Review Paper

Systematic review of the neural basis of social cognition in patients with mood disorders

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Background: This review integrates neuroimaging studies of 2 domains of social cognition — emotion comprehension and theory of mind (ToM) — in patients with major depressive disorder and bipolar disorder. The influence of key clinical and method variables on patterns of neural activation during social cognitive processing is also examined. **Methods:** Studies were identified using PsycINFO and PubMed (January 1967 to May 2011). The search terms were "fMRI," "emotion comprehension," "emotion perception," "affect comprehension," "affect perception," "facial expression," "prosody," "theory of mind," "mentalizing" and "empathy" in combination with "major depressive disorder," "bipolar disorder," "major depression," "unipolar depression," "clinical depression" and "mania." **Results:** Taken together, neuroimaging studies of social cognition in patients with mood disorders reveal enhanced activation in limbic and emotion-related structures and attenuated activity within frontal regions associated with emotion regulation and higher cognitive functions. These results reveal an overall lack of inhibition by higher-order cognitive structures on limbic and emotion-related structures during social cognitive processing in patients with mood disorders. Critically, key variables, including illness burden, symptom severity, comorbidity, medication status and cognitive load may moderate this pattern of neural activation. **Limitations:** Studies that did not include control tasks or a comparator group were included in this review. **Conclusion:** Further work is needed to examine the contribution of key moderator variables and to further elucidate the neural networks underlying altered social cognition in patients with mood disorders. The neural networks underlying higher-order social cognitive processes, including empathy, remain unexplored in patients with mood disorders.

Introduction

Major depressive disorder (MDD) and bipolar disorder are associated with alterations in multiple domains, including interpersonal and social functioning.[1–4] Recent studies have examined the nature of social impairment in patients with mood disorders through the lens of social cognition, involving the ability to understand and respond to the thoughts and feelings of others and thought central to successful social interactions.[5,6] The goal of the present review was to examine the findings of neuroimaging studies concerning social cognitive processing in patients with MDD and bipolar disorder. Here, we focus on studies investigating 2 different but overlapping aspects of social cognition — emotion comprehension and theory of mind (ToM) — that have recently been investigated in patients with mood disorders. Emotion recognition refers to an individual's ability to infer the emotional state of another from observable information, such as prosody and facial expression. By contrast, ToM has been defined as the ability to ascribe mental states, such as beliefs, desires and intentions, to oneself and others.[7] Taken together, these theoretical definitions reveal substantial overlap and distinct processes involved in these key components of social cognition. For example, theoretical models propose that the ability to recognize another's emotion is critical to ToM,[8] with empirical evidence supporting this view.[9–15] Hence, we

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included these 2 domains of social cognition in our review to provide a broad understanding of the neural correlates of social cognition in patients with mood disorders. Other domains of social cognition, including empathy and moral reasoning, remain unexplored in these patients.

In healthy individuals, the neural basis of social cognition consists of a complex network of brain areas involved in cognitive and affective processes (for a recent review, see Adolphs[16]). Key regions that contribute to this network include prefrontal regions, such as the ventromedial prefrontal cortex, an area involved in the regulation of emotion and reward evaluation,[17] and the dorsolateral prefrontal cortex (DLPFC), an area implicated in higher-order cognitive processes, such as cognitive control and executive functioning.[18,19] The anterior cingulate cortex, involved in conflict monitoring and integration of information to motivate behaviour, has also been implicated.[16] The amygdala, which is critical to processing and evaluation of emotional stimuli, and the ventral striatum, which is involved in emotional and motivational aspects of behaviour, also constitute important nodes in the social cognition network.[5] Finally, temporal regions, such as the temporoparietal junction, which is involved in a sense of agency as well as perspective-taking, and the temporal poles, which are implicated in diverse memory functions, have been shown to be recruited across various social cognitive tasks, including ToM, empathy and facial emotion processing.[20–22] Critically, many of the same neural regions thought to mediate the cognitive (e.g., memory, executive functioning) and affective (e.g., emotion evaluation) processes necessary for social cognitive responding have been implicated in patients with bipolar disorder and MDD, showing altered metabolic functioning and/or structural abnormalities (for a recent review see Price and Drevets[23]). Coupled with growing evidence of cognitive and affective processing impairments among patients with MDD and bipolar disorder,[20,24–28] we expected our review to reveal that patients with mood disorders show alterations in neuronal functioning during social cognitive processing. Specifically, we expected that individuals with MDD and bipolar disorder would show lowered activation in prefrontal areas involved in emotion regulation and higher-order cognitive processes and increased activity in subcortical and limbic regions implicated in emotion appraisal and generation, indicating a lack of inhibition of higher-order cognitive centres on limbic and emotion-related structures.

