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REVIEW ARTICLE

Amygdala structure and function in paediatric bipolar disorder and high-risk youth: A systematic review of magnetic resonance imaging findings

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ABSTRACT

Objective: Converging evidence from structural and functional magnetic resonance imaging (MRI) studies points to amygdala alteration as crucial in the development of paediatric bipolar disorder (pBP). The high number of recent studies prompted us to comprehensively evaluate findings. We aimed to systematically review structural and functional MRI studies investigating the amygdala in patients with pBP and in youth at high-risk (HR) for developing pBP.

Methods: We searched PubMed from any time to 25 September 2020 using: 'amygdala AND (MRI OR magnetic resonance imaging) AND bipolar AND (pediatr* OR child OR children OR childhood OR adolescent OR adolescents OR adolescence OR young OR familial OR at-risk OR sibling* OR offspring OR high risk)'. In this review, we adhered to the *PRISMA* statement.

Results: Amygdala hyperactivity to emotional stimuli is the most commonly reported finding in youth with pBP and HR compared to healthy peers (HC), whereas findings from structural MRI studies are inconsistent.

Conclusions: Hyperactivation of the amygdala might be an endophenotype of pBP.

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Introduction

Paediatric bipolar disorder (pBP) runs a chronic course and has a worse outcome when it persists, compared to adult onset BP; prepubertal and adolescent BP differ from adult onset BP in comorbidities (Janiri et al. 2021) and traumatic experiences (Aas et al. 2016). It is characterised by a more severe illness course than adult-onset bipolar disorder (BP), including episodes with more mixed features and rapid cycling, complicating treatment (Singh, Chang, et al. 2014). Treatment for pBP is often delayed for many years because of the lack of specificity of its prodromal features (Hernandez et al. 2017) together with the partial overlap of its symptoms with other childhood disorders (Leverich et al. 2007). For these reasons, insights into the neurobiology of pBP could be helpful to identify biomarkers that facilitate early diagnosis and more effective treatment planning (Leibenluft and Rich 2008).

Magnetic resonance imaging (MRI) studies have identified some of the neurobiological mechanisms of pBP (Kondo et al. 2014), including dysfunctional neural networks involved in mood modulation. These networks involve the prefrontal cortex (PFC), ventral striatum, thalamus, and the limbic regions (Soares and Mann 1997; Phillips et al. 2003; Strakowski et al. 2005). The amygdala, a core component of the limbic system, has a prominent role in emotion regulation (Usher et al. 2010). Accordingly, it could serve as a possible biomarker of pBD (Mwangi et al. 2014).

Findings from studies using structural (sMRI) and functional (fMRI) MRI to examine the involvement of the amygdala in prodromes, onset and progression of pBP are mixed. One meta-analysis (Usher et al. 2010)

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reported a significantly smaller amygdala and amygdala hyperactivity in response to emotional stimuli in patients with pBP compared to healthy controls (HC). Functional abnormalities in youth with pBP partially overlap with those of adults with BP (Deveney et al. 2014) and healthy relatives of patients with BP, while structural changes do not (Olsavsky et al. 2012; Brotman et al. 2014; Singh, Kelley, et al. 2014; Singh, et al. 2015). This suggests that abnormal amygdala activation could be a biomarker for high risk for developing or progressing to pBD.

Thus, despite the number of studies published, the actual role of the amygdala in the onset and progression of pBP still defies clarification. Although some reviews have addressed the functional and structural neurobiological differences between pBP and HR populations (Pavuluri and Passarotti 2008; Usher et al. 2010; Fusar-Poli et al. 2012), none have focussed specifically on the amygdala.

Because of the importance of the amygdala in emotion regulation and potential differences between pBP and youth at high risk for developing BP (HR), we review here structural and functional MRI studies that investigated the amygdala in patients with pBP and in HR children and adolescents.

Methods

PubMed was searched from any time to 25 September 2020 using the following terms: amygdal* AND (MRI OR "magnetic resonance" OR MRI) AND bipolar AND (paediatr*OR pediatr* OR child OR children OR childhood OR adolescen*OR young OR youth OR familial OR at-risk OR sibling* OR offspring OR 'high risk'). Two researchers independently performed the search. The following criteria were applied for papers to be included in this review: (i) original research articles (not reviews or meta-analyses, although we used their reference lists to seek possible additional studies); (ii) include individuals aged between 6 and 18 years; (iii) use the amygdala as a region of interest (ROI) or have the specific aim to find differences in amygdala structure or function between the study subjects; (iv) use fMRI or sMRI to assess amygdala structure and function; (v) include patients with a diagnosis of paediatric bipolar disorder type 1 (pBPI), paediatric bipolar disorder type 2 (pBPII) or paediatric bipolar disorder not otherwise specified (pBP-NOS), based on Structured Clinical Interview for DSM-IV SCID or Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) or other recognised clinical diagnostic criteria (e.g. diagnostic interview for genetic studies); (vi) include high-risk (HR) youth defined as children or adolescents between 6- and 18 years old with at least one first degree relative affected by BP, but who themselves do not meet DSM-IV/5 criteria for pBPI or pBPII. Exclusion criteria were: (i) reviews and meta-analyses, (ii) unfocused studies, in which the aim is not consistent with the scope of the review (e.g. studies that do not consider the amygdala, studies that focussed on adult samples, or used techniques other than sMRI or fMRI), (iii) studies combining youth and adults, (iv) combining subjects with bipolar and non-bipolar diagnoses, i.e. studies that did not provide separate data for subjects with or without bipolar disorder, (v) editorials, opinions, and comments, (vi) case reports and case series with no reliable statistics, and (vii) animal, post-mortem, or *in vitro* studies. Reference lists of the selected articles were also checked for additional publications. Inclusion and exclusion of papers were based on consensus discussions among authors; unanimity was required for both and was achieved through Delphi rounds. Two rounds were sufficient to reach complete agreement for paper inclusion or exclusion.

In developing this systematic review, we adopted the *P*referred *R*eporting *I*tems for *S*ystematic reviews and *M*eta-*A*nalyses (*PRISMA*) statement (Moher et al. 2009). The *PRISMA* checklist and flowchart as well as detailed results of database searches are provided in the Supplement. To assess Risk of Bias (RoB), i.e. the risk of an overestimation or an underestimation of an outcome or effect due to flaws in design, conduct, analyses, and reporting, we followed the Cochrane RoB method as described in the Cochrane Handbook (Higgins et al. 2020). We used RoB 2: A revised Cochrane risk-of-bias tool for randomised trials to assess longitudinal studies (Sterne et al. 2019). We registered our review on PROSPERO, ID 183907. Overall judgments and comments for each rated study are provided in the Supplement.

Results

The search produced 246 records on 25 September 2020, of which 64 papers were eligible. Detailed reasons for exclusion are provided in Supplemental Figure 1. Included studies were published between June 2005 and July 2020; the complete output of the search spanned from November 1993 to September 2020. Results are split according to the type of population and MRI technique used (Tables 1–8). Specifically, we first described findings from sRMI (Tables 1 and 2) and fMRI techniques (Tables 3 and 4) in subjects with pBP, then we described findings from

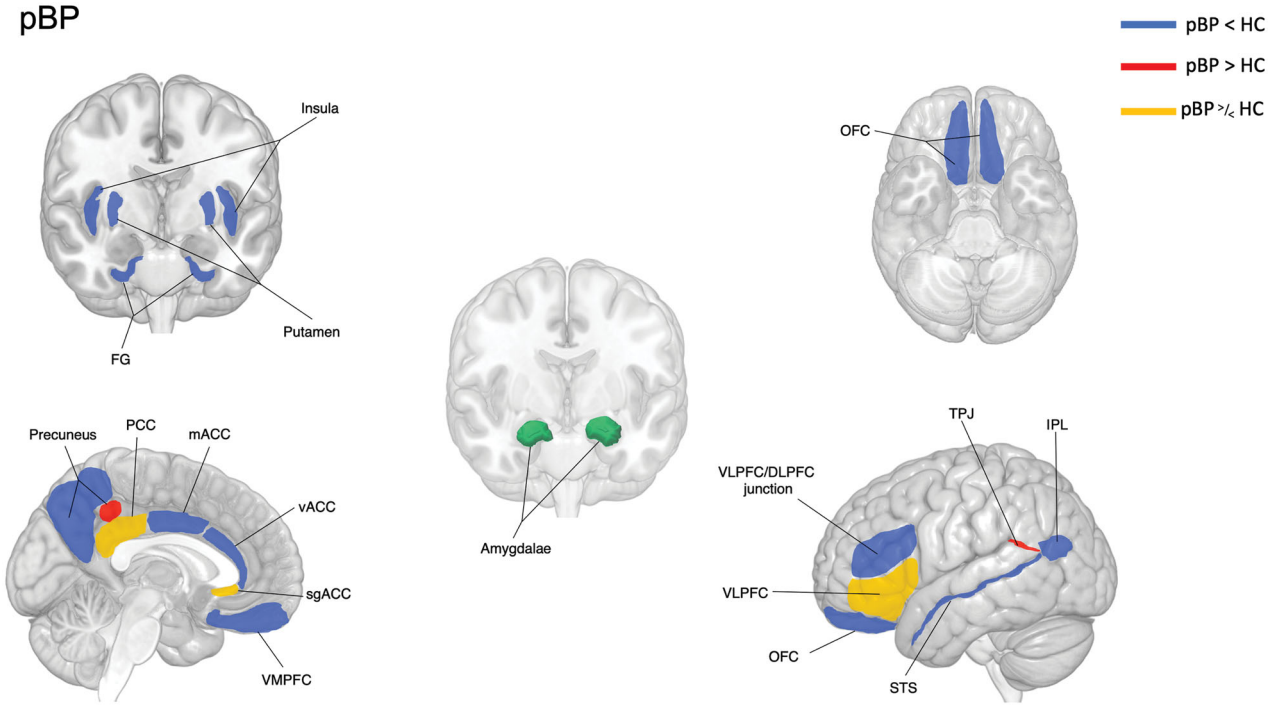

Figure 1. Findings on fMRI studies in pBP. DLPFC: dorsolateral prefrontal cortex; FG: fusiform gyrus; IPL: inferior parietal lobule; mACC: medial anterior cingulate cortex; OFC: orbitofrontal cortex; PCC: posterior cingulate cortex; STS: superior temporal sulcus; TPJ: temporoparietal junction; sgACC: subgenual anterior cingulate cortex; vACC: ventral anterior cingulate cortex; VLPFC: ventrolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex.

sRMI (Tables 5 and 6) and fMRI techniques (Tables 7 and 8) in HR youth.

sMRI in pBP

Thirteen studies investigated amygdala volume in individuals with pBP. Detailed descriptions of studies characteristics, i.e. samples used, and studies designs, are included in the Supplement. Demographic and clinical characteristics of studies samples are in Table 1. Main outcomes are in Table 2.

Five cross-sectional studies reported smaller amygdala volumes in individuals with pBP, compared to HC (Chang et al. 2005; Dickstein et al. 2005; Kalmar et al. 2009; Cui et al. 2020; Xiao et al. 2020). Two reported smaller volumes only on the left side (Dickstein et al. 2005; Xiao et al. 2020), one reported smaller volumes only in manic (Xiao et al. 2020), whereas another reported smaller volumes only in euthymic (Cui et al. 2020) subjects. Nonsignificantly smaller volumes in pBP were reported by two additional studies (Frazier et al. 2005, 2008). A longitudinal study in pBPI patients (Bitter et al. 2011) reported no differences at baseline compared to HC but smaller bilateral amygdala volumes after 12 months. Another (Akbaş et al. 2017) reported greater volumes in pBP youth than HC, although the difference was not statistically significant. Geller et al (2009) showed no differences between study groups but did not provide the direction of comparison.

