Appendix 1 to Cusi AM, Nazarov A, Holshausen K, et al. Systematic review of the neural basis of social cognition in patients with mood disorders. *J Psychiatry Neurosci* 2012.

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Table S1: Social cognition studies in patients with major depressive disorder and bipolar disorder

Study	Design	No. patients (mean [SD] age, yr, and sex ratio)	Controlled for*		Medication	Illness history†	Tests/assessments	Findings
			Neurol.	Substance				
Emotion processing in patients with MDD								
Sheline et al.[41]	Longitudinal design: scans conducted pre- and post-treatment with fluoxetine	11 MDD (40.3 [N/A], 5M:6F) 11 HC (39.8 [N/A], 5M:6F)	✓	✓	Unmedicated pts assigned to 8 wk of sertraline	N/A	Affect: passive viewing (masked facial expression task)	MDD showed greater activation in the left amygdala compared to HCs in response to masked fearful, happy and neutral faces. Following antidepressant treatment, MDD showed reduced activation bilaterally in amygdala in response to fearful faces. No associations between depression severity and magnitude of response in the left or right amygdale.
Thomas et al.[42]		5 pediatric MDD (12.3 [2.7], 0M:5) 12 pediatric generalized anxiety disorder and/or panic disorder (12.8 [2.1], 7M:5F) 12 HC (12.1 [2.6], 7M:5F)	✓	✓	All pts unmedicated	N/A	Affect: passive viewing (emotional faces)	Pediatric MDD pts showed reduced activity in the left amygdala for fearful faces. Anxious pts showed hyperactivity in the right amygdala in response to fearful expressions.
Fu et al.[43]		19 MDD pre- and post-treatment with fluoxetine (43.2 [8.8], 6M:13F) 19 HC (42.8 [6.7], 8M:11F)	✓	✓	Unmedicated pts assigned to 8 wk of fluoxetine	N/A	Affect: gender identification	At baseline, MDD showed greater activity in the left-sided amygdala, insula, caudate nucleus, anterior, dorsal and posterior cingulate cortex, precentral gyrus, as well as enhanced bilateral activation in the ventral striatum and thalamus. Following 8 wk of fluoxetine, MDD showed reduced activation in the above neural regions. Reduced activity in frontal cortex and ventral striatum increased significantly after fluoxetine treatment.
Canli et al.[44]	Longitudinal design: scans conducted at visit 1 (T1) and 8 mo later (T2)	16 MDD [45.6 [12.3], 8M:9F) 21 HC [42.0 [12.9], 9M:12F)	✓	✓	9 on antidepressants	N/A	Affect: (gender identification with implicit processing of emotional information)	Increased amygdala activation at baseline was associated with reduced levels of depression at T2 for sad, happy and fearful faces. No relation between reaction times and level of depression.
Gotlib et al.[45]		18 MDD (35.2 [N/A], 5M:13F) 18 HC (30.8 [N/A], 5M:13F)	✓	✓	2 TCAs, 1 TCA+SSRI, 6 other antidepressants	N/A	Affect: gender identification	In response to sad faces, MDD pts showed greater activation in the left inferior frontal gyrus and left subgenual ACC. The MDD group showed enhanced activation in the left subgenual ACC, left middle frontal gyrus and right superior frontal gyrus in response to happy faces. No differences in gender identification task (accuracy or response time).
Keedwell et al.[46]		12 MDD (43 [9.3], 4M:8F) 12 HC (36 [14.6], 4M:8F)	✓	✓	4 venlafaxine, 1 citalopram, 1 lofepramine, 1 sertraline, 1 fluoxetine, 1 mirtazapine, 1 dothiepin	N/A	Affect: mood induction; rate mood level in response to emotional faces	Elevated VMPFC response to happy v. sad faces in MDD. Decreased activity in VMPFC to happy relative to sad faces in HCs. Compared to HCs, MDD pts showed enhanced activity within posterior cingulate gyrus, fusiform gyrus and insula regions. Higher doses of medication were associated with an exaggerated VMPFC response to both happy and sad faces, relative to neutral faces.
Surguladze et al.[47]		16 MDD (42.3 [8.4], 10M:6F) 14 HCs (35.1 [13.2], 8M:6F)	✓	✓	9 on medium-high antidepressant dosage (Sackheim, 2001), 7 on low antidepressant dosage	Length of illness MDD 7.5 (5.1) yr	Affect: gender identification	HCs showed linear increases in activation in the right putamen and bilateral fusiform gyri in response to expressions of increasing happiness, while patients showed reductions in activation in these same regions. MDD showed increases in neural response in the left putamen, left parahippocampal/amygadala and right fusiform gyrus to expressions of increasing sadness. Negative correlation between level of depression and neural response in the right fusiform gyrus to prototypical happy faces.
Chen et al.[48]	Longitudinal design: scans conducted pre- and post-treatment with fluoxetine	17 MDD (44.1 [8.4], 5M:12F)	✓	✓	Unmedicated pts assigned to 8 wk of fluoxetine	N/A	Affect: gender identification	Less severe depressive symptom scores were associated with greater activation in the ACC at baseline. Faster improvement was predicted by greater functional activation of the ACC.
Dannlowski et al.[49]		35 MDD inpatients (38.6 [12.2], 11M:24F)	✓	×	All pts on antidepressants		Affect: attention bias (masked facial expression task; emotional face priming task)	Amygdala hyperactivity to masked sad and angry faces associated with negative biases on affective priming task. Negative judgmental bias also associated with a more severe course of illness.

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Chen et al.[50]	Longitudinal design: scans conducted pre- and post-treatment with fluoxetine	Participant characteristics and paradigm reported in Fu et al.[51]	✓	✓	Unmedicated pts assigned to 8 wk of treatment with fluoxetine	N/A	Affect: gender identification	In both HC and MDD groups, the amygdala showed positive functional coupling with medial temporal regions and ventral occipital regions, and negative coupling with the ACC. MDDs show increases in functional coupling between the amygdala and right frontal regions and ACC after 8 wk of fluoxetine.