Here, the neural basis of each of these social cognitive domains is briefly reviewed and is followed by a synopsis of relevant behavioural studies of patients with mood disorders. The neuroimaging literature concerning social cognition in patients with mood disorders is then summarized. Where possible, neuroimaging findings involving patients with mood disorders are contextualized based on several key variables, including illness burden (e.g., number of affective episodes), illness state (e.g., active v. remitted), medication status, age, cognitive load and comorbidity, thought to moderate cognitive performance in patients with mood disorders.[29] Depending on data availability, results for patients with MDD and bipolar disorder are presented separately and are subsequently compared. We conclude the review by discussing future research directions and the clinical implications of alterations in the neural circuitry underlying social cognition with respect to improving treatment interventions and preventing relapse in patients with mood disorders.

On balance, patients with mood disorders experience substantial disruptions in interpersonal function,[30–34] and deficits in social cognition may underlie these difficulties. An enhanced understanding of the neural correlates of social cognition may help improve diagnostic accuracy and early intervention among patients with these disorders. This is particularly pertinent to the study of bipolar disorder, given that patients with this illness experience depression more than hypomania or mania,[35,36] which may result in the misdiagnosis of bipolar depression as MDD,[37,38] suboptimal treatment and poor outcome.[39,40] Elucidating the neural correlates of social cognition may also assist in identifying the neuroanatomical basis of vulnerability to these disorders. Improved knowledge of the underlying neural mechanisms and nature of social cognitive deficits in patients with mood disorders may also assist in clarifying the nature of social dysfunction in patients with MDD and bipolar disorder and may aid in the development of psychologic interventions aimed at improving social perception and adjustment in these patient populations.

Methods

A search of the literature using PsycINFO and PubMed (from January 1967 to the second week of May, 2011) was conducted using the following key words: "fMRI," "emotion comprehension," "affect comprehension," "emotion perception," "affect perception," "facial expression," "prosody," "theory of mind" and "mentalizing" in combination with the diagnostic terms "major depressive disorder," "major depression," "unipolar depression," "clinical depression," "bipolar disorder" and "mania." Reference lists of retrieved articles were also manually searched for relevant publications. All neuroimaging articles investigating the perception of affective stimuli (facial expressions and prosody), ToM and empathic responding in patients with a diagnosis of MDD or bipolar disorder were evaluated. Given the dearth of papers investigating the domains of ToM in patients with mood disorders, we adopted a liberal approach to the inclusion of relevant articles in these domains. Cross-sectional studies with both a patient sample and matched controls as well as longitudinal studies comprising only a patient sample were included. Only studies that involved an experimental task or survey measuring affective responding or ToM were included. Studies that recruited patients with a primary diagnosis of MDD or bipolar disorder and those that used recognized diagnostic criteria were included. Given that most studies using neuroimaging technology to examine the neural correlates of social cognitive processing in patients with mood disorders rely on functional magnetic resonance imaging (fMRI), we focused our review on this paradigm. We excluded from our evaluation studies that included only behavioural data, observational reports, case studies and studies that were not written in English.

Results

A total of 65 studies[41–105] met the appropriate criteria and were included in this review. Appendix 1 (available at cma.ca/jpn) summarizes the results of the reviewed papers.

Facial emotion processing

Neural correlates of facial emotion processing

Lesion studies of patients with neurologic insult or injury and neuroimaging studies of healthy individuals have revealed a complex neural network involved in the processing of emotional faces. For example, whereas the fusiform gyrus and superior temporal sulcus have been implicated in the perception of facial expressions, the amygdala, anterior insula, orbitofrontal cortex (OFC) and ventral striatum have been shown to be involved in recognizing emotion and generating emotional reactions in response to provocation stimuli (for a review, see Phillips and colleagues[106]). The anterior cingulate cortex and prefrontal cortical regions have also been shown to play a prominent role in the regulation of emotion (for reviews, see Ochsner and Gross[107] and Phillips and colleagues[108]). Specifically, recent theoretical models of emotion regulation implicate both top–down and emotion regulation processes in prefrontal cortical regions and the anterior cingulate cortex and bottom–up subcortical and limbic regions involved in emotion appraisal and generation.[106,109,110] The DLPFC, which is implicated in working memory and cognitive control, may be involved in the generation and maintenance of emotional reappraisal strategies or ways of transforming/reframing the meaning of an emotional event or stimuli.[111–113] The medial prefrontal cortex (mPFC) is thought to be involved in self-monitoring processes,[113,114] including evaluating internal states relative to external stimuli.[115] The dorsal anterior cingulate cortex has been implicated in conflict error and monitoring,[116] including the interference between top–down and bottom–up processes involved in emotion reappraisals and generation.[115] These models posit that prefrontal regions, such as the lateral prefrontal cortex, mPFC, OFC and dorsal anterior cingulate, modulate activity in subcortical (e.g., amygdala) and limbic regions.[106,113] The amygdala has been implicated in the unconscious and rapid detection of emotionally salient stimuli, including faces,[117–119] and a more detailed evaluation of the significance of the emotional stimulus takes place in paralimbic (e.g., thalamus, hippocampus) and cortical regions.[120,121]