Youth with pBP had smaller bilateral amygdala volumes compared with youth affected by schizophrenia (Frazier et al. 2008), whereas pBP youth showed similar amygdala volumes compared to those with ADHD at onset of illness. However, patients with pBP showed progressive amygdala volumetric shrinkage over time, whereas those with ADHD did not (Bitter et al. 2011).

Regarding pBP subpopulations, no differences emerged between psychotic or nonpsychotic (Frazier et al. 2008) or between manic and euthymic samples (Cui et al. 2020; Xiao et al. 2020).

Greater bilateral amygdala volume predicted treatment response in manic/mixed youth, suggesting that amygdala volumes might be a potentially useful prognostic indicator of clinical outcome (Bitter et al. 2011). Amygdala volumes also correlated inversely with illness duration and number of adverse life events (Geller et al. 2009).

Medications seem to have an impact on the amygdala volumes. Chang et al. (2005) found that lithium or sodium valproate treatment was related to a trend towards bilateral amygdala enlargement compared to

Table 1. Summary of clinical characteristics in structural MRI studies.

Study	Design	Sample(s)	Age (years)	HC (N)	Duration of illness	Family history	Comorbidity	Mood state	Medications
Cui et al. 2020	CS	20 pBP-manic 20pBP euthymic	15.30 ± 1.81 (pBP-manic); 15.60 ± 1.64 (pBP euthymic)	20	15.90 ± 12.96 months	35% (pBP-manic; 20% pBP-euthymic)	N.R.	100% manic (pBP-manic); 100% euthymic (pBP-euthymic)	65% AP, 55% VPA, 40% Li, 10% AD (pBP-manic); 75% AP, 65% VPA, 40% Li (pBP-euthymic)
Xiao et al. 2020	CS	21 pBP-manic 19 pBP-euthymic	14.95 ± 1.75 (pBP-manic); 15.11 ± 1.85 (pBP-euthymic)	18	15.43 ± 12.77 months (pBP-manic); 22.63 ± 18.14 months (pBP-euthymic)	31.25% has family history of BP (pBP-manic); 26.6% has family history of BP (pBP-euthymic);	N.R	100% manic (pBP-manic); 100% euthymic (pBP-euthymic)	66.7% AP; 42.9% Li; 52.4%VPA, 9.52 AD (pBP-manic); 66.7% AP; 42.9% Li; 52.4%VPA, 9.52 AD (pBP-euthymic);
Cazala et al. 2018	L (6 weeks)	14 pBP	13.43 ± 3.05	None	N.R.	N.R.	ADHD, CD, ODD and ANX.	N.R	VPA monotherapy
Akbaş et al. 2017	CS	18 pBP 18 HR	16.2 ± 1.5 (pBP) 15.4 ± 1.6 (HR)	18	34.1 ± 20.7 months	22.2% have parent(s) with BP (BP); 100% have parent(s) with BP (HR)	88.8% have at least 1 comorbidity (pBP) 38.9% have at least 1 comorbidity (HR)	N.R.	100% AP, 88.8% MS; 16.6% AD, 11.1% BDZ, 16.7% stimulants; 5.5% AP, 5.5% AD
Mwangi et al. 2014	CS	16 pBP	14.39 ± 2.41	16	4.46 ± 2.54 years	N.R.	31.25% SAD, 12.5% OCD, 18.75% phobia, 31.25% GAD, 6.25% PTSD, 6.25% So-Pho, 18.75% enuresis, 6.25% CD, 43.75% ODD, 18.75% ADHD	N.R.	81% medication naïve
Bitter et al. 2011	L (1 year)	30 pBPI, 29 ADHD	15.0 ± 1.4 (baseline); 15.8 ± 1.8 (follow-up) (pBP); 15.3 ± 1.8 (baseline); 16.3 + 1.7 (follow up) (ADHD)	24	First episode	N.R.	N.R.	20% manic, 80% mixed (baseline). 12% manic, 88% euthymic (follow up)	50% AP; 27% MS 3% AD (baseline); 41% AP; 6 35% MS; 18% AD (follow up)
Simeonova et al. 2009	CS	20 pBPI	14.6 ± 2.8	None	1.7 ± 1.8 years	100% have parent(s) with BP	85% ADHD, 35% ANX, 60% ODD (BPI).	100% euthymic	35%AP, 65% MS, 80%AD, 60% stimulant.
Geller et al. 2009	CS	21 pBPI	14.1 ± 3.1	26	First episode	N.R.	N.R. No one has PTSD	38.1% Manic /hypomanic; 33.3% depressed	28.6% AP, 23.8% MS, 9.5% AD, 33.3% stimulant.
Kalmar et al. 2009	CS	21 pBPI	15.10 ± 2.05	30	N.R.	N.R.	N.R.	52.4% manic /hypomanic/mixed, 9.5% depressed, 38.1% euthymic	52.4% AP, MS 61%, 28.6% AD, 23.8% Stimulants, 4.8% BDZ, 19% unmedicated.
Frazier et al. 2008	CS	35 pBPI-non PSY; 19 pBPI-PSY, 20 S	10.4 ± 3.0 (pBPI-nonPSY),	29	2.4 ± 3.1 years (BP-nonPSY) 3.0 ± 2.75 years	N.R.	63.2% ADHD (pBP-nonPSY),	N.R.	73.5% AP, 50% MS, 26.5% AD, 20.6% stimulant, 17.6% other (BPI-

(*continued*)

Table 1. Continued.

Study	Design	Sample(s)	Age (years)	HC (N)	Duration of illness	Family history	Comorbidity	Mood state	Medications
			11.6 ± 2.6 (pBPI-PSY) 13.5 ± 2.9 (S)		(BP-PSY), 4.2 ± 3.4 years (S)		62.9% ADHD (pBPI-PSY)		nonPSY); 84.2% AP, 89.5% MS, 36.8% AD, 17.6% stimulant, 10.5% sedative, 21.1% other (BPI-PSY); 94.4% AP, 38.9% MS, 27.8% AD, 10.0% stimulant, 5.6% sedative, 5.6% other (S)
Frazier et al. 2005	CS	43 pBP	11.3 ± 2.7	20	3.3 years	N.R.	67% ODD, 51% ADHD	15.9% manic, 52.3% mixed, 11.4% depressive, 20.5% euthymic	76% AP, 66% MS, 30% AD, 19% other
Dickstein et al. 2005	CS	20 pBP	13.4 ± 2.5	20	3 years	N.R.	70% ANX 70%, 60% ADHD	100% euthymic	100% MS 65% AP, 15 AD
Chang et al. 2005	CS	20 pBPI	14.6 ± 2.8	20	N.R.	100% have parent(s) with BP	80% ADHD, 35% ANX, 55% ODD	N.R.	N.R.

CS: cross-sectional; L: longitudinal, N.R.: not reported. *Psychopathology:* ADHD: attention deficit and hyperactivity disorder; ANX: anxiety disorder; CD: conduct disorder; GAD: generalised anxiety disorder; HC: healthy controls; OCD: obsessive-compulsive disorder; ODD oppositional defiant disorder; pBP: paediatric bipolar disorder; pBPI: paediatric bipolar disorder, type I; pBPI-PSY: paediatric bipolar disorder type I with psychotic features; pBPI-non PSY: paediatric bipolar disorder type I without psychotic features; PTSD: post-traumatic stress disorder; S: schizophrenia; SAD: seasonal affective disorder; So-Pho: social phobia; SUD: substance use disorder. *Medications:* AD: antidepressants; AP: antipsychotics; BDZ: benzodiazepines; Li: Lithium; MS: mood stabilisers; VPA: valproate.

no treatment in pBP youth. Conversely, Cazala et al. (2018) showed progressive amygdala reduction with valproate monotherapy.

fMRI in pBP

Thirty-three fMRI studies focussed on the amygdala or specifically sought alterations in amygdala function in youth with pBP. The vast majority of fMRI studies used tasks evaluating implicit and explicit emotion regulation in response to emotional cues, while others investigated prepotent response inhibition (Cerullo et al. 2009; Pavuluri et al. 2012; Metcalfe et al. 2016), reward processing (Singh et al. 2013), sustained attention (Schneider et al. 2012), and irritability (Barzman et al. 2014), or used a resting-state approach (Dickstein et al. 2010; Stoddard et al. 2015; Son et al. 2017; Guo et al. 2020). Emotional cues consisted of emotional faces, mostly fearful, happy, angry, sad and neutral, although pictures or words were also used. A detailed description of the study designs, tasks used, and sample characteristics are given in the Supplement. Sample characteristics are described in Table 3. Study designs, paradigms, and main findings are described in Table 4.

Results from studies involving emotional faces as cues showed greater activation in the left (Ladouceur et al. 2011), right (Pavuluri et al. 2007; Garrett et al. 2012; Kim, Thomas, et al. 2012) or bilateral (Rich et al. 2006; Passarotti et al. 2011; Brotman et al. 2014; Deveney et al. 2014) amygdala, for both explicit and implicit emotion regulation paradigms, in individuals with pBP compared to HC. Such activation was related to happy, fearful, angry or neutral faces, or to emotional faces cumulatively (Pavuluri et al. 2009; Garrett et al. 2012; Kim et al. 2012). Studies using emotional words reported similar results, showing hyperactivation in the right amygdala for neutral, positive, and negative words (Yang et al. 2013), or hyperactivation in the left amygdala for negative words (Pavuluri et al. 2008).

Functional connectivity studies, i.e. studies of large-scale distributed neural systems, reported blunted connectivity between the amygdala and several interrelated networks involved in emotional perception, processing and control in pBP. Poor amygdala-anterior paralimbic cortical connectivity was reported for implicit regulation of fearful, happy, and neutral stimuli in pBP youth compared to HC (Ladouceur et al. 2011; Wang et al. 2012). These findings were confirmed by another study that used neutral and angry stimuli (Passarotti et al. 2011). However, this study described

Table 2. Main findings of structural MRI studies.

Study	Approach	Main findings
Cui et al. 2020	ROI (amygdala subnuclei)	pBB-manic showed smaller l-amygdala and r-amygdala than HC. pBP-manic showed smaller l- and r-basal nucleus, l- and r- accessory basal nucleus, r-central nucleus, l- and r-cortico-amygdaloid transition and l-paralaminar nucleus than HC. PBP-euthymic showed smalle l- and r-cortico-amygdaloid transition than HC. No differences between pBP-manic and pBP-euthymic.
Xiao et al. 2020	Whole brain	pBP-euthymic showed decreased l-amygdala volumes than HC. No significant differences between pBP-manic and HC and pBP-manic and pBP-euthymic.
Cazala et al. 2018	ROIs (33 subcortical, 34 cortical)	Reduction in amygdala volumes bilaterally.
Akbaş et al. 2017	ROI (amygdala, hippocampus and thalamus)	No differences. Negative correlation between duration of manic episodes and l-amygdala volume.
Mwangi et al. 2014	ROI (amygdala)	Using the amygdala as neuroanatomical signature, the model predicted with 78.12% diagnostic accuracy and 81.25% sensitivity if the subject is pBP or HC.
Bitter et al. 2011	Whole brain + ROI (amygdala)	No differences at baseline. At 12 months pBPI demonstrates smaller l- and r- amygdala volumes than both ADHD and HC. L-amygdala volumes increased in ADHD and HC but not in pBPI. R-amygdala increased in patients with ADHD but not in HC and pBPI. Volume changes were significantly different for l- and r- amygdala for ADHD and HC as compared with pBPI.
Simeonova et al. 2009	ROI (amygdala, hippocampus)	No correlation between total (l + r) amygdala volume and levels of anxiety.
Geller et al. 2009	ROI (medial OFC, rACC, hippocampus, amygdala, NAcc)	No differences. For all subjects a greater number of ILE was significantly associated with smaller total (l + r) amygdala volume. Use of stimulant medication at the time of the scan was associated with larger total amygdala volume.
Kalmar et al. 2009	ROI (amygdala)	Amygdala volume is smaller in pBP than HC bilaterally.
Frazier et al. 2008	ROI (amygdala, hippocampus, striatum)	No differences between pBPI-PSY, pBPI-nonPSY and HC. pBPI-PSY and BPI-nonPSY males have smaller l-amygdala volumes than S. pBPI-PSY and BPI-nonPSY have an inverse correlation between bilateral amygdala volumes and MRS scores.
Frazier et al. 2005	ROI (amygdala, hippocampus, thalamus)	No differences.
Dickstein et al. 2005	ROI (amygdala, Nacc, hippocampus, DLPFC, OFC)	pBP showed smaller l-amygdala than HC.
Chang et al. 2005	ROI (amygdala, hippocampus, thalamus, caudate)	pBPI showed smaller bilateral amygdala than HC.

Psychopathology: ADHD: attention deficit and hyperactivity disorder; HC: healthy controls; pBP: paediatric bipolar disorder; pBPI paediatric bipolar disorder, type I; pBPI-PSY: paediatric bipolar disorder type I with psychotic features; pBP-nonPSY: paediatric bipolar disorder type I without psychotic features; S: schizophrenia. *Brain regions:* ACC: anterior cingulate cortex; DLPFC: dorso-lateral prefrontal cortex; Nacc: nucleus accumbens; OFC: orbito-frontal cortex; rACC: rostral anterior cingulate cortex, ROI: region of interest. *Rating scales:* ILE: independent life events; MRS: mania rating scale.

blunted connectivity within a broader network related to emotion evaluation and regulation and including ventrolateral PFC, putamen, fusiform gyrus, inferior parietal lobe, superior temporal sulcus, and the amygdala. Poorer connectivity in pBP compared to HC was also present in the facial emotion processing network, which includes the amygdala, the fusiform gyrus, the posterior cingulate, the parahippocampal gyrus, and the emotional component of the working memory network, which in turn is composed of the amygdala, the dorsolateral PFC, ventrolateral PFC, cingulate and orbitofrontal cortices, and precuneus (Passarotti et al. 2011). On the other hand, greater amygdala connectivity with areas belonging to prefrontal and parietal cortices were also sporadically reported (Stoddard et al. 2015; Hafeman et al. 2017; Son et al. 2017) (see Figure 1).

Compared to adult BP patients, pBP youth showed higher amygdala activity for implicit *vs.* explicit processing of happy, angry and fearful emotions (Kim et al. 2012; Deveney et al. 2014). Greater activity was also reported in pBP youth compared to those with ADHD for implicit regulation of fear (Brotman et al. 2010). Connectivity studies reported different patterns between youth with pBP and those with ADHD. Connectivity between bilateral amygdala and ventrolateral PFC/subgenual cingulate cortex was greater for processing of emotional as compared to nonemotional content in pBP, whereas ADHD showed greater connectivity for nonemotional *vs*. emotional content. One study compared pBPI patients with BP-NOS (Ladouceur et al. 2011), and found that the latter had blunted amygdala activation compared to the former for implicit emotion regulation of neutral stimuli.

Studies investigating the effect of medications on brain circuitry in pBP mainly focussed on risperidone, valproate or lamotrigine. Pavuluri et al. (2011) showed decreased bilateral amygdala activation for implicit regulation of positive and negative emotions in response to risperidone. Using the same paradigms, another study showed that responders to either risperidone, valproate or lamotrigine, showed greater

Table 3. Summary of clinical characteristics of functional MRI studies.

Study	Design	Sample(s)	Age (years)	HC (N)	Duration of illness	Family history	Comorbidity	Mood state	Medications
Guo et al. 2020	CS	16 pBP	15.1 ± 1.7	16	2 years	45%	25% ADHD, 6% ODD, 6% OCD, 19% ANX, 6% Tic Disorder	100% euthymic	81% AP, 69% AE, 38% Li
Son et al. 2017	CS	22 pBPI	14.8 ± 2.2 (BPI) 14.0 ± 1.6 (ADHD)	22	N.R.	N.R.	N.R.	N.R.	N.R.
Hafeman et al. 2017	CS	30 pBP 30 ADHD	14.1 ± 1.8 (BP) 14.1 ± 1.9 (ADHD)	26	N.R.	N.R.	13% ADHD, 36% ODD, 45% ANX (pBP); 53% MDD, 53% ODD, 3% CD, 23% ANX (ADHD)	N.R.	50% AP; 23% MS; 18%AD; 41% stimulants (BD); 10% AP; 10% AD; 43% stimulants.
Metcalfe et al. 2016	CS	32 pBP	16.8 ± 1.4	20	2 years	N.R.	46.7% ADHD, 33.3% ODD, 10% CD, 63% ANX, 30% SUD	16.7%, hypomanic, 23.3% depressed, 26.7% mixed, 33.3% euthymic	70.0% AP, 20% MS, 16.7% AD, 6.7% stimulants
Stoddard et al. 2015	CS	14 pBP 19 SMD	14.6 ± 2.5 (BP) 13.9 ± 2.5 (SMD)	20	N.R.	N.R.	79% ADHD, 50% ODD or CD, 86% ANX, 57% GAD, 50% SAD, 36% So-Pho (pBP); 84% ADHD, 84% ODD or CD, 89% Any ANX, 79% GAD, 58% SAD, 16% So-Pho (SMD)	15.4% hypomanic, 7.7% depressed, 7.7% mixed, 69.2% euthymic (pBP)	50% AP ,65% MS, 14% AD, 29% stimulants (pBP); 50%AP, 26% MS, 37% AD, 21% stimulants (SMD)
Barzman et al. 2014	CS	10 pBPI	15 ± 1	None	N.R.	N.R.	N.R.	N.R.	N.R.
Hafeman et al. 2014	CS	15 U-pBP, 19 M-pBP, 59 NonBP	14.4 ± 2.1 U-pBP; 13.6 ± 2.1 M-pBP; 13.8 ± 1.9 NonBP	29	N.R.	N.R.	40% ADHD, 27% DBD (U-pBP); 52% ADHD, 26% DBD (M-pBP); 73% ADHD, 39% DBD (NonBP).	N.R.	26.2% stimulant, 13% nonstimulants (U-pBP); 68% AP, 79% MS, 32% AD, 53% stimulants (M-pBP), 7% AP, 5% MS, 12% AD, 44% stimulant, 3% nonstimulant (NonBP)
Deveney et al. 2014	CS	19 pBP; 22 BP	15.7 ± 2.3 (pBP); 35.54 ± 11.2 (BP)	25 youth; 19 adults	5 years (pBP); 17 years (BP)	N.R.	52.6% ADHD, 26.3% ODD, 47.4% ANX (pBP); 13.6% ADHD, 40.9% ANX (BP)	5.6% hypomanic/manic, 5.6% depressive, 5.6%mixed, 83.3% euthymic (pBP); 31.6% depressive, 68.4% euthymic (BP)	42.1% AP, 100% MS, 47.4% AD, 36.8%, stimulants ,10.5% unmedicated (pBP);
Brotman et al. 2014	CS	36 pBP; 26 BP	14.77 ± 2.6 (pBP) 41.70 ± 10.3 (BP)	57 youth; 62 adults	4 years (pBP); 22 years (BP)	N.R.	41.7% ADHD, 31% ODD or CD (pBP), 38.9% ANX; 34.6% ANX, 3.8% SUD (BP).	25% hypo/manic, 8.3% depressed, 5.6% mixed, 61.1% euthymic (pBP); 4.2%, hypo/manic, 29.2% depressed, 8.3% mixed, 58.3% euthymic (BP)	45.7% AP, 85.7% MS, 28.6% AD, 22.9% stimulants, 25.7% unmedicated (pBP); 25% AP, 100% MS (BP)
Perlman et al. 2013	CS	20 pBP, 20 NON-pBP	13.5 ± 2.0 (pBP), 13.7 ± 1.9 (NON-pBP)	20	N.R.	N.R.	30% ADHD ,20% DBD,10% ANX (BP); 65% ADHD, 25% DBD, 10% ANX, 15% MDD (NON-BP)	N.R.	50% AP, 20% MS, 35% stimulants, 20% AD (pBP); 15% AP, 5% MS, 20% AD, 55% stimulants (NON-BP)

(*continued*)

Table 3. Continued.

Study	Design	Sample(s)	Age (years)	HC (N)	Duration of illness	Family history	Comorbidity	Mood state	Medications
Singh et al. 2013	CS	24 pBP	15.7 ± 1.7	24	1 year	N.R.	38% ADHD, 4% ODD, 17% ANX, 38% CD	25% manic, 38% depressed, 21% mixed, 17% euthymic	N.R.
Yang et al. 2013	L (3 years)	13 pBP	13.3 ± 2.3	10	3 years	N.R.	46% ADHD	N.R.	Unmedicated (baseline). 45% AP, 82% MS, 18% SSRI, 36% stimulants, , 9% benztropine (baseline to 16 weeks); 92% AP,85% MS, 46% stimulants, 15% NON-stimulants, 8% benztropine (16 weeks to 3 years)
Diler et al. 2013	L (6 weeks)	10 pBP	15.6 ± 0.9	10	N.R.	N.R.	ADHD (% N.R.)	100% depressed (baseline)	30% unmedicated; 30% stimulants, %for AP, MS, AD N.R. (baseline); 50% AP, 70% MS, 10% AD (follow up)
Wang et al. 2012	CS	21 pBPI	15.8 ± 1.8	36	N.R.	N.R.	29% ADHD, 4.7% OCD, 4.7% phobia, 4.7% PAD	29% manic/hypomanic/ mixed, 19% depressed, 52% euthymic	AP 57%, 67% MS, 29% AD, 38% stimulants, 14.3% unmedicated
Passarotti et al. 2012	CS	41 pBPI	14.0 ± 2.3	16	N.R.	N.R.	34% ADHD, 12% GAD, 9% ODD	64% manic, hypomanic 12%, 24% mixed	100% unmedicated
Garrett et al. 2012	CS	20 pBP	15.6 ± 2.1	21	N.R.	100% with BP parent(s)	85% ADHD, 40% ODD, 5% CD, 75% ANX	100% euthymic	35% AP, 100% MS, 40% AD
Schneider et al. 2012	L (4 weeks)	14 Zip-pBPI 9 PCB-pBPI	15.0 ± 1.8	10	N.R.	N.R.	33% ADHD (Zip-pBPI); 50%ADHD (PCB-pBPI)	100% manic or mixed	Zip (Zip-pBPI) PCB (PCB-pBPI)
Kim et al. 2012	CS	18 pBP 17 BP	14.3 ± 2.5 (pBP), 40.0 ± 10.1 (BP)	15 youth; 22 adults	N.R.	N.R.	66.7% ADHD, 16.7% ODD, 44.4% ANX (pBP); 11.8% ADHD; 41.2% ANX (BP)	5.6% hypomanic,11.1% depressed, 83.3% euthymic (pBP); 47.1% depressed, 52.9% euthymic (BP)	61.1% AP, 83.3% MS, 44.4% AD, 27.8% stimulants, 16.7% unmedicated (pBP); 47% AP, 100% MS, 53% AD (BP)
Pavuluri et al. 2012	L (6 weeks)	11 VPA-pBPI; 11 RISP-pBPI	12.1 ± 2.5 (VPA-pBPI); 12.6 ± 1.7 (RISP-pBPI)	14	N.R.	N.R.	9% SAD, 9% CD (RISP-pBPI); 9% GAD, 9% SUD (VPA-pBPI)	100% manic or mixed	RISP (RISP-pBPI); VPA (VPA-pBPI)
Ladouceur et al. 2011	CS	18 pBPI; 16 pBP-NOS	14.6 ± 2.0 (pBPI) 12.6 ± 2.3 (pBP-NOS)	18	6 BPI; 3 BP-NOS	N.R.	62% ANX, 95% ADHD, 22% ODD (pBPI); 50% ANX, 100% ADHD, 100% ODD (pBP-NOS)	22% manic, 45% mixed, 33% euthymic (pBPI); 6% manic, 6% depressed, 50% mixed, 37.5% euthymic (pBP-NOS)	78% AP, 67% MS, 34% AD, 34% stimulants, 56% other (pBPI); 81% AP, 19%MS, 25% AD, 50% stimulants, 39% other (pBP-NOS)
Pavuluri et al. 2011	L (6 weeks)	12 VPA-pBPI; 12 RISP-pBPI	12.7 ± 2.5 (VPA-pBPI); 12.6 ± 1.6 (RISP-pBPI)	14	N.R.	N.R.	N.R.	100% manic or mixed	RISP (RISP-pBPI); VPA (VPA-pBPI)
Passarotti et al. 2011	L (14 weeks)	17 pBP	14.3 ± 2.1	13	N.R.	N.R.	6% ODD, 6% So-Pho, 6% GAD	N.R.	Unmedicated (baseline); AP (LAM titration phase-% N.R.), 100% LAM (maintenance phase)

(*continued*)

Table 3. Continued.

Study	Design	Sample(s)	Age (years)	HC (N)	Duration of illness	Family history	Comorbidity	Mood state	Medications
Wegbreit et al. 2011	L (6 weeks)	22 pBPI-R; 12 pBPI-NR	13.5 ± 2.4 (pBPI-R); 13.3 ± 2.0 (pBPI-NR)	14	N.R.	N.R.	N.R.	100% manic or mixed	29% RISP, 29% VPA ,42% LAM
Dickstein et al. 2010	CS	15 pBPI		15	N.R.	33% has a 1st degree relative with BP	73.3% ADHD, 86.7% ODD, 6.7% OCD, 20% GAD, 20% phobia, 13.3% ANX, 13.3% So-Pho, 6.7% transient tic disorder	100% euthymic	87% AP, 40% MS
Brotman et al. 2010	CS	43 pBP, 29 SMD, 18 ADHD	14.8 ± 2.7 (pBP); 12.9 ± 1.9 (SMD); 13.9 ± 2.3 (ADHD)	15	N.R.	N.R.	47% ADHD , 47% ANX, 28% ODD (pBP); 83% ADHD , 52% ANX, 59% ODD (SMD)	56% euthymic (pBP); 96% euthymic (SMD)	44% AP, 86% MS, 30%AD, 23% stimulants, 12% other, 26% unmedicated (pBP); 37% AP, 59% MS, 30%AD, 37% stimulants, 19% other 22% unmedicated (SMD); 100% unmedicated (ADHD)
Cerullo et al. 2009	CS	11 pBPI; 10 ADHD	14.2 ± 1.5 (pBP), 14.0 ± 2.0 (ADHD)	13	N.R.	N.R.	9% CD, 9% GAD (BPI); 9% SUD, 9% phobia; 20% transient tic disorder, 20% ODD (ADHD)	100% manic or mixed	100% unmedicated
Kalmar et al. 2009	CS	21 pBPI	15.1 ± 2.1	30	N.R.	N.R.	N.R.	52.4% manic/hypomanic/ mixed, 9.5% depressed, 38.1% euthymic	524% AP, MS 61%, 28.6% AD, 23.8% Stimulants, 4.8% BDZ, 19% unmedicated
Pavuluri et al. 2009	CS	10 pBPI	16.2 ± 1.3	14	N.R.	N.R.	10% ADHD	100% euthymic	100% unmedicated
Chang et al. 2008	L(8 weeks)	8 pBP	15.9 ± 1.4	None	N.R.	N.R.	75% ADHD, 50% ODD, 25%, 12% CD GAD	100% depressed	100% LAM + 12.5% AP 12.5% MS, 12.5% stimulants
Pavuluri et al. 2008	CS	10 pBPI	15.0 ± 2.4	10	N.R.	N.R.	50% ADHD	100% euthymic	100% unmedicated
Rich et al. 2008	CS	33 pBP	14.4 ± 3.0	24	N.R.	N.R.	48.5% ADHD, 47% ODD, 39.4% ANX, 24.2% SANX, 15.2% GAD	33% hypomanic; 9% depressed; 3% mixed, 54.5% euthymic	51.5% AP; 39.4% MS; 30.3 AD, 27% stimulants
Pavuluri et al. 2007	CS	10 pBP	14.9 ± 1.8	14	N.R.	N.R.	ADHD (% N.R.)	100% euthymic	100% unmedicated
Rich et al. 2006	CS	22 pBP	14.2 ± 3.1	21	N.R.	N.R.	40.9% ADHD, 36.4% ANX, 18.2% GAD, 13.6% SANX	54% euthymic, 27% hypomanic, 18% depressed	45.5% AP ; 63.6% MS; 31.8% AD; 22.7% stimulants, 18.2% sedatives

CS: cross-sectional; L: longitudinal, N.R.: not reported. *Psychopathology:* ADHD: attention deficit and hyperactivity disorder; ANX: anxiety disorder; BP: bipolar disorder; CD: conduct disorder; DBD: disruptive behaviour disorder; GAD: generalised anxiety disorder; HC: healthy controls; M-pBP: paediatric bipolar disorder under medications; MDD: major depressive disorder; NON-BP: absence of bipolar-spectrum disorder; OCD: obsessive-compulsive disorder ODD: oppositional defiant disorder; pBP: paediatric bipolar disorder; pBPI paediatric bipolar disorder, type I; pBP-NOS: paediatric bipolar disorder not otherwise specified; pBPI-NR: paediatric bipolar disorder type I, treatment non-respondent; pBPI-R: paediatric bipolar disorder type I, treatment respondent; PCB-BP: paediatric bipolar disorder under placebo; RISP-BP: paediatric bipolar disorder under risperidone treatment; SAD: seasonal affective disorder; SANX: separation anxiety; SMD: severe mood dysregulation; So-Pho: social phobia; SUD: substance use disorder; U-BP: paediatric bipolar disorder, unmedicated; VPA-pBP: paediatric bipolar disorder under divalproex treatment; Zip-pBP: paediatric bipolar disorder under ziprasidone treatment. *Medications:* AD: antidepressants; AP: antipsychotics; BDZ: benzodiazepines; LAM: lamotrigine; Li: lithium; MS: mood stabilisers; SSRI: selective serotonin reuptake inhibitors; RISP: risperidone; VPA: valproate, Zip: ziprasidone.

Table 4. Main findings of functional MRI studies.

Study	Technique	Task	Results
Guo et al. 2020	Functional connectivity, ROI (l-IFG, l-ACC, l-SFG, r-OFC, r-SOC, SPG, precuneus (seed), whole brain	Resting state	pBP showed decreased connectivity between the r-OFC and l-amygdala than HC.
Son et al. 2017	ROI (amygdala, thalamus, hippocampus, OFC, ACC, insula, IFG, MFG, TPJ. IPS FEF)	Resting state	pBPI showed increased functional correlation between the r-IFG and r-amygdala than HC. pBPI showed increased functional correlation between the r-amygdala and l-and r-TPJ. ADHD showed increased functional correlation between l-OFC and l-amygdala than HC.
Hafeman et al. 2017	Inverse functional connectivity, amygdala (seed), ROI (VLPFC, ACC)	Faces (neutral, happy, angry, fearful, sad), morphed from neutral to emotional, and shapes. Colour labelling task (implicit emotion regulation task)	Faces vs shapes: pBP showed significant positive inverse functional connectivity (emotions > shapes), HC and ADHD groups showed significant inverse inverse functional connectivity (emotions < shapes).
Metcalfe et al. 2016	Whole brain + ROI (striatum, rACC)	Go/no-go task	pBP exhibited more activation in the r-amygdala than HC for go trials.
Stoddard et al. 2015	Intrinsic functional connectivity, basolateral, superficial,and centromedial amygdala (seed), whole brain	Resting state	pBP are more connected than both HC and SMD in an area between l-basolateral amygdala and r-PCC, extending to the l-PCC and the adjacent precuneus. pBP are also more connected than SMD and HC in an area between the basolateral l-amygdala and the medial SFG.
Barzman et al. 2014	Whole brain	Frustrative non-reward task	Rigged feedback pre-test vs baseline: increased activation of the r-amygdala. Rigged feedback pre-test vs baseline: associations between activation of amygdala and Tumour Necrosis Factor gene expressions. Rigged feedback post-test vs rigged feedback pre-test: inverse correlation between r-amygdala activation and BRACHA scores.
Hafeman et al. 2014	ROI (amygdala, ACC, VLPFC, OFC)	Faces (neutral, happy, angry, fearful, sad), morphed from neutral to emotional, and shapes. Colour labelling task (implicit emotion regulation task)	No differences. In the entire sample, emotions vs. shapes condition diffusely activated the amygdala bilaterally.
Deveney et al. 2014	Whole brain + ROI (amygdala)	Faces (happy, angry, neutral) with different degrees of intensity. Implicit (nose) or explicit (hostility and fear ratings) emotion regulation task	Angry faces, all kinds of tasks: HC showed increased amygdala activity related to increase angry face intensities, while both pBP and BP do not show this increase. No differences between pBP and BP.
Brotman et al. 2014	Whole brain + ROI (amygdala, putamen, ACC, IFG)	Faces (happy, angry, sad, fearful). Implicit (nose) or explicit (hostility ratings) emotion regulation task, passive viewing task	Fearful faces (hostility ratings) and angry faces (passive viewing): both pBP and BP showed greater activation of l-amygdala than HC. Angry and neutral faces (passive viewing): pBP and BP showed greater activation in r-amygdala than HC. All kinds of faces and all tasks: pBP showed greater l-amygdala activation than BP. Both pBP and BP showed greater activation in the r-amygdala than HC.
Perlman et al. 2013	Whole brain + ROI (amygdala, FG, STS)	Faces (neutral, happy, angry, fearful, sad), morphed from neutral to emotional, and shapes. Colour labelling task (implicit emotion regulation task)	No differences.
Singh et al. 2013	Whole brain + ROI (amygdala, caudate, putamen, NAcc, globus pallidus, insula, ACC)	Monetary incentive delay task + affective priming task	No differences.
Yang et al. 2013	Whole brain	Words (positive, negative, neutral). Word-colour matching task (implicit emotion regulation task)	Happy vs neutral and angry vs neutral faces: pBP showed greater r-amygdala activation than HC at baseline. No differences after three years.
Diler et al. 2013	Whole brain + ROI (amygdala, VLPFC, DLPFC, ACC)	Faces: hih- or mild- intensity happy and fearful faces, neutral faces. Gender labelling (implicit emotion regulation task)	No differences.
Wang et al. 2012	Functional connectivity, amygdala (seed), whole brain	Faces (fearful, happy, neutral). Gender labelling (implicit emotion regulation task)	Happy and neutral faces: pBP showed decreased functional connectivity between bilateral amygdala and bilateral OFC and ventral ACC than HC; neutral faces: pBP showed decreased functional connectivity between bilateral amygdala and r-insula.

(*continued*)

Table 4. Continued.

Study	Technique	Task	Results
Passarotti et al. 2012	Functional connectivity, ICA algorithm, whole brain	Faces (angry, neutral). Affective working memory task	All kinds of faces: pBP showed lesser bilateral amygdala connectivity within the affective working memory network and in the affective evaluation and regulation network than HC. In the face emotion processing network there is a negative correlation between YMRS scores and l-amygdala connectivity.
Garrett et al. 2012	Whole Brain	Faces (happy, sad, neutral, scrambled). Gender labelling (implicit emotion regulation task)	All kinds of faces vas scrambled faces (pBP showed greater r-amygdala activation than HC.
Schneider et al. 2012	ROI (amygdala, PFC BA 10, 11, 47)	CPT- sustained attention task	Baseline: BPI (Zip-pBPI + PCB-pBPI) and HC showed deactivation in the l-amygdala during task performance. HC exhibited a significantly larger decrease in l-amygdala activation during task performance as compared to pBPI. No differences at endpoint.
Kim et al. 2012	Whole brain + ROI (amygdala)	Faces (neutral, angry, fearful). Gender labelling (implicit emotion regulation task)	All kinds of faces: pBP showed greater r-amygdala activation than both BP and HC. Youth showed greater activation than adults, irrespective of the presence/absence of a diagnosis. Fearful faces: patients (pBP + BP) showed greater r-amygdala activation than HC.
Pavuluri et al. 2012	Functional connectivity, ICA algorithm, whole brain	Go/no-go task	RISP-pBPI showed decreased change in connectivity of the l-amygdala within the Reactive Affective Circuit (bilateral OC, amygdala, MFG and insula) than HC. VPA-pBPI showed decreased change in connectivity in the r-amygdala within the Reactive Affective Circuit (bilateral OC, amygdala, MFG and insula) than HC.
Ladouceur et al. 2011	Whole brain + ROI (amygdala, VMPFC, DLPFC) + Functional connectivity, Psychophysiological Interaction method, VMPFC (seed), ROI (amygdala, DLPFC)	Faces (happy, fearful, neutral). Gender labelling (implicit emotion regulation task)	Happy faces: pBPI showed greater l-amygdala activation than HC. Neutral faces: pBP-NOS have reduced activity in l-amygdala than pBPI. Fearful faces: pBPI showed reduced coupling between l-amygdala and VLPFC than HC.
Pavuluri et al. 2011	Whole brain	Words (positive, neutral, negative) and coloured circles (implicit emotion regulation task)	Negative vs neutral faces: RISP-pBPI (baseline): negative correlation between improvement in YMRS scores and baseline activation in r-amygdala. RISP responders showed decreased activation in bilateral amygdala than non-responders. Positve vs Neutral: RISP responders showed decreased activation in bilateral amygdala than non-responders. No differences between VPA-pBPI and RISP-pBPI or HC. No differences in VPA-pBP group between baseline or follow-up.
Passarotti et al. 2011	Whole brain	Faces (angry, happy, neutral). Affective working memory task	Happy vs neutral faces, baseline: pBP showed greater activation in the r-amygdala than HC. Happy vs neutral faces, follow-up: pBP showed greater activation in the l-amygdala than HC. Happy vs neutral faces, follow-up vs baseline: pBP showed reduced activation in the r-amygdala. Angry vs neutral, follow up: pBP showed greater activation in the r-amygdala than HC at follow up. Angry vs neutral faces, follow-up vs baseline: BP showed lesser activation in r-amygdala than HC. In pBP there is a positive correlation between percent improvement in YMRS scores and percent of reduction in r-amygdala activation from baseline to follow-up.
Wegbreit et al. 2011	Functional connectivity, ICA algorithm, ROI (Frontolimbic Affective Circuit), ROI (amygdala and VLPFC)	Words (positive, neutral, negative) and coloured circles (implicit emotion regulation task)	Before treatment, network engagement: pBPI-R and pBPI-NR showed decreased Frontolimbic Affective Circuit engagement in response to negative words relative to HC. No difference between pBPI-R and pBPI-NR. After treatment, network engagement: BPI-R showed increased network engagement compared with HC in response to the

(*continued*)

Table 4. Continued.

Study	Technique	Task	Results
			positive words. pBPI-NR did not differ from either pBPI-R or HC. Before treatment, amygdala connectivity within the frontolimbic network: pBPI-R showed significantly greater l-amygdala connectivity than pBPI-NR. No differences between pBPI-R or pBPI-NR with HC. After treatment, amygdala connectivity within the frontolimbic network: pBPI-R showed greater r-amygdala activation than pBPI-NR. No differences between pBPI-R or pBPI-NR with HC. The logistic regression model revealed that the l-amygdala pre-treatment and r-amygdala post-treatment ROI values successfully classified 76% of participants as pBPI-R or pBPI-NR.
Dickstein et al. 2010	Resting state functional connectivity, amygdala, DLPFC, NAcc (seed), whole brain	Resting state	No differences.
Brotman et al. 2010	ROI (amygdala)	Faces (neutral). Implicit (nose) or explicit (hostility and fear ratings) emotion regulation task + passive viewing.	Nose rating: pBP show trend-level greater activation in the r-amygdala than HC, SMD showed greater activation in the l-amygdala than pBP; fear vs nose rating: ADHD showed greater activation in l-amygdala than BP while SMD showed lesser activation.
Cerullo et al. 2009	Whole brain	Continuous performance task	No differences.
Kalmar et al. 2009	ROI (amygdala)	Faces (happy, fearful or neutral). Gender labelling (implicit emotion regulation task)	Fearful vs neutral and happy vs neutral. pBP showed greater amygdala activation than HC bilaterally. Happy vs neutral: a significant inverse association was observed between bilateral amygdala volume and the average amygdala activation in pBP.
Pavuluri et al. 2009	Whole brain + ROI (amygdala)	Faces (happy, angry). Implicit and explicit emotion regulation task	Implicit: pBPI showed increased activation of r-amygdala than HC. Implicit vs explicit: r-amygdala activation was greater in the pBPI group compared with that in the HC.
Chang et al. 2008	ROI (amygdala, DLPFC)	Pictures (positive and neutral). Emotional feeling ratings (explicit emotion regulation task)	pBP showed decrease in activation of bilateral amygdala with CDRS scores improvement.
Pavuluri et al. 2008	Whole brain + ROI (amygdala, hippocampus, parahippocampal gyrus)	Words (positive, neutral, negative) and coloured circles (implicit emotion regulation task)	Negative vs neutral words: pBPI showed greater activation in l-amygdala than HC. Positive vs neutral words: pBP showed greater activity in the r-amygdala than HC at trend level.
Rich et al. 2008	Functional connectivity, l-amygdala (seed), whole brain	Faces (happy, angry, fearful, and neutral). Implicit (nose) or explicit (hostility and fear ratings) emotion regulation task	Across all face stimuli and ratings: reduced connectivity between l-amygdala and a) a region bordering the r-posterior cingulate and precuneus, b) a region bordering the r-FG, c) parahippocampal gyrus than HC.
Pavuluri et al. 2007	ROI (amygdala, hippocampus, parahippocampal gyrus MFG, insula, CC, visual processing areas, STS, MPFC, OFC)	Faces (angry, happy, neutral faces). Passive viewing	Angry vs neutral: pBP showed increased activation in r-amygdala than HC.
Rich et al. 2006	ROI (amygdala, NAcc, putamen, caudate, VPFC).	Faces (neutral): Implicit (nose) or explicit (hostility and fear ratings) emotion regulation task.	Hostility vs nose rating: BP showed greater activity in l-amygdala than HC. Hostility rating: BP showed greater activation in the bilateral amygdala than HC. Fear vs nose rating: BP showed greater activation in l-amygdala vs HC; Fear rating: BP showed greater activation in bilateral amygdala than HC.

Psychopathology: ADHD: attention-deficit and hyperactivity disorder; BP: bipolar disorder; HC: healthy controls; pBP: paediatric bipolar disorder; pBPI paediatric bipolar disorder, type I; pBP-NOS: paediatric bipolar disorder, not otherwise specified; pBPI-NR: paediatric bipolar disorder type I, treatment non-respondent; pBPI-R: paediatric bipolar disorder type I, treatment respondent; RISP-pBP: paediatric bipolar disorder under risperidone treatment; VPA-pBP:: paediatric bipolar disorder under valproate treatment; SMD: severe mood dysregulation; Zip-pBP: paediatric bipolar disorder under ziprasidone treatment. *Brain areas:* BA: Brodmann area; ACC: anterior cingulate cortex; CC: cingulate cortex; DLPFC: dorsolateral pre frontal cortex; FEF: frontal eye fields; FG: fusiform gyrus; IFG: inferior frontal gyrus; IPS: intraparietal sulcus; MFG: middle frontal gyrus; MPFC; medial prefrontal cortex; NAcc: nucleus accumbens; OC: occipital cortex; OFC: orbito-frontal cortex; PCC: posterior cingulate cortex; PFC: prefrontal cortex; rACC: rostral anterior cingulate cortex; ROI: region of interest; SFG: superior frontal gyrus; SOC: superior occipital gyrus; SPG: superior parietal gyrus; STS: superior temporal sulcus; TPJ: temporo-parietal junction; VLPFC: ventrolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex; VPFC: ventral prefrontal cortex; *Rating scales:* BRACHA: Brief Rating of Aggression by Children and Adolescents; CDRS: Children depression Rating Scale; ICA: independent component analysis; YMRS: Young Mania Rating Scale.

engagement of the frontolimbic affective regulation circuit, which comprises parahippocampal gyrus, hippocampus, ventrolateral PFC and orbitofrontal cortex, anterior insula, superior temporal pole, cerebellum and the amygdala (Wegbreit et al. 2011). Conversely, using a go/no-go task without affective cues, Pavuluri et al. (2012) reported decreased functional connectivity in the left (risperidone group) and right (divalproex group) amygdala within the evaluative affective circuit. The evaluative affective circuit includes occipital and parietal cortices, contributes to impulsive automatic response tendencies and is regulated by medial PFC regions. Passarotti et al. (2011) found that pBP patients showed reduced right amygdalar activity in response to angry *vs.* neutral and happy *vs.* neutral faces in a working memory task after 14 weeks of lamotrigine monotherapy. Furthermore, they found a positive correlation between the reduction of manic symptoms and reduction of right amygdala activation.

sMRI in HR youth

Eight studies evaluated structural brain abnormalities in first-degree relatives of patients with BP. Detailed descriptions of study samples and designs are present in the Supplement. Demographic and clinical characteristics of studies samples are presented in Table 5. Main outcomes are in Table 6.