Fales et al.[52]		27 MDD (33.4 [8.0], 10M:17F) 24 HC (36.4 [9.0], 12M:12F)	✓	×	Medication-free within last 4 wk	N/A	Affect: fMRI (attention bias): identify if 2 targets are the same (emotional faces and houses)	MDD pts showed increased amygdala activation to unattended fear-related stimuli relative to unattended neutral stimuli (conversely, HCs showed increased activity in the right DLPFC). MDD pts had slower response times than HCs.
Fu et al.[53]	Longitudinal design: scans conducted at baseline (T0), after 16 wk of CBT sessions (T1)	16 MDD (40.0 [9.4], 3M:13F) 16 HC (39.2 [9.3], 3M:13F)	✓	✓	All pts unmedicated	Length of current episode 1.6 (range 0.2–4) yr No. of episodes 0.1 (range 0–2) Age at onset of illness 33.8 (range 18–53) yr	Affect: gender identification	At T0, relative to HCs, MDDs showed increased activity in the fusiform and lingual gyri, left lateral temporal and inferior parietal cortices, posterior cingulate cortex, precuneus and cerebellum. At T1, MDDs and HCs showed comparable activity in these aforementioned regions. Positive clinical response at T1 was significantly related to reduced baseline anterior cingulate activity.
Lee et al.[54]		21 MDD (46.8 [9.1], 3M:18F) 15 HC (48.7 [3.5], 2M:13F)	✓	×	7 venlafaxine, 3 mirtazapine	Length of illness 14.9 (8.8) mo No. of previous episodes 1.9 (0.8)	Affect: passive viewing (emotional faces; rate valence and arousal level of each face)	MDDs showed hypoactivation bilaterally in DLPFC, inferior OFC, medial OFC, caudate and hippocampus in response to sad faces. MDDs showed lower levels of activation bilaterally in inferior OFC and medial OFC in response to angry faces. No differences in neural response between medicated and unmedicated pts. MDDs did not differ from HCs in subjective ratings for valence and arousal.
Matthews et al.[55]		15 MDD (24.5 [5.5], 3M:12F) 16 HC (24.3 [5.0], 6M:10F)	×	✓	All pts unmedicated	Age at first episode 17.6 (5.7) yr No. of previous episodes 4.7 (3.0)	Affect: emotion identification (match faces)	Relative to HCs, MDDs showed increased activity in bilateral extended amygdala, more task-related coactivation of the subgenual cingulate and less coactivation of the supragenual cingulate during exposure to emotional faces. In MDD group, depressive symptom severity was positively correlated with decreased functional coupling between supragenual cingulate and bilateral extended amygdala.
Beesdo et al.[56]		26 adolescent MDD (14.1 [2.2], 11M:15F) 14 with anxiety disorders 12 without anxiety disorders 16 adolescents with anxiety disorders (12.8 [1.8], 11M:5F) 45 HC (13.9 [2.2], 21M:24F)	✓	×	All pts unmedicated	N/A	Affect: rate threat level of emotional face; rate fearful response to the face; judge nonemotional facial feature; passively view face	Relative to HCs, both patient groups reported similar levels of hostility and fearful responses to emotional faces. Compared to HCs, pts in both the MDD and anxiety groups showed enhanced left amygdala activation when viewing fearful faces and focusing on internally experienced fear, relative to passive viewing. Anxious pts showed activation whereas MDD pts showed deactivation of the left amygdala in response to passive viewing of fearful v. happy faces.
Costafreda et al.[57]	Longitudinal design: scans conducted at baseline (T0), after 16 sessions of CBT (T1)	16 MDD (40.0 [9.4], 3M:13F)	N/A	N/A	All pts unmedicated	N/A	Affect: gender identification	Activation of the anterior cingulate, superior and middle frontal cortices, superior parietal cortex, precuneus and cerebellum predicted clinical remission following CBT. Neural responses to lowest and highest intensities of sad facial expressions identified clinical response to CBT.
Dannlowski et al.[58]		34 MDD inpatients (36.9 [12.6], 11M:23F) 31 HC (37.0 [11.5], 13M:18F)	✓	×	All pts on antidepressants, 2 on APD	Length of illness 113.5 (118.4) mo No. of previous episodes 4.1 (4.2) Lifetime hospitalization 7.0 (9.8) wk	Affect: passive viewing (emotional faces)	MDDs showed reduced connectivity between amygdala and prefrontal regions (DLPFC, dorsal ACC) compared to HCs. Reduced amygdala–prefrontal coupling (DLPFC, dorsal ACC, medial PFC) associated with a severe and recurrent course of illness. No effect of medication on functional connectivity.
Fales et al.[59]	Longitudinal design: scans conducted pre- and post-treatment with antidepressants	23 MDD (36.4 [9.4], 10M:13F) 17 recurrent illness, 6 first-episode 18 HC (33.4 [8.2], 9M:9F)	×	✓	All pts on SSRIs	Age at onset of illness 29.3 yr	Affect: emotion identification (faces — same/ different judgments)	MDDs showed a significant increase in DLPFC activity to fearful faces following 8 wk of antidepressant treatment.
Lau et al.[60]		31 adolescents with MDD and/or an anxiety disorder (13.5 [2.3], 13M:18F) 33 HC (13.7 [2.7], 15M:18F)	✓	✓	All pts unmedicated	N/A	Affect: rate threat level of emotional face; rate fearful response to the face; judge nonemotional facial feature; passively view face	Relative to HCs, the pt group rated higher levels of hostility and fear-to-face emotions. Among pts, greater right amygdala activity was found among the long-allele carriers of the serotonin transporter (LL individuals) in response to fearful and happy faces.

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Keedwell et al.[61]	Longitudinal design: scans conducted in the early stages of antidepressant treatment (T0) and after 12 wk of treatment with antidepressants (T1)	12 MDD (49 [N/A], 6M:6F)	✓	✓	All pts on antidepressants	N/A	Affect: passive viewing (emotional faces)	At T0, depression severity score was negatively correlated with responses to happy stimuli in left visual cortex and right caudate, and positively correlated with responses to sad faces in the subgenual cingulate hippocampus, anterior temporal pole and the right visual cortex. At T1, decreases in depressive symptoms were correlated with decreases in right subgenual cingulate and right visual cortex to sad faces.
Peluso et al.[62]		14 MDD (37.9 [14], 5M:9F) 15 HC (37.9 [12], 7M:8F)	✓	✓	All pts unmedicated	N/A	Affective: emotion identification (faces)	Compared to HCs, MDDs showed increased activity in the left amygdale. Increased depressive symptoms were associated with greater activity in the left and right amygdale.
Baeken et al.[63]		12 MDD (36.0 [10.9], 0M:12F) 12 HC (30.2 [8.1], 0M:12F)	N/A	N/A	All pts unmedicated	N/A	Affect: passive viewing (emotional faces)	Relative to HCs, MDD pts showed higher activity in the bilateral subgenual ACC in response to positive and negative emotional faces.
Frodl et al.[64]		25 MDD (39.4 [10.4], 16M:9F) 15 HC (35.5 [10.8], 10M:5F)	✓	✓	15 benzodiazepines, 10 unmedicated	Length of illness 51.8 (63.9) mo No. of episodes 1.52(0.6)	Affective: emotion identification (match faces) and gender identification	During the explicit task, MDDs, relative to HCs, showed less connectivity between OFC and the right middle temporal cortex, right precuneus, and the left parahippocampal, left fusiform and left paracentral cortices. In the implicit task, MDDs showed less OFC connectivity with the right thalamus, right precuneus, left cerebellum and left lingual cortex.
Keedwell et al.[65]	Longitudinal design: scans conducted in the early stages of antidepressant treatment (T0) and after 12 wk of treatment with antidepressants (T1)	12 MDD (49 [N/A], 6M:6F)	✓	✓	N/A	N/A	Affect: gender identification	Enhanced activity in the right visual cortex and subgenual cingulate to sad but not happy faces were associated with a good clinical outcome. Increased activity in the ventrolateral PFC to both happy and sad faces were predictive of a poor outcome.
Miskowiak et al.[66]		19 MDD randomly assigned to 10 erythropoietin (33.4 [8.8], 6M:4F) 9 placebo (35.2 [11.9], 6M:3F)	×	✓	Erythropoietin 5 SSRIs, 1 mirtazapine and/or venlafaxine, 1 MAOI, 3 APDs, 1 lithium, 3 benzodiazepines, 1 thyroid hormones, 1 unmedicated Placebo 3 SSRIs, 2 mirtazapine and/or venlafaxine, 2 MAOIs, 1 APDs, 1 lithium, 1 benzodiazepines, 1 thyroid hormones, 1 unmedicated	No. of episodes Erythropoietin 4 (4) Placebo 3 (2) Age at onset of illness Erythropoietin 25 (6) Placebo 27 (8) Length of illness Erythropoietin 11 (7) Placebo 8 (6)	Affect: passive viewing (emotional faces) and emotion identification (faces)	Three days after administration, erythropoietin reduced neural response in the left amygdala and hippocampus to fearful compared with happy faces, and in the right precuneus, superior temporal and occipitoparietal regions to fearful faces v. baseline. Relative to those who received placebo, erythropoietin-treated pts showed a reduction in the recognition of fearful faces.
Moses-Kolko et al.[67]		14 postpartum MDD (45.6 [11.2], 0M:14F) 16 HC (44.8 [11.7], 0M:16F)	✓	✓	None	N/A	Affect: emotion identification (fear, anger; match images)	No differences in accuracy or reaction time between groups. In comparison to HC, MDD had reduced left DMPFC activity and DMPFC–amygdala connectivity in response to negative faces. Higher depression symptoms were associated with lower left amygdala activation.
Norbury et al.[68]		16 euthymic MDD (36.2 [13.9], 7M:9F) 21 HC (32.3 [12.9], 11M:10F)	N/A	N/A	All pts unmedicated	All pts experienced ≥ 2 previous episodes of depression	Affect: emotion identification (match faces)	Relative to HCs, MDDs showed increased bilateral responses in the DLPFC and right caudate to fearful faces. Amygdala responses did not differ between HCs and MDDs.
Scheuerecker et al.[69]		13 MDD inpatients (37.9 [10.1], 10M:3F) 15 HC (35.5 [10.9], 10M:5F)	✓	✓	Medication-free for at least 1 yr	Duration of illness 52.3 71.5) mo No. of episodes 1.4 (0.7) 8 pts with recurrent MDD	Affect: emotion identification	MDDs had increased activity in the middle frontal cortex, caudate, precuneus and lingual gyrus v. HCs. Association between lower OFC volumes and higher activation of the above neural regions in MDD but not in HC. No correlation between level of depression and neural response in the MDD group.

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Surguladze et al.[70]		9 MDD (42.8 [7.2], 5M:4F) 9 HC (39.7 [14.6], 5M:4F)	✓	✓	4 SNRI, 3 SSRI, 1 MAOI, 1 TCA, 2 lithium, 1 benzodiazepine, 1 phenothiazine		Affect: gender identification and emotion identification (faces)	MDD pts did not differ from HCs on the emotion labeling task. Relative to HCs, the MDD group showed greater activation in right middle temporal gyrus and left middle/inferior temporal gyrus, OFC and insula to expressions of disgust. MDD pts also showed reduced activation in left inferior parietal lobe to fearful faces. No measurable effect of medication level on neural response was observed.
Suslow et al.[71]		30 MDD inpatients (38.8 [11.4], 17M:13F) 26 HC (36.2 [13.4], 12M:14F)	✓	✓	All patients on antidepressants	No. of episodes 2.7 (2.0) Lifetime hospitalization 7.6 (8.7) wk Length of illness 72.2 (75.0) mo	Affect: attention bias (masked facial expression task)	MDDs showed higher amygdala responses to sad faces than happy faces. HCs showed stronger amygdala responses to happy rather than sad faces. Depression severity was negatively correlated with amygdala response to happy faces. No measureable effects of medication level, number of episodes, comorbidity status or duration of illness on amygdala responsiveness was observed.
Townsend et al.[72]		15 MDD (45.6 [11.2], 9M:6F) 20 HC (44.8 [11.7], 9M:6F)	×	✓	None for at least 1 mo; 6 had never received medication	Duration of illness 14.7 (13.3) yr No. of episodes, median 3 Duration of current episode 2.2 (2.7) yr	Affect: emotion identification (matching, labelling; sad and angry)	HCs showed greater activation in the right insula, inferior and middle temporal gyri, hippocampal gyrus, putamen, occipital gyrus, fusiform gyrus and cerebellum. No differences in accuracy or reaction time. No effect of depressive symptoms on neuronal activation. Anxious subgroup showed less activation in left OFC in whole-brain analysis.
Victor et al.[73]	Longitudinal design: scans conducted at baseline (T0), after 8 wk of sertraline hydrochloride in currently depressed group	22 currently depressed MDD (dMDD) (31.1 [7.8], 10M:12F) 16 MDD in full remission (rMDD) (30.8 [9.8], 5M:11F) 25 HC (28.8 [9.3], 10M:15F)	✓	✓	Unmedicated currently depressed patients assigned to 8 wk of sertraline treatment; remitted patients unmedicated	Age at onset dMDD 16.7 (6.0) rMDD 18.3 (4.3)	Affect: attention bias (N-back mask: matching identities with implicit emotional processing)	HCs and rMDDs were more likely to detect neural faces in the masked position than dMDDs. dMDD and rMDD groups had greater amygdala activation in response to masked sad faces relative to HCs. HCS showed increased amygdala activation to masked happy faces. Bias towards sad faces in dMDD v. HCs normalized after sertraline, with concomitant increases in amygdala response to happy faces. In dMDD group, higher HAMD scores were associated with decreased amygdala activation in response to masked happy faces.
Yang et al.[74]		12 adolescent MDD (15.9 [1.4], 7M:5F) 12 HC (15.4 [1.7], 7M:5F)	✓	✓	All pts unmedicated	N/A	Affect: emotion identification (match faces)	Adolescent MDD pts did not differ from HCs on the emotion identification task. Relative to HCs, the MDD group showed greater activation in the left amygdala and bilateral ACC in response to emotional faces. Hyperactivity in the amygdala was associated with elevated depression scores.
Lisiecka et al.[75]	Longitudinal design: visits conducted pre- and post-treatment with venlafaxine or mirtazapine	23 MDD inpatients Mirtazapine (37.7 [8.5], 7M:3F) Venlafaxine(38.9 [9.6], 8M:5F)	✓	✓	No medication in last 12 mo	Mirtazapine group 4 on first episode Illness duration 75 (72.3) mo Venlafaxine group 6 on first episode Illness duration 38.5 (51.6) mo	Affect: emotion identification (sad, angry)	Response times did not change in responders v. nonresponders. Responders had higher OFC connectivity with left motor areas and OFC regions at baseline. Nonresponders were characterized by higher OFC connectivity with cerebellum at baseline. Change in HAMD score was positively correlated with baseline functional coupling of the left OFC with bilateral thalami. Among treatment responders a decrease in connectivity of the OFC was observed in the right caudate nucleus and the thalamus.
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Yurgelun-Todd et al.[76]		14 BD (31.6 [10.2], 7M:7F) 10 HC (N/A, 5M:5F)	✓	✓	12 mood stabilizer, 13 APDs	Age at onset of illness 21.9 (5.4) yr	Affect: emotion identification (faces)	Compared to HCs, BDs showed hypoactivation in right DLPFC and hyperactivation in left amygdala during presentation of fearful faces. Regional brain activation did not differ between groups during presentation of happy faces. In the female BD group, negative association between age at illness onset and signal intensity change in left DLPFC. No other significant associations were found between levels of brain activation and other clinical variables (illness duration, HAMD, YMRS). Pts had difficulties identifying fearful but not happy faces.
Lennox et al.[77]		10 BD-I with mania (37.3 [12.8], 8M:2F) 12 comparison subjects (32.6 [10.7], 6M:6F)	×	×	8 lithium carbonate, 3 sodium valproate, 4 carbamazepine, 3 haloperidol, 4 olanzapine, 1 sulpiride	N/A	Affect: identify intensity of facial expression	Manic pts reported lower subjective ratings of sadness. Reduced activation in subgenual anterior cingulate and bilateral amygdala, increased activation in posterior cingulate and left insula. No differences in neural response to happy faces.
Mitchell et al.[78]		11 BD (42.8 [1.8], 11M:0F) 12 SCZ (45.7 [2.7], 12M:0F) 13 HC (32.3 [3.6], 13M:0F)	✓	✓	BD 9 lithium carbonate or sodium valproate, 4 APDs, 5 antidepressants	Length of illness BD 8.2 (1.4) yr	Affect: passively listen to affective prosody; actively attend to emotional prosody	Compared to HCs, during passive listening task, BDs showed hypoactivation in amygdala, uncus, bilateral superior temporal gyrus and right inferior frontal gyrus in response to pure emotional prosody and hyperactivation of left superior temporal gyrus in response to unfiltered emotional prosody.

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Altshuler et al.[79]		9 BD-I with mania (34.6 [8.0], 3M:6F) 9 HC (30.4 [7.6], 3M:6F)	✓	✓	4 sodium valproate, 2 lithium, 2 anticonvulsants, 1 atypical APD, 2 unmedicated	Length of illness 14.8 (5.1) yr No. of manic episodes 4.2 (2.0)	Affect: emotion identification (match faces)	Compared to HCs, during facial affect matching task, BDs showed elevated activation in the left amygdala and reduced bilateral activation in the OFC.
Blumberg et al.[80]		12 BD-I medicated outpatients (45.8 [9.4], 8M:4F) 4 manic/hypomanic/mixed, 1 depressed, 7 euthymic 5 BD-I unmediated (40.0 [12.3], 2M:3F) 1 mixed, 2 depressed, 2 euthymic 14 HC (14.0 [2.4], 11M:3F)	×	✓	MED group 8 on anticonvulsants, 4 on lithium, 3 on antidepressants, 1 on atypical antipsychotics	N/A	Affect: passive viewing (happy, sad, fearful or neutral Ekman faces)	Amygdala activation was higher in unmedicated BD pts relative to HCs for happy faces. Medicated BD pts had lower amygdala activation in comparison to HC for happy faces. No effects for mood state, history of alcohol dependence, depression severity, duration of illness, age of onset or number of hospitalizations.
Rich et al.[81]		22 pediatric BD (14.2 [3.1], 10M:12F) 21 HC (14.5 [2.5], 11M:10F)	×	✓	14 mood stabilizers, 10 APDs, 7 antidepressants, 6 lithium, 5 stimulants, 4 sedatives		Affect: rate threat level of emotional face; rate fearful response to the face; judge nonemotional facial feature; passive viewing (emotional faces)	BD pts perceived more hostility and reported greater fearful responses to neutral faces relative to HCs. Pts had greater activation in the left amygdala, accumbens, putamen and ventral PFC when rating the hostility of emotional faces. Relative to HCs, BDs showed increased activation in the left amygdala and bilateral accumbens when rating their fear of neutral faces.
Malhi et al.[82]		10 euthymic BD-I (33.5 [8.7], 0M:10F) 10 HC (32.4 [6.4], 0M:10F)	✓	✓	7 mood stabilizers, 3 unmedicated	Length of illness 12.0 (7.7) yr No. of previous depressive episodes 10.4 (8.7) No. of previous manic episodes 4.7 (3.4)	Affect: emotion identification (faces)	BDs equally accurate to HCs in identifying all facial expressions (neutral, disgust, fear), but slower to respond when identifying neutral faces. In response to disgust faces, HCs showed hyperactivation in frontal cortex (left middle and inferior frontal gyri, right precentral gyrus), right insula and visual processing regions (right fusiform gyrus, post-central gyrus, supramarginal gyrus). In response to fearful faces, BDs showed elevated activation in hippocampal regions (left hippocampus, bilateral parahippocampal gyrus), the left superior temporal gyri, inferior parietal lobule, claustrem and right-sided lingual gyrus and cerebellum.
Pavuluri et al.[83]		10 euthymic, pediatric BD (14.9 [1.8], 6M:4F) 10 HC (14.3 [2.4], 5M:5F)	✓	✓	Unmedicated pts		Affect: passive viewing (emotional faces)	Relative to HCs, BDs showed reduced activation in the bilateral DLPFC and OFC and hyperactivity in the bilateral parahippocampal gyrus and pregenual anterior cingulate to angry faces. In response to happy faces, hypoactivity was observed in the DLPFC, medial PFC and OFC and hyperactivity in the right amygdala and bilateral pregenual anterior cingulated.
Altshuler et al.[30]		11 BD-I depressed (32 [7.3], 5M:6F) 17 HC (29.5 [6.6], 9M:8F)	✓	✓	2 lamotrigine, 3 divaloprex sodium, 1 carbamazepine, 1 lithium, 2 atypical APDs, 2 SSRIs, 1 venlaflaxine, 2 unmedicated	N/A	Affect: emotion identification (faces; match word with facial emotion)	Compared to HCs, BDs showed hypoactivation in right and left OFC and right DLPFC. BDs also showed increased activation in the left lateral OFC.
Foland et al.[84]		9 manic or hypomanic BD-I (34.6 [8.0], 3M:6F) 9 HC (30.4(7.6], 3M:6F)	✓	✓	4 divalproex sodium, 2 lithium, 2 gabapentin, 1 olanzapine, 2 unmedicated	No. of manic episodes 4.2 (2.0)	Affect: emotion identification (match faces)	Relative to HCs, BDs showed reduced connectivity between the ventrolateral PFC and amygdala. Reduced connectivity between the ventrolateral PFC and amygdala was associated with severity of manic symptoms, number of previous manic episodes and illness duration.
Haldane et al.[85]	Longitudinal design: scans conducted pre- and post-treatment with lamotrigine	12 BD-I (42.1 [11.8], 5M:7F)	✓	✓	At baseline 4 anticonvulsant and serotonin reuptake inhibitor (4 sodium valproate, 1 carbamazepine), 7 sodium valproate monotherapy	Age at onset of illness 23.1 (5.6) yr No. of previous episodes 10.1 (6.5)	Affect: emotion identification (faces)	Relative to baseline, BDs showed increased activations in frontal (left media frontal gyrus, precentral gyrus, cingulate gyrus) and temporal regions (right middle temporal gyrus) in response to angry faces. No performance differences found in identifying angry faces between baseline and study endpoint (post-lamotrigine treatment).
Hassel et al.[86]		19 BD (32.5 [8.8], 10M:9F) 18 euthymic, 1 depressed 24 HC (27.8 [8.7], 11M:13F)	✓	✓	1 medication-free, 1 lithium, 5 antipsychotics, 12 multiple medications	Duration of illness 10.6 (6.6) yr No. of episodes N/A Age at onset 22.5 (8.0)	Affect: gender discrimination (mild happy, intense happy, mild fear, intense fear faces, neutral) and emotion identification (non-sad, angry, fearful, happy, disgust, neutral)	Relative to HCs, BDs had higher left striatal activity in response to mild happy faces. BDs showed decreased right DLPFC activity in response to all three intensities of happy faces (intense, mild, neutral) and reduced activity in left DLPFC in response to all three intensities of fear. No effect of medication type, load or symptom severity. Trending correlation between increased right amygdala activation with a younger age of illness onset. BD with comorbid disorders showed near-significant increases in left striatum activation in response mild happy faces v. BDs without comorbidities. Emotion identification and gender discrimination accuracy was equal across diagnosis groups.

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Jogia et al.[87]	Longitudinal design: scans conducted pre- and post-treatment with lamotrigine	12 BD-I (42.1 [11.8], 5M:7F) 12 HC (41.8 [10.9], 5M:7F)	✓	✓	N/A	Age at onset of illness 23.1 (5.6) yr No. of illness episodes 10.1 (6.5)	Affect: emotion identification (faces)	At baseline, relative to HCs, BDs showed hyperactivation in temporal regions (left hippocampus/parahippocampal gyrus) and less activation in frontal areas (right-sided superior and inferior gyri, precentral and cingulate gyri) in response to sad faces. After lamotrigine treatment, BDs showed increased activation in dorsomedial and ventrolateral prefrontal cortices and reductions in activation in left inferior temporal gyrus in response to sad faces. Accuracy in recognizing sad facial affect did not differ between baseline and following lamotrogine monotherapy.
Killgore et al.[88]		14 BD in (28.1 [11.2], 11M:3F) 13 HC (25.5 [4.7], 12M:1F)	×	×	12 atypical antipsychotics, 5 mood stabilizers, 4 benzodiazepine, 1 antidepressant, 1 beta blocker	First inpatient admission, duration of illness <1 yr Treatment with mood stabilizers or antipsychotics <3 mo	Affect: passive viewing (fearful faces)	During early stages of emotional processing, HCs showed a smaller area of activation in the left calcarine cortex. During late stages of emotional processing, BDs showed greater activation in the right superior temporal pole. HCs showed greater activation than BDs in left putamen, left caudate, left ACC, medial orbital front gyrus, right middle frontal gyrus, superior temporal pole and inferior orbital frontal gyrus. BD pts showed premature onset of activation and delayed offset after removal of stimuli.
Rich et al.[89]		33 pediatric BD-I remitted (14.4 [3.0], 13M:20F) 24 HC (14.4(2.2], 9M:15F)	×	✓	17 APDs, 13 mood stabilizers, 10 antidepressants, 10 lithium, 9 anticonvulsants, 9 stimulants, 4 sedatives		Affect: rate threat level of emotional face; rate fearful response to the face; judge nonemotional facial feature; passive viewing (emotional faces)	Relative to HCs, both euthymic and noneuthymic BD youth showed reduced functional connectivity between the left amygdala and the right posterior cingulate/precuneus. Lower connectivity was also observed between the right amygdala and a region bordering the right fusiform gyrus and parahippocampal gyrus. Connectivity was not related to mood state. Connectivity deficits were seen in BD pts without comorbid ADHD, oppositional defiant disorder or anxiety.
Robinson et al.[90]		15 remitted BD-I (38.5 [13.0], 6M:9F) 16 HC (36.3 [10.5], 7M:9F)	✓	✓	6 antidepressants, 11 anticonvulsants, 7 atypical APDs, 1 lithium	Age at onset of symptoms 20.4 (10.4) yr Age at diagnosis 30.8 (10.6) yr Length of illness 8.0 (7.4) yr	Affect: emotion identification (match faces)	No difference between groups in amygdala activation during emotional face matching task. Compared to HCs, BDs showed greater activation in the right inferior frontal gyrus. BDs showed bilateral hyperactivation of the inferior frontal gyrus after controlling for effects of anticonvulsant medication. No significant effects of gender or comorbidity.
Hassel et al.[91]		14 euthymic BD-I (32.6 [9.9], 6M:8F) 16 HC (28.5 [9.3], 8M:8F)	✓	×	12 on medications	Duration of illness 11.7 (6.3) yr No. of episodes N/A Age at onset 22.0 (9.0)	Affect: gender discrimination (mild happy, intense happy, mild fear, intense fear faces) and emotion identification (non-sad, angry, fearful, happy, disgust, neutral)	HCs were more accurate in labelling facial emotions. Relative to HCs, BDs showed decreased right dorsal PFC in response to happy and fearful faces. BDs showed decreased activity in left caudate to intense and mild happy faces relative to neural faces (HC did not show this effect). BDs and HCs showed decreased activity in the bilateral caudate to fearful faces relative to neural faces. Higher eating disorder spectrum scores were associated with increased activity to intense happy faces within the right ventral putamen. Increased levels of substance use were associated with reduced activity in the right caudate and right PFC. An increased medication load was associated with increased activity within left caudate to neural faces and decreased activity in the right dorsal PFC to mild fear faces. Age at onset of illness was negatively correlated with right dorsal PFC activity to mild fear and neutral faces.
Kalmar et al.[92]		21 adolescent BD-I (15.1 [2.1], 11M:10F) 11 manic, mixed or hypomanic, 2 depressed, 8 euthymic 30 HC (14.2 [2.1], 19M:11F)	✓	×	4 lithium carbonate, 9 anticonvulsants, 11 atypical APDs, 6 antidepressants, 5 stimulants, 1 benzodiazepine, 1 lovothyroxine, 4 unmedicated	N/A	Affect: gender identification	Relative to HCs, BDs showed enhanced amygdala activation to emotional faces. BDs with smaller amygdala volumes demonstrated higher amygdala activation during processing of emotional faces. No significant relationships between amygdala activation and medication status or mood state during processing of emotional faces.
Pavuluri et al.[93]		10 euthymic pediatric BD (15.2 [2.0], 5M:5F) 10 HC (14.3 [2.1], 5M:5F)	✓	✓	None	N/A	Affect: emotion identification (happy v. angry; age recognition)	No difference in response time or accuracy between groups. Relative to the emotional condition, age discrimination condition elicited higher activation in right amygdala, right insula, left middle frontal gyrus and left posterior cingulate cortex in euthymic BD youth. HCs showed greater activation in the right superior frontal gyrus in the same comparison. Relative to visual fixation, both emotional and age discrimination conditions elicited less activation in the right PFC and pregenual ACC in BD pts relative to HC. BD youth showed greater activation in the posterior visual and face-processing regions. BD pts showed increased L and R amygdala activation for age discrimination condition v. fixation.

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Wang et al.[94]	33 BD (31.8 [9.6], 10M:23F) 10 manic/mixed or hypomanic, 7 depressed, 16 euthymic 31 HC (30.4 [10.8], 14M:17F)	✓	×	9 lithium carbonate, 16 anticonvulsants, 14 atypical APDs, 12 antidepressants, 7 benzodiazepines, 6 unmedicated	N/A	Affect: gender identification	Relative to HCs, BDs showed decreased perigenual ACC–amygdala functional connectivity during presentation of fearful and happy faces. Both BDs and HCs demonstrated a significant association between perigenual ACC–amygdala functional connectivity measures and fractional anisotropy values in the uncinate fasciculus and surrounding ventrofrontal white matter, during fearful and happy face processing. No significant effects of mood state, rapid cycling, history of substance abuse related disorders, or medication status on perigenual ACC–amygdala connectivity.
Brotman et al.[95]	43 pediatric BD (14.8 [2.7], 17M:26F) 40 BD-I, 3 BD-II, 24 euthymic 29 Severe mood dysregulation (12.9 [1.9], 17M:12F) 18 ADHD (13.9 [2.3], 13M:5F) 37 HC (13.7 [2.7], 21M:16F)	✓	✓	BD 19 atypical APDs, 15 lithium, 22 anticonvulsants, 13 antidepressants, 10 stimulants, 5 other, 11 unmedicated Severe mood dysregulation 10 atypical APDs, 4 lithium, 12 anticonvulsants, 8 antidepressants, 10 stimulants, 5 other, 6 unmedicated	N/A	Affect: passive viewing (emotional faces), rating perceived threat and subjective fear of emotional faces	Relative to HCs, BDs rated neutral faces as more fear producing. BDs did not differ from HCs in neural response while rating perceived threat or subjective fear of emotional facial expressions. While rating subjective fear of neutral faces, ADHD pts showed hyperactivation in the left amygdala relative to BDs, severe mood dysregulation subjects, and HCs.
Surguladze et al.[96]	20 remitted BD-I (42.7 [10.4], 9M:11F) 20 unaffected first-degree relatives of BD (43.0 [13.8], 12M:8F) 20 HC (41.9 [11.6], 10M:10F)	✓	✓	9 lithium, 7 mood stabilizers, 4 APDs, 2 antidepressants, 4 unmedicated	N/A	Affect: gender identification	BD pts and unaffected relatives showed enhanced activity in the medial PFC relative to HCs during presentation of happy and fearful faces. Relative to HCs, BD pts showed increased activity in the putamen in response to high-intensity happy faces. Increased left amygdala activity in the BD and relatives groups was observed in response to intensely happy faces. No significant effect of medication load or gender.
Versace et al.[97]	31 BD-I (35.9 [8.8], 11M:20F) 14 depressed (BDd), 17 remitted (BDr) 24 HC (29.5 [9.6], 11M:13F)	✓	×	BD depressed 12 mood stabilizers, 4 lithium, 9 APDs, 7 antidepressants, 7 benzodiazepines BD remitted 10 mood stabilizers, 6 lithium, 9 APDs, 8 antidepressants, 3 benzodiazepines	Age at onset of illness BDd 21.7 (7.0) yr BDr 25.4 (10.8) yr Length of illness BDd 11.8 (6.3) yr BDr 12.3 (9.8) yr	Affect: emotion identification (faces)	BDs were less accurate than HCs in labeling happy faces. No significant differences in emotion labeling found between depressed and remitted BDs. All BDs showed greater right amygdale–OFC functional connectivity than HCs to sad faces of varying intensity. Female BD depressed pts showed greater left amygdala–OFC connectivity than female HCs to these faces. Relative to HCs, depressed BD but not remitted BD pts showed reduced bilateral amygdala–OFC connectivity to intense happy faces. In all BDs, antidepressant usage was associated with reduced left amygdala–OFC connectivity to mildly sad faces. A greater age at illness onset was associated with reduced connectivity to mildly sad faces.
Passarotti et al.[98]	23 pediatric BD (13.6 [2.5], 10M:13F) 19 manic, 4 hypomanic 14 ADHD (13.0 [2.4], 9M:5F) 19 HC (13.5 [3.2], 9M:10F)	✓	✓	None	N/A	Affect: emotion identification (2-N back task; matching emotion and identity)	Among BD pts, higher accuracy for angry faces was associated with decreased activation in the left DLPFC; in the BD group, increased CDRS scores were associated with lower activation in the right medial frontal gyrus to angry faces. BD pts showed greater activation for angry v. neutral faces in the right inferior frontal gyrus, at the junction of DLPFC and VLPFC, and in the right fusiform, parahippocampal and middle temporal gyri. In response to happy v. neutral faces, BD pts showed increased activation in the right VLPFC, bilateral amygdala, fusiform gyrus, caudate, temporal regions and right posterior cingulate gyrus.

Emotion processing in patients with mixed mood disorders

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Lawrence et al.[99]		12 BD-I (N/A) 9 MDD (N/A) 11 HC (N/A)	✓	✓	BD 5 SSRIS, 5 atypical APDs, 9 mood stabilizers MDD 3 SSRIs, 4 SNRIs, 1 MAOI, 1 TCA	Length of illness BD 15.4 (13.4) yr MDD 8.0 (5.0) yr	Affect: identify facial emotion; identify gender of emotional face	Relative to HCs, BDs showed hyperactivation in subcortical regions in response to positive and negative faces: right globus pallidus and thalamus in response to mildly fearful faces; left amygdala and ventrolateral PFC to intense fearful faces; left amygdala, caudate nucleus, putamen to mildly happy faces; left ventral PFC and hippocampus to mild sadness; right ventral PFC to intense sadness. Relative to HCs and BDs, MDDs showed reduced neural activation in similar subcortical and ventral prefrontal regions to all emotional expressions except mild sadness (increased putamen activation relative to BDs). Relative to both pt groups, HCs showed increased activation in right DLPFC to mild fear and within the bilateral DLPFC to intense sadness. No associations between depression severity and neural response in BD pts, but positive association between level of depression and neural response to mildly sad faces in left parahippocampal gyrus in MDD.
Schaefer et al.[100]	Longitudinal design: scans conducted before and after 22 wk of venlafaxine treatment	9 MDD (36.5 [9.9], 3M:6F] 7 MDD, 2 dysthymia 14 HC (28.2 [7.9], 4M:10F)	✓	✓	Unmedicated patients assigned to venlafaxine	N/A	Affect: passive viewing	Viewing human faces produced increased activation compared to positive images without human faces or appetitive items for MDDs after treatment and HCs at scan 1in the left inferior, medial and superior frontal gyri, bilateral insula, medial dorsal nucleus of the thalamus and right fusiform gyrus. Changes in neural activation after treatment were not associated with clinical improvement or drug dose.
Almeida et al.[101]		15 BD-I depressed (36.6 [11.9], 1M:14F) 16 acute MDD (32.3 [9.7], 3M:13F) 16 HC (28.3 [8.4], 4M:12F)	✓	×	BD 9 mood stabilizers, 10 APDs, 7 antidepressants, 6 benzodiazepines MDD 1 APD, 13 antidepressants, 5 benzodiazepines	Age at onset of illness BD 22.3 (10.4) yr MDD 18.9 (7.3) yr Length of illness MDD 13.4 (9.6) yr BD 14.2 (9.8) yr	Affect: identify facial emotion	Relative to HCs, both MDD and BD depressed pts showed significantly reduced top–down connectivity between the orbitomedial PFC and amygdala during the happy condition. In the MDD group, orbitomedial PFC–amygdala connectivity was positively correlated with medication load and negatively associated with age of illness onset. BD depressed pts showed abnormal bottom–up connectivity between the amygdala and orbitomedial PFC compared to HCs.
Almeida et al.[102]		15 BD depressed (36.6 [11.9], 1M:14F) 15 BD remitted (33.3 [7.8], 5M:10F) 15 MDD actively depressed (32.7 [9.9], 2M:13F) 15 HC (32.7 [8.0], 3M:12F)	✓	✓	2 BD depressed, 2 MDD, 1 BD remitted were medication-free	Age at onset of illness BDd 22.3 (10.4) yr BDr 18.8 (6.8) yr dMDD19.1(7.5) yr Length of illness BDd 14.2 (9.8) yr BDr 14.7 (5.5) yr dMDD 13.7 (9.9) yr	Affect: identify facial emotion	Relative to HCs, BD-remitted pts and MDDs, BD depressed pts showed greater left amygdala activity to mild and neutral faces in the sad condition, but not other emotion conditions. In the BD depressed group, amygdala activity to intense sad faces was negatively correlated with illness duration and medication load.
Lelli-Chiesa et al.[103]		40 BD (44.0 [11.9], 19M:21F) 25 healthy relatives of BD (34.9 [14.3], 15M:10F) 22 relatives with another Axis I diagnosis (32.5 [11.4], 9M:14F) 15 MDD, 7 anxiety 50 HC (34.9 [13.2], 26M:24F)	✓	✓	N/A	BD group Illness duration 19.9 (10.5) yr No. of episodes 11.0 (15.0)	Affect: emotion identification (sad, neutral faces)	BD had longer reaction times v. HC and healthy relatives. No difference in accuracy between groups. No effect of medication status. In pts with an Axis-I disorder (including BD), Met158 allele was associated with highest left VLPFC activity, whereas Val158 was associated with lowest left VLPFC activity.
Theory of mind in patients with MDD and patients with bipolar disorder								
Malhi et al.[104]		20 euthymic BD-I (35.3 [9.4], 11M:9F) 20 HC (35.8 [10.4], 11M:9F)	✓	✓	2 lithium, 3 lithium + lamotrigine, 1 lithium + valproate, 5 valproate, 1 carbamazepine, 7 medication-free	Length of illness 13.1 (9.2) yr No. of previous depressive episodes 9.9 (7.1) No. of previous manic episodes 6.9 (6.4)	ToM: Animated sequences depicting bluffing, persuasion, surprise, mockery	HCs demonstrated activation in cortical (bilateral supramarginal, angular and middle temporal gyri, insula, inferior frontal gyri) and subcortical regions (bilateral thalamus, right-sided hippocampus and putamen) in response to ToM animated sequences. BDs showed activation in left anterior cingulate gyrus and bilateral precuneus and cuneus in response to ToM stimuli. BDs performed worse than HCs on ToM task.
Kim et al.[105]		14 euthymic BD-I (30.4 [5.9], 8M:6F) 14 HC (27.5 [3.3], 8M:6F)	✓	✓	7 lithium, 11 divalproex, 6 antidepressants	Duration of illness 4.3 (4.4)yr No. of episodes Mania 2.2 (1.9) Depression 1.2 (1.3)	Affect: attribute rationale for expressed facial emotions in virtual humans (avatars)	BDs showed delayed reaction times in identifying potential reasons for Avatars emotions compared to HCs. BD and HCs had comparable response accuracy. Relative to HCs, BDs showed hypoactivation in the right inferior frontal gyrus, right middle frontal gyrus, right insula, right precentral gyrus and premotor cortex, mostly during happy and angry conditions.

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ACC = anterior cingulate cortex; ADHD = attention deficit hyperactivity disorder; APD = antipsychotic drug; BD = bipolar disorder; CBT = cognitive behavioural therapy; CDRS = Children's Depression Rating Scale; DLPFC = dorsolateral prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; DTI = diffusion tensor imaging; HAMD = Hamilton Depression Rating Scale; HC = healthy control; MAOI = monamine oxidase inhibitor; MDD = major depressive disorder; OFC = orbitofrontal cortex; PFC = prefrontal cortex; Pts = patients; SCZ = schizophrenia; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; ToM = theory of mind; VLPFC = ventrolateral prefrontal cortex; VMPFC = ventromedial prefrontal cortex; YMRS = Young Mania Rating Scale.
*Studies controlled for neurological abnormalities/seizures/disorders (Neural.) and/or substance abuse/dependence (Substance).
†Values are expressed as mean (standard deviation) unless otherwise specified.