Facial emotion processing in patients with major depressive disorder

Most studies of social cognition in patients with MDD have examined the perception and recognition of affective stimuli, particularly facial expressions (for a review see Leppänen[122]). Given the ubiquitous nature of facial expressions, the ability to recognize facial expressions is crucial for intact interpersonal functioning.[123] On average, studies examining facial emotion processing in acutely depressed patients have reported a generalized emotion recognition deficit[124–133] and impaired recognition of happy facial expressions relative to matched controls.[127,129,134–142] Enhanced recognition of sad facial expressions has also been consistently reported in acutely depressed patients.[73,143–148] Other studies have reported evidence of a negative bias during facial expression recognition and detection tasks,[138,140,149–156] including a tendency to identify neutral faces as sad in patients with moderate to severe depressive symptoms compared with healthy controls.[157–159] This bias is accompanied by selective attention to negatively valenced faces depicting sadness[134,147,155,160] and anger.[161] Overall, these studies point toward a processing bias involving enhanced attention to and recognition of negatively valenced faces during active states of depression that may be accompanied by a tendency to mislabel positively valenced faces as sad and to misjudge (i.e., amplify) the amount of negative emotion conveyed in faces.

Neuroimaging studies of facial emotion processing in patients with MDD

Emotion perception paradigms used in neuroimaging studies of facial emotion processing in patients with mood disorders typically consist of tasks that employ identification and discrimination formats. Identification tasks involve labelling the emotion depicted in individual facial expressions from a fixed set of choices. Although most of these tasks involve recognizing static or still pictures of facial expressions, some studies employ a morphing design that involves dynamic recognition of facial affect by morphing the expression from neutral to beyond the prototypical emotional expression (i.e., 100% emotional expression). Discrimination tasks involve presenting participants with a pair of faces and asking them to judge whether the people in the 2 pictures are expressing the same or a different emotion, or judging the intensity of individual emotional facial expressions.

Mood state

Evidence from fMRI studies suggests that patients with acute MDD differ from healthy controls in the pattern of neural responding arising from exposure to a variety of emotional facial expressions (see Phillips and colleagues[162]). Specifically, increased activation in the amygdala, ventral striatum and orbitofrontal cortices, regions key to the representation of emotion and to the processing of reward, has been reported in response to masked[41,49,71,73] and unmasked[44,47,51,55,62,70] displays of negatively valenced faces (e.g., expressions of fear, sadness, disgust) in these patients. However, numerous conflicting findings exist.[47,62,163,164] They may stem from different emotional processing paradigms and from differences in the clinical status of patients in terms of medication use, illness burden, comorbidity and depression severity. For example, Scheuerecker and colleagues[69] recruited a heterogeneous sample of patients experiencing first-episode and recurrent depression and failed to find differences from controls in patterns of neural activation in response to emotional faces; given earlier behavioural and neuroimaging findings that cognitive processing is more vulnerable to disruption in patients with recurrent mood disorders than in first-episode patients (for example, see MacQueen and colleagues,[165] Basso and Bornstein,[166] Lebowitz and colleagues,[167] Milne and colleagues[168] and vanGorp and colleagues[169]), it is possible that

this null finding stemmed from the inclusion of first-episode patients in the mood disorders group.

Actively depressed patients also show increased neural responses to positive and negative facial expressions in the subgenual portion of the anterior cingulate cortex, a region involved in the physiologic response of emotional processing.[45,46,52,63] Increased activity in the subgenual cingulate cortex suggests that individuals with MDD show stronger autonomic emotional responses than controls.[63] By contrast, reduced amygdala activation in response to positive stimuli has been demonstrated across a small number of studies.[71,99] Suslow and colleagues[71] suggest that amygdala hyperactivity to negative stimuli in patients with MDD is associated with negative biases during automatic stages of affective processing,[49] including facial affect recognition. Hyporesponsivity of the amygdala to positive stimuli on an automatic processing level is conversely thought to stem from a reduced allocation of cognitive resources for positive stimuli.[71,170] A recent report by Lee and colleagues[54] also demonstrated reduced activation in the DLPFC in response to the passive presentation of negative facial stimuli among patients with MDD. Similarly, Fales and colleagues[52] found that during an emotional distractor task, patients with MDD showed increased amygdala activity and a failure to recruit the DLPFC in response to unattended fearful faces. In contrast, controls demonstrated increased activity in the DLPFC and no activation differences in the amygdala when ignoring fearful faces. These findings are in line with theories of emotion regulation that posit that prefrontal regions, such as the DLPFC, inhibit activity in subcortical (e.g., amygdala) and cortical regions involved in emotional appraisal and emotion generation systems (for example, see Ochsner and Gross[109] and Phan and colleagues[110]).

Recent research has also begun to examine the interactions between prefrontal and subcortical regions in patients with MDD. Specifically, during negative facial processing tests (implicit and explicit) consisting of angry and sad facial expressions, the dorsal anterior cingulate and the precuneus, a region implicated in self-related mental representations, show reduced connectivity with the OFC in unmedicated patients with depression.[64] Decreased connectivity between the dorsal anterior cingulate and OFC may contribute to dysfunction in the cognitive control of emotional processing (e.g., rewarding value of stimuli) mediated by orbitofrontal regions. The precuneus has been strongly implicated in the mental representation of self and related processes, such as autobiographical recollection and first-person perspective taking; decreased connectivity with the OFC may contribute to the disturbances in self-related processes in patients with mood disorders. Finally, functional connectivity between the OFC and DLPFC was increased in patients compared with controls during negative facial processing; enhanced connectivity between the orbitofrontal region and this key cognitive region, respectively, may give rise to the negative processing bias inherent in the disorder.[64] Similarly, another study found that a chronic and recurrent course of illness was significantly associated with reduced functional connectivity between the amygdala and DLPFC while passively viewing angry and sad faces.[58] Finally, disruptions in functional coupling between the amygdala and subgenual cingulate, a region also implicated in assessing the salience of emotion and regulating of emotions, have been reported during facial processing tasks.[50,55]

In contrast, few studies have examined the neural correlates of facial affective processing in euthymic patients with MDD. Preliminary findings by Norbury and colleagues[68] demonstrate elevated DLPFC activation in response to fearful faces in euthymic patients compared with controls. Levels of amygdala activation did not differ between patients and matched controls during the presentation of fearful faces. The authors interpreted the increased level of dorsolateral prefrontal activation as a compensatory cortical control mechanism acting to limit emotional dysregulation in limbic regions, including the amygdala, in patients with remitted illness. A recent study by Victor and colleagues,[73] however, found that remitted patients with MDD showed exaggerated responses in the amygdala to masked sad faces and a lack of amygdalar response to masked happy faces compared with controls. A possible reason for the discrepant findings in amygdala activation in euthymic patients with MDD may stem from differences in method variance. Specifically, Victor and colleagues[73] used an implicit or masked emotional face paradigm, whereas Norbury and colleagues[68] used an explicit facial emotion task, which likely engaged the DLPFC to regulate amygdala activity.[110,113] The DLPFC has been shown to be activated by explicit emotional tasks relative to tasks that are more implicit in nature.[171]

Preliminary work has also examined the relation between patterns of neural activation in response to emotional facial expressions and mood state. For example, level of depression severity has been shown to correlate negatively with the extent of activation in the fusiform gyrus,[43,47] anterior cingulate cortex[48] and amygdala[71,74] in response to happy and negative faces.[62] It should be noted, however, that an equal number of studies failed to find a significant association between level of depression and neural activity in response to facial emotions.[41,49,59,67,69,72] These studies were likely not able to detect a relation between this illness variable and neuronal response because of their limited sample sizes and the inclusion of patients with varying levels of depression.

Illness burden

Few studies have examined the relation between burden of illness variables and neural activity during a facial emotion task. Suslow and colleagues[71] reported that amgydala responsiveness to masked sad and happy faces was independent of illness burden variables, such as number of episodes or duration of illness. Similarly, Dannlowski and colleagues[49] were unable to detect an association between course of illness variables (duration of illness, number of episodes, total hospital admission time, time since first inpatient treatment and time since first outpatient treatment) and amygdala activity in response to masked displays of angry, sad and happy facial expressions. