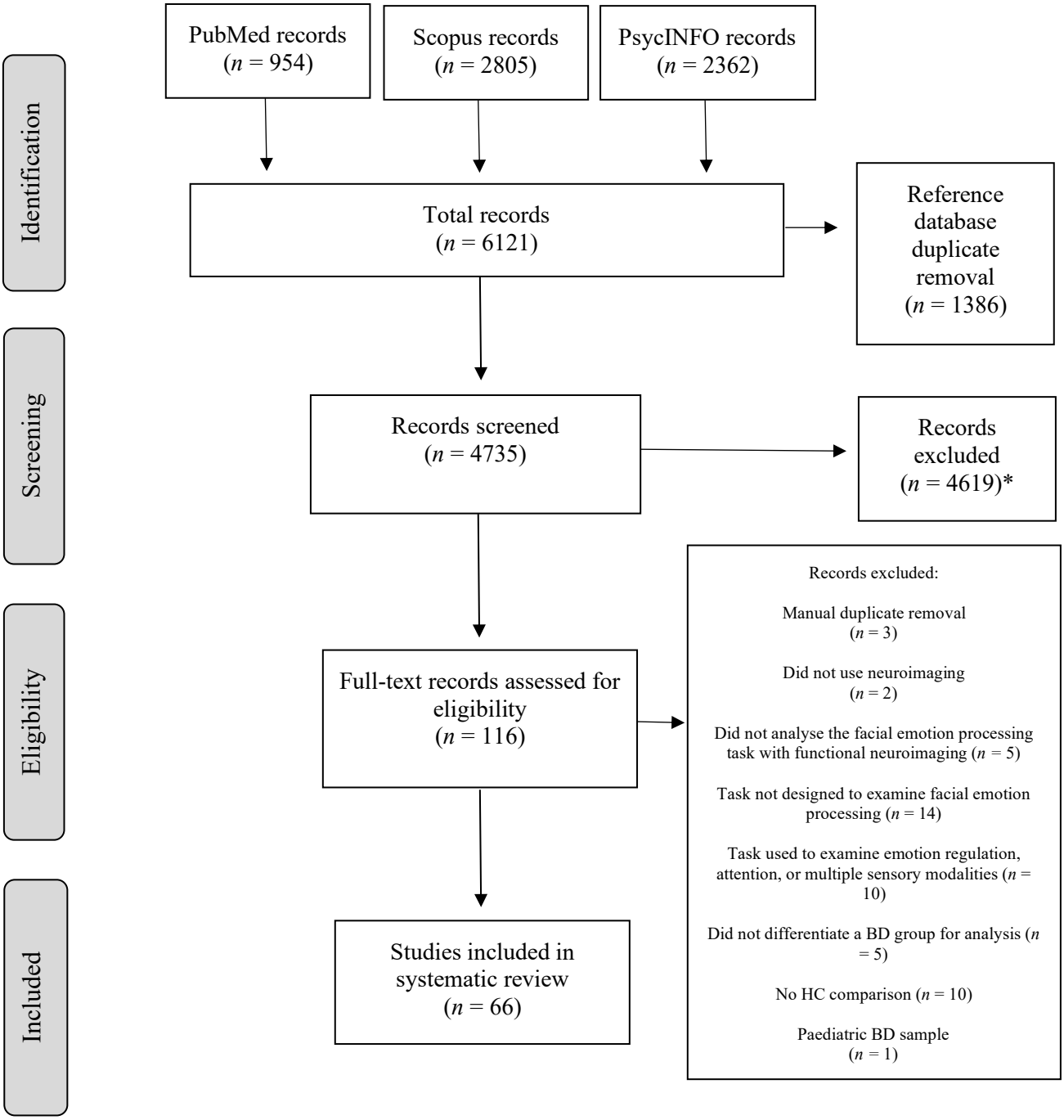

Fig. 1. PRISMA flow diagram of the record screening and selection process. Record selection was conducted in accordance with the PRISMA guidelines for reporting systematic reviews (Moher et al., 2009). BD, bipolar disorder; HC, healthy control. *The search strategy was deliberately broad to ensure no relevant literature was overseen. Hence, a substantial number of exclusions were made at the abstract screening stage.