Eight studies found no differences in left and right amygdala volumes between HR youth and HC (Ladouceur et al. 2008; Singh et al. 2008; Simeonova et al. 2009; Karchemskiy et al. 2011; Kelley et al. 2013; Bauer et al. 2014; Park et al. 2015; Palacio-Ortiz et al. 2019). Bauer et al. (2014) evaluated differences among HR for pBP who were diagnosed with a variety of mental disorders except BP, unaffected HR individuals, and HC. They found no differences between affected HR and HC, while unaffected HR had greater right amygdala volumes than both affected HR and HC.

Only one study evaluated differences between pBP youth and HR (Kelley et al. 2013). HR showed greater radial volume in basolateral and superficial subregions of the left and the superior region of the right amygdala than pBP.

Clinical variables apparently do not impact amygdala structure in HR, whereas data on medication effects are mixed. Two studies investigated the effects of medications (Karchemskiy et al. 2011; Park et al. 2015) without finding any volumetric changes in the amygdala. Chang et al. (2008) examined the effect of 12-week valproate treatment in HR subjects with a major depressive disorder (MDD), ADHD, oppositional defiant disorder, or cyclothymia and found no volumetric changes. Kelley et al. (2013) found that HR individuals exposed to antidepressants had significantly smaller left amygdalar radial distances compared to HR subjects who had not taken antidepressants.

fMRI in HR youth

Fourteen studies used fMRI techniques in HR subjects. A detailed description of the studies' characteristics and outcomes are presented in the Supplement. Study sample characteristics are present in Table 7. Characteristics of tasks and fMRI techniques used, and main findings, are in Table 8.

The vast majority of studies investigating amygdala activity used implicit or explicit emotion regulation tasks with faces or pictures. One study administered a go/no go-task (Kim et al. 2012) and another used a monetary incentive task (Singh, Kelley, et al. 2014) without emotional stimuli. Two studies adopted a resting state approach (Singh, Ketter, et al. 2014; Singh et al. 2018).

Right amygdala activity was increased in HR *vs.* HC for both explicit and implicit emotion regulation tasks for fearful faces (Olsavsky et al. 2012; Chang et al. 2017), or for implicit regulation of emotional faces taken as a whole (Manelis et al. 2015). Another study used an emotional n-back task and found bilateral amygdala hyperactivity across emotional faces (Ladouceur et al. 2013). Conversely, Brotman et al. (2014) investigated amygdala response during a task with faces showing progressive intensity in anger and found reduced increments in bilateral amygdala activity with increasing anger face intensity in HR youth than HC.

Studies using connectivity techniques reported conflicting results. Greater amygdala-ventrolateral PFC functional connectivity was reported for implicit emotion regulation of happiness and fear in HR youth compared to HC (Manelis et al. 2015; Chang et al. 2017), although reduced connectivity between the amygdala and ventrolateral PFC/occipital cortex was also documented for implicit emotion regulation of fear (Ladouceur et al. 2013; Chang et al. 2017). Similarly, connectivity between the amygdala and anterior cingulate cortex was reported as either decreased or increased using implicit control of emotions (Manelis et al. 2015) or a resting state approach (Singh, Ketter, et al. 2014; Singh et al. 2018). Conflicting results also involved conversion risk. In fact, risk of conversion into pBP was associated either

Table 5. Summary of clinical characteristics of structural MRI studies in high-risk children.

Study	Design	Sample(s)	Age (years)	HC (N)	Family history	Comorbidity	Mood state	current medications
Palacio-Ortiz et al. 2019	CS	7 HR-AD, 7 HR-nonAD	15 ± 2.3 HR-AD; 14.4 ± 1.9 HR-nonAD	7	At least one parent with BP	100% MDD, 28.6% BP, 28.6% BP-NOS, 57.1% bipolar spectrum, 14.3% Panic disorder, , 42.9% specific phobia, 14.3% OCD, 71% ADHD, 28.6% ODD, 28.6% PTSD, 14.3% ODD, 28.6% CD 14.3% alcohol abuse (HR-AD); 28.6% social phobia, 14.3% agoraphobia, 28.6% specific phobia, 57.1% ADHD, 14.3% ODD (HR-nonAD); 28.6 separation anxiety, 14.3% social phobia, 14.3% agoraphobia, 14.3% specific phobia, 14.3%OCD, 28.6% ADHD, 14.3% ODD (HC)	N.R.	Unmedicated
Park et al. 2015	CS	29 HR	13.9 ± 3.1	17	At least one parent with BP	14% pBP-NOS, 45% ADHD, 14% ODD, 3.5% CD, 17% GAD, 3.5% SAD	N.R.	3.5% AP, 21% MS, 10 AD, 14% stimulants
Bauer et al. 2014	CS	18 HR-unaffected, 19 HR-affected	10.5 ± 3.4 (HR-unaffected) 12.9 ± 3.3 (HR-affected)	45	At least one parent with BP	None (HR-unaffected); 37% pBP-NOS, 10.5% MDD, 10.5% MDD-NOS, 10.5% ADHD, 5% GAD, 10.5% ADJ (HR-affected)	N.R.	37% medicated (AP, AE, AD, stimulants – % N.R.) (HR-affected)
Kelley et al. 2013	CS	22HR, 26 pBPI	12.7 ± 2.2 (HR) 13.7 ± 2.3 (pBPI)	24	At least one parent with BP	27% pBP-NOS, 23%, MDD, 100% ADHD, 32% ODD, 27% ANX, (HR); 76% ADHD, 58% ODD, 26% ANX, (pBPI)	Moderate affective symptoms (HR)	32 %AP, 86% MS, 59% AD, 55% stimulants (HR), 43% AP, 100% MS, 69% AD, 62% stimulants (pBPI).
Karchemskiy et al. 2011	CS	22 HR	12.3 ± 2.5	22	At least one parent with BP	36% BP-NOS, 41% MDD, 100% ADHD; 36% ANX, 41% ODD	N.R.	18% AP, 50% MS, 32% stimulants.
Chang et al. 2009	L (12 weeks)	11 HR	11.3 ± 3.4	5	At least one parent with BP	55% MDD, 82% ADHD, 45% ANX, 45% ODD, 18% Cyclothymia	Moderate affective symptoms	100% VPA
Singh et al. 2008	CS	21 HR	9.7 ± 1.5	24	At least one parent with BPI	76% at least one psychiatric disorder, 33% more than one psychiatric disorder, 19% MDD, 19% ADHD, 24% Anxiety, 9.5% ODD, 10% Cyclothimia; 14% Dysthymia	N.R.	4% AP, 17% AD, 8% stimulants
Ladouceur et al. 2008	CS	20 HR	13.0 ± 2.7	13	At least one parent with BP	10% ANX	N.R.	N.R.

CS: Cross-sectional; L, longitudinal, N.R.: not reported. *Psychopathology:* ADHD: attention deficit and hyperactivity disorder; ADJ: adjustment disorder; ANX: anxiety disorder; BP: bipolar disorder; BPI: bipolar disorder, type I; BPII bipolar disorder, type II; CD: conduct disorder; GAD: generalised anxiety disorder; OCD: obsessive-compulsive disorder; ODD: oppositional-defiant disorder; PTSD: post-traumatic stress disorder; HC: healthy controls; HR: high-risk for developing paediatric bipolar disorder; HR-affected: non-bipolar diagnosis and high-risk for developing paediatric bipolar disorder; HR-unaffected: absence of psychiatric diagnosis and high-risk for developing paediatric bipolar disorder; MDD: major depressive disorder; MDD-NOS: patients with major depressive disorder not otherwise specified; ODD: oppositional defiant disorder; pBPI: paediatric bipolar disorder, type I; pBP-NOS: paediatric bipolar disorder, not otherwise specified; SAD: seasonal affective disorder. *Medications:* AP: antipsychotics; AD: antidepressants; MS: mood stabilisers; VPA: valproate.

Table 6. Main findings of structural MRI studies in at-risk children.

Study	Approach	Major findings
Palacio-Ortiz et al. 2019	Whole brain	No differences.
Park et al. 2015	ROI (amygdala)	No differences. Negative correlation between bilateral amygdalar volumes and MASC social anxiety score, only in those with level of MASC > 55 (high anxiety group)
Bauer et al. 2014	Whole brain	HR-unaffected showed greater r-amygdala than HC, HR-affected and HR-affected with pBP-NOS. No differences between HR-affected and HC
Kelley et al. 2013	ROI (amygdala)	No differences between HR and HC. pBPI showed smaller radial distances in basolateral and superficial subregions of the l- and r- amygdala than HC. pBPI showed smaller radial disctances in the basolateral and superficial subregions of the l- amygdala and r- superior amygdala than HR.
Karchemskiy et al. 2011	ROI (hippocampus, thalamus, amygdala)	No differences
Chang et al. 2009	ROI (total brain volume, amygdala)	No differences
Singh et al. 2008	ROI (total intracranial volume, amygdala, thalamus, striatum, PFC)	No differences
Ladouceur et al. 2008	ROI (amygdala, OMPFC)	No differences

Psychopathology: HR: high-risk for developing paediatric bipolar disorder; HR-affected: non-bipolar diagnosis and high-risk for developing paediatric bipolar disorder; HR-unaffected: absence of psychiatric diagnosis and high-risk for developing paediatric bipolar disorder; pBPI: paediatric bipolar disorder, type I; pBP-NOS: paediatric bipolar disorder, not otherwise specified. *Brain areas:* OMFC: orbitomedial prefrontal cortex; PFC: prefrontal cortex. *Rating scales:* MASC: Multidimensional Anxiety Scale for Children.

with greater amygdala-occipital cortex or poorer amygdala-orbitofrontal cortex connectivity for implicit control of emotions (Hanford et al. 2019) (Figure 2).

No differences emerged in amygdala activity and connectivity between HR and pBP (Olsavsky et al. 2012; Brotman et al. 2014) or between offspring and siblings of BP patients (Olsavsky et al. 2012; Brotman et al. 2014). However, HR showed poorer bilateral amygdala-anterior cingulate cortex connectivity for implicit control of happiness than individuals at-risk for other psychopathological conditions (Manelis et al. 2015), and higher bilateral amygdala–posterior cingulate cortex connectivity than those at-risk for developing MDD (Singh et al. 2018).

There is little information about medication effects on amygdala activity in HR, and the findings are inconsistent. Garrett et al. (Garrett et al. 2012), found greater activation of the bilateral amygdala for implicit control of happiness after four months of psychotherapy. Conversely, Chang et al. (2009) found no changes after 12 weeks of valproate monotherapy in HR, already ill youth.

3.5. Bias

The risk of bias detected in included studies raised concerns for all eligible longitudinal studies. Concerns are mainly related to the insufficient or absent description of randomisation procedures. Other concerns regard the description of blinding processes and limited assessment of the effects of individual types of interventions separately in some studies (see Supplemental Table 1).

Discussion

We summarise findings from structural and functional studies as follows: (i) sMRI studies on amygdala volumetric alteration in pBP individuals are inconsistent. Furthermore, no structural difference in the amygdala between HR and HC emerged. (ii) fMRI studies more consistently found amygdala hyperactivation in both HR and pBP youth for explicit and implicit emotional processing. (iii) In both HR and pBP youth, altered connectivity between the amygdala and other brain regions, mainly prefrontal areas, were also reported. However, although there is consistent evidence of blunted connectivity in networks involving the amygdala in pBP, results in HR are mixed.

Amygdala-PFC connections and the pathophysiology of pBP

The amygdala is a heterogeneous complex of nuclei comprised in multiple networks modulating subprocesses related to social cognition, including evaluation, rule-based actions, emotional processes, attention, goal-directed behaviour, and memory (Salzman and Fusi 2010). In these networks, the main role of the amygdala is to encode the emotional valence and the motivational significance of certain stimuli (LeDoux 2007). The amygdala serves this role through (i) a broad input from associative sensory cortices and from areas involved in providing information about the internal state, such as the orbitofrontal cortex (Reiman et al. 1997; Arciniegas et al. 2013), and through (ii) projecting to a wide range of target structures, including PFC, striatum, sensory cortices, hippocampus, perirhinal and entorhinal cortices, and to

Table 7. Summary of clinical characteristics of functional MRI studies in high-risk children.

Study	Design	Sample(s)	Age (years)	HC (N)	Family history	Comorbidity	Mood state	Medications
Hanford et al. 2019	CS	25 HR	14.1 ± 2.4	22	At least one parent with BP (HR);	8% MDD, 4% Mood-NOS, 16% ADHD, 4% ODD, 8% ANX, 8% ED, 4% ADJ, 12% other	N.R.	N.R.
Acuff et al. 2019	CS	32 HR 30 HR-nonBP	13.81+ ± 2.5 (HR); 14.0 ± 2.3 (HR-nonBP)	24	At least one parent with BP (HR); At least one parent with MDD or ADHD or ANX (HR-nonBP)	12.5% MDD, 21.8% ADHD, 6.3% ODD, 12.5% ANX, 6.3% ED (HR); 13.3% MDD, 23.3% ADHD, 10.0% ODD, 20.0 % ANX, 6.7% OCD (HR-nonBP);	N.R.	9.37% were medicated (HR); 100 U unmedicated (HR-nonBP)
Singh et al. 2018	CS	26 HR 37 MDD-HR	11.6 ± 2.7 (HR); 13.0 ± 2.6 (MDD-HR)	26	At least one 1st degree relative with BPI	None	N.R.	None
Chang et al. 2017	CS	50 HR	13.5 ± 2.9	29	At least one 1st degree relative with BP	66% MDD, 52% ADHD, 30% ANX, 6% dysthymia.	N.R.	20% AP, 32% MS, 41% AD, 43% BDZ, 32% stimulants, 45% unmedicated
Manelis et al. 2015	CS	29 HR 29 HR-nonBP	13.8 ± 2.5 (HR); 13.8 ± 2.4 (HR-nonBP)	23	At least one parent with BP (HR); At least one parent with non-bipolar disorder psychopathology (HR-nonBP).	10.3% MDD, 20.4%, ADHD, 3.5%, ODD, 6.9% ANX, 6.9% phobia, 3.5% Tourette, 3.5% ED (HR); 16.9% MDD, 20.7% ADHD, 6.9% ODD, 10.3% ANX, 6.9% phobia, 6.9% OCD, (HR-nonBP)	100% euthymic	6.9% AP, 3.5% stimulants, 6.9% Atomoxetine (HR); 3.5% AD, 10.3% stimulants (HR-nonBP).
Garrett et al. 2015	L (4 months)	12 HR, 12 HCs	13.6 ± 3.4	12	At least one 1st degree relative with BP	41.7% pBP-NOS, 58% MDD, 50% ADHD, 50% ANX, 25% CD, 8.3% cyclothymia	N.R.	50% medicated at baseline (% N.R.), family focussed therapy or treatment-as-usual.
Brotman et al. 2014	CS	15 HR, 20 pBP	14.5 ± 2.2 (HR); 15.6 ± 2.3 (pBP)	29	At least one 1st degree relative with BP	6.7% ADHD, 6.7 ANX (HR); 65% ADHD, 25% ODD, 45% ANX (pBP)	85% euthymic; 5% depressive, 5% hypo/manic, 5% mixed	N.R.
Singh, Kelley, et al. 2014	CS	20 HR	12.7 ± 2.9	25	At least one 1st degree relative with BPI	None	N.R	None
Singh, Ketter, et al. 2014	CS	24 HR	12.3 ± 3.0	25	At least one 1st degree relative with BPI	N.R.	N.R.	N.R.
Ladouceur et al. 2013	CS	16 HR	14.2 ± 2.3	15	At least one 1st degree relative with BP	N.R.	N.R.	N.R.
Olsavsky et al. 2012	CS	13 HR, 32 pBP	14.0 ± 2.4 (HR); 14.7 ± 2.7 (pBP)	56	At least one 1st degree relative with BP	8% ADHD, 8% ANX (HR); 41% ADHD, 22% ODD, 47% ANX (pBP)	100% euthymic (pBP)	N.R.
Mourão-Miranda et al. 2012	CS	16 HR	14.8 ± 1.8	16	At least one 1st degree relative with BP	N.R.	N.R.	N.R.
Kim et al. 2012	CS	13 HR; 28 pBP	13.9 ± 2.0 (HR); 14.4 ± 2.6 (pBP)	21	At least one 1st degree relative with BP	None (HR); 64% ADHD, 32% ODD or CD, 36% ANX (pBP)	68% euthimic (pBP)	100% unmedicated (HR); 44% AP, 78% MS, 22% AD, 37% unmedicated (pBP)
Chang et al. 2009	L (12 weeks)	11 HR	11.3 ± 3.6	5	At least one parent with BPI and BPII	55% MDD, 82% ADHD, 45% ANX, 45% ODD, 18% Cyclothymia.	N.R.	100% VPA

CS: Cross-sectional; L: longitudinal, N.R.: not reported. *Psychopathology:* ADHD: attention deficit and hyperactivity disorder; ADJ: adjustment disorder; ANX: anxiety disorder; BP: patients with bipolar disorder; BPI patients with bipolar disorder, type I; CD: conduct disorder; ED: eating disorder; HR: high-risk for developing paediatric bipolar disorder; HR-nonBP: high-risk for developing disorders other than BP; MDD: major depressive disorder; MDD-HR: high-risk for developing major depressive disorder; Mood-Nos: mood disorder, not otherwise specified; ODD: oppositional defiant disorder; pBP: paediatric bipolar disorder. *Medications:* AP: antipsychotics; AD: antidepressants; BDZ: benzodiazepines; MS: mood stabilisers; VPA: valproate.

Table 8. Main findings of functional MRI studies in high-risk children.

Study	Approach	Task	Amygdala
Hanford et al. 2019	Whole brain + functional connectivity, Psychophysiological Interaction method, amygdala, ventral striatum (seed), whole brain	Faces (all emotions considered as a whole) and shapes (implicit emotion regulation task); reward processing task.	Emotions vs shapes: for higher risk of conversion to pBP (higher risk calculator scores), HR showed positive correlation between r-amygdala activity and number of recent negative stressful life events. For higher risk to conversion to pBP (higher risk calculator scores), HR showed positive correlation between bilateral amygdala and r-OC. This association was inverse for lower risk for developing pBP (lower risk calculator scores)
Acuff et al. 2019	ROI (amygdala, VLPFC, and cACC, rACC); + WM tracts (forceps major/minor; bilateral anterior thalamic radiation, cingulum-angular bundle, cingulate gyrus, corticospinal tract, inferior longitudinal fasciculus, superior longitudinal fasciculus-parietal and -temporal, and uncinate fasciculus)	Faces (positive, negative) and shapes (implicit emotion regulation task).	No relationship between WM and amygdala activity.
Singh et al. 2018	Functional connectivity, PCC (seed), whole brain.	Resting state	HR showed greater bilateral amygdala concordant connectivity with PCC than MDD-HR; HC showed discordant connectivity between these regions.
Chang et al. 2017	Whole brain + ROI (r-amygdala, VLPFC, sgACC) + functional connectivity, Psychophysiological Interaction method, amygdala (seed), whole brain	Faces (fearful, neutral, calm) and scrambled images. Gender evaluation (implicit emotion regulation task).	Fearful faces: HR showed grater activation in the r-amygdala than HC. HR showed greater r-amygdala connectivity with VC and r-VLPFC.
Manelis et al. 2015	ROI (face emotion processing circuitry) + functional connectivity, Psychophysiological Interaction method, ACC, OFC, VLPFC (target)	Faces (happy, angry, fearful, and sad) and shapes (implicit emotion regulation task).	Faces vs shapes: HR and HRnonBP had significantly greater r-amygdala activation than HC. No differences between HR and HrnonBP Happy faces vs shapes: HR, relative to HRnonBP and HC, showed significantly less positive r-amygdala-ACC functional connectivity. HR without psychopathology have greater r-amygdala-l-VLPFC functional connectivity than HC without psychopathology. HR without medication have greater r-amygdala-l-VLPFC connectivity than HRnonBP without medication and HC. No differences between HC and HRnonBP
Garrett et al. 2015	Whole brain	Faces (fearful) and scrambled images. Gender evaluation (implicit emotion regulation task).	Fearful faces: HR showed greater activation in the bilateral amygdala at post treatment vs pre-treatment.
Brotman et al. 2014	Whole brain + ROI (amygdala)	Faces (happy, angry): implicit (nose) or explicit (hostility and fear ratings) emotion regulation task. Five morph intensities (100% neutral; 25% emotion and 75% neutral; 50% emotion and 50% neutral; 75% emotion and 25% neutral)	Angry faces (both implicit and explicit conditions): HR and pBP showed a reduced increase of l- and r- amygdala activation with increasing anger of the face
Singh, Kelley, et al. 2014	Whole brain + functional connectivity + ROI (amygdala, insula, NAcc)	Monetary incentive task	HR showed positive correlations between l- and r- amygdala activations and increased novelty seeking while anticipating losses. These correlations were not evident in HC.
Singh, Ketter, et al. 2014	ROI (dorsal and ventral default mode and bilateral executive control networks) + Functional connectivity, ICA algorithm, amygdala, VLPFC, sgACC) (seed), whole brain.	Resting state	HR have reduced connectivity between l-amygdala and pgACC
Ladouceur et al. 2013	ROI (amygdala, striatum, VLPFC, DLPFC, dACC,) + functional connectivity, Psychophysiological Interaction method, VLPFC (seed), amygdala, DLPFC (target)	Faces (neutral, fearful, happy, or no distractor), N-back task (0-back, 2 back)	All kinds of faces (2 back-condition): HR showed greater activation in bilateral amygdala than HC. Fearful faces: HR had significantly reduced VLPFC modulation of the r-amygdala than HC. Happy faces: HR showed reduced modulation of the l-amygdala

(*continued*)

Table 8. Continued.

Study	Approach	Task	Amygdala
Olsavsky et al. 2012	Whole brain + ROI (amygdala)	Faces (happy, angry, fearful, neutral). Implicit (nose) or explicit (hostility and fear ratings) emotion regulation task; passive viewing task.	Fearful faces (afraid rating vs passive viewing): pBD and HR have greater activation in the r-amygdala than HC. No differences between pBP and HR.
Mourão-Miranda et al. 2012	Whole brain	Faces (happy, fearful, neutral): expressions ranging from neutral, to mild (50%), and to intense (prototypical; 100%). Gender labelling (implicit emotion regulation task).	Happy vs neutral faces: Gaussian Process Classifier differentiates HR from HC with 75% accuracy. The spatial pattern that best discriminated the groups does not include the amygdala
Kim et al. 2012	Whole Brain + ROI: ACC	Go/No-go task	No differences between HR, HC and pBP
Chang et al. 2009	ROI: amygdala, DLPFC	Images (negative, positive, neutral). Feeling ratings (explicit emotion regulation task)	No differences between HR and HC

Psychopathology: HC: healthy controls; HR: high-risk for developing paediatric bipolar disorder; HR-nonBP: high-risk for developing disorders other than BP; MDD-HR: high-risk for developing major depressive disorder; pBP: paediatric bipolar disorder; *Brain regions:* ACC: anterior cingulate cortex; cACC: caudal anterior cingulate cortex; dACC: dorsal anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; NAcc: nucleus accumbensOC: occipital cortex; PCC: posterior cingulate cortex; pgACC: pregenual ACC; OFC: orbitofrontal cortex; rACC: rostral anterior cingulate cortex; ROI: region of interest; sgACC: subgenual anterior cingulate cortex; VLPFC: ventrolateral prefrontal cortex; VC: visual cortex; WM: white matter.

subcortical structures responsible for physiological responses related to emotion, such as autonomic responses, hormonal responses, and startle (Davis 1992). In the field of affective neuroscience, great importance is given to the amygdala-PFC circuitry, because of its role in emotion generation and control, and the subsequent modulation of social behaviour. The amygdala is densely connected with the paleocortical, ventromedial regions of PFC, namely the orbitofrontal cortex, the mediodorsal PFC, and the rostral and subgenual anterior cingulate cortices (Phillips et al. 2008). These connections mediate the production and perception of emotional states, representation of reward value of a stimulus and the way in which this representation guides goal-directed behaviour (Rolls and Grabenhorst 2008). These areas are involved also in implicit (i.e. automatic) emotion regulation processes through the extinction of previously acquired behaviours, inhibition of stress response, regulation of emotional attentional resources, automatic behavioural monitoring, and rule learning (Phillips et al. 2008). Emotion regulation also occurs voluntarily through selective attention (Erk et al. 2007; Goldstein et al. 2007), emotion suppression and reinterpretation of the emotional content (Ochsner et al. 2013). Voluntary emotion suppression relies on the activation of ventrolateral and dorsolateral cortices, which are mainly involved in cognitive and higher-order executive functions, and deliver indirect connections to the amygdala *via* the paleocortex (Bickart et al. 2014).

Alterations in the amygdala-PFC circuits were proposed as the key neurobiological finding in both paediatric and adult BP (Phillips and Swartz 2014). Disruption in PFC inhibitory control on the amygdala might lead to aberrant amygdala hyper-reactivity to emotional internal and external stimuli. On the other hand, blunted connectivity between the amygdala and PFC might result in the inability of the latter to rapidly adapt/regulate behaviour when emotionally/motivationally charged, or to correctly interpret social cues (e.g. emotional expressions) and adapt behaviour to social situations (Adolphs et al. 1998). Such alterations might lead to depressive and manic-like behaviours, such as humourlessness, fear, emotionality, disinhibition, mood lability, excessive involvement in hedonically-driven context, euphoria, irritability, distractibility, psychomotor agitation, hypersexuality grandiosity, and paranoia (Flor-Henry 1969; Bear and Fedio 1977; Cummings and Mendez 1984; Rolls et al. 1994; Bechara et al. 1999). On the other hand, disruption in networks connecting the amygdala with areas involved in basic biological rhythms and neurovegetative processes might also result in insomnia/hypersomnia, anorexia or hyperorality (Blond et al. 2012).

fMRI findings in pBP and in HR youth

Findings from fMRI studies investigating amygdala activity in pBP mainly replicated finding in adults and support the aforementioned model. There is sufficient evidence reporting amygdala hyperactivity, together with poor activity or blunted connectivity in paleocortical (i.e. ventromedial, mediodorsal, orbitofrontal and anterior cingulate cortex) (Pavuluri et al. 2009; Passarotti et al. 2011, 2012; Garrett et al. 2012; Hafeman et al. 2014; Stoddard et al. 2015) or neocortical (i.e. ventrolateral and dorsolateral PFC) (Pavuluri

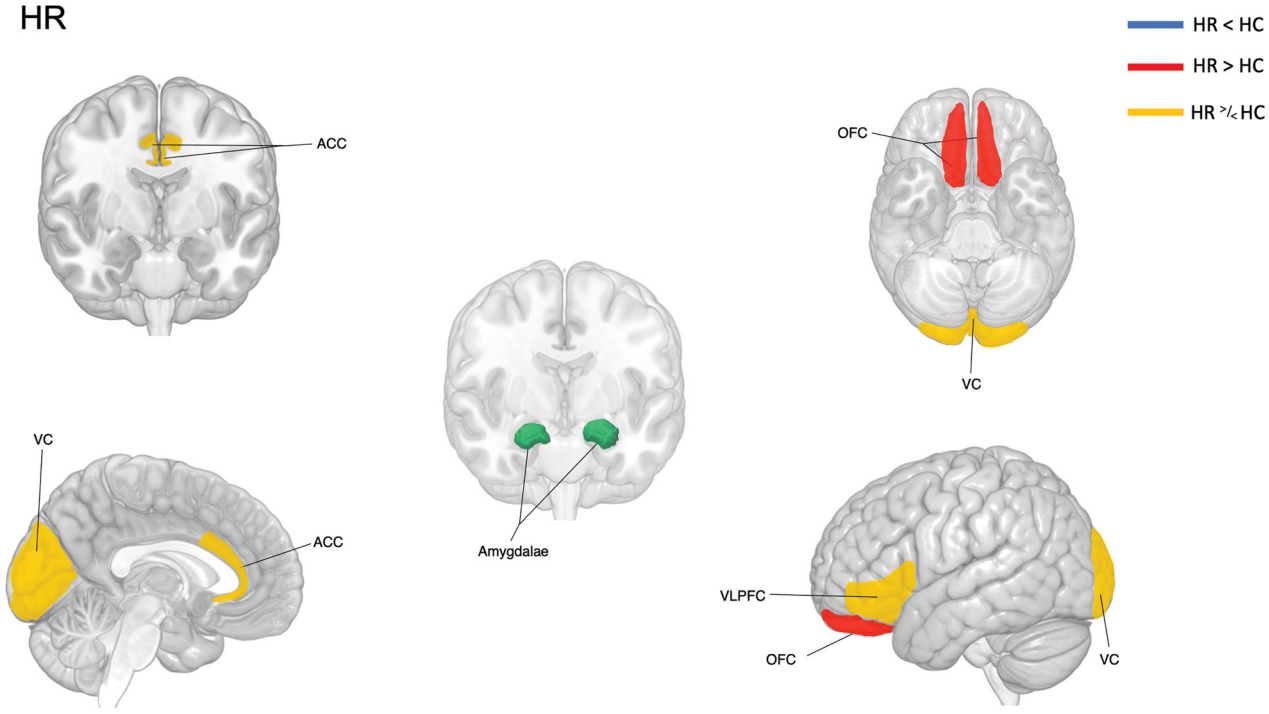

Figure 2. Findings on fMRI studies in HR. ACC: anterior cingulate cortex; OFC: orbitofrontal cortex; VC: visual cortex; VLPFC: ventrolateral prefrontal cortex.

et al. 2008, 2009; Ladouceur et al. 2011; Passarotti et al. 2011; Garrett et al. 2012; Kim, Thomas, et al. 2012) areas in pBP for both implicit and explicit emotion paradigms. Amygdala hyperactivation also appears to be a robust finding in HR youth. This might suggest that amygdala hyperactivation could emerge as a possible biomarker of illness susceptibility (Surguladze et al. 2010). However, directions of amygdala-PFC connectivity patterns between HR youth and those with pBP differ, with the former showing either hypo- or hyperconnectivity, or greater PFC activity. The meaning of increased PFC activity and greater amygdala-PFC connectivity in HR is unclear and has been addressed as either a resilience factor (Pompei et al. 2011), or as a risk factor for developing BP (Phillips and Swartz 2014; Manelis et al. 2015). Regarding the latter hypothesis, overconnectivity might reflect aberrant activation of circuits deputed to the elaboration of emotionally salient contents and related adjustment of behaviour (Chang et al. 2017). Accordingly, greater PFC engagement to emotive content, specifically to happy emotions, has been related to the predisposition to mania (Phillips and Swartz 2014; Manelis et al. 2015). Amygdala-PFC hyperconnectivity may turn into hypoconnectivity conversion from HR to BP (Chang et al. 2017). Possible underlying mechanisms include immune system hyperactivation, inflammatory mediator release, hypothalamic-adrenal axis dysregulation and noradrenergic release related to the occurrence of either major depressive, mixed, or manic episodes. Inflammatory cascades and hyperactivation of noradrenergic systems might exert toxic effects on brain circuitry, disrupting connections between functional engaged areas (Berk et al. 2011; Fitzgerald 2011; Swann et al. 2013; Rosenblat et al. 2014).

sMRI findings in pBP and in HR youth

In the last decade, structural amygdala shrinkage in pBP compared to HC was considered a robust finding (Usher et al. 2010). However, in more recent years, results became less consistent. Possible explanations could be related to sample selection strategies, which recently included mixed samples of BPI and BPII. In fact, when restricting the review to patients with pBPI, a more consistent finding of reduced amygdala volume in patients with pBP as compared to HC emerges. BPII diagnosis is less reliable than BPI (Andreasen et al. 1981) and is associated with high levels of comorbidity (Baek et al. 2011), which might have affected findings. Furthermore, higher levels of inflammatory mediators in BPI than BPII (Bai et al. 2014) patients suggest that consistent findings of amygdala shrinkage in samples with BPI might be due to higher neuroinflammation-mediated structural amygdala damage than in studies enrolling combined samples.

In HR, no structural alterations of the amygdala were found. Again, sample selection strategies could have affected results. In fact, the vast majority of studies included HR who had psychopathological symptoms and were already ill. The only study selecting unaffected HR showed greater bilateral amygdala than HC (Bauer et al. 2014), suggesting that amygdala enlargement could represent a possible marker of resilience. Therefore, more studies on samples including unaffected HR are needed.

Limitations

A major limitation of this systematic review is the substantial heterogeneity of the analytical approaches used in the included studies. Specifically, the size, and location of the amygdala and connected areas were quite diverse, making it difficult to compare results between studies. For this reason, we also were unable to conduct a meta-analysis. Furthermore, we discuss results and make conclusions mainly based on *p*-values, whose reliability has been recently criticised (Goodman 1999). Other measures, such as Bayesian statistics, confidence intervals or statistical power analyses should accompany *p*-values in order to strengthen the reliability of the results (Concato and Hartigan 2016; Simonetti et al. 2019). Additionally, results are biased by possible effects of psychotropic medications, which could affect brain structure and function (Centorrino et al. 2005; Lostia et al. 2009; Hafeman et al. 2012; Simonetti et al. 2016; Sani et al. 2018) and have not been always addressed in included studies. One more limitation regards the pooling of results of pre-pubertal with those of post-pubertal onset bipolar disorder. While there is still much debate about the mere existence of prepubertal BP (Duffy et al. 2020), it should be made clear that young brains are in developmental trajectories that may change the volume of the amygdala according to age and gender (Uematsu et al. 2012). Another major limitation is the difficulty of describing fMRI and sMRI differences in HR youth who develop symptoms compared with those who remained resilient. This is mainly due to the absence of adequate follow-ups of the selected studies.

Conclusions

Summarising, functional hyperactivity in the amygdala is present in both pBP and HR youth, whereas direction of prefrontal alterations in the two groups is less consistent. Structural amygdala alterations seem to not be present in HR youth, but seem to be related to a more severe form of illness in pBP individuals. Therefore functional, rather than structural, amygdala alterations might serve as possible endophenotypes of pBP. Although additional evidence is needed, findings from fMRI studies prompt research on possible targeted interventions specifically aimed at decreasing amygdala activation in order to delay or interrupt pathological cascades leading to illness onset and progression.

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Disclosure statement

None to declare.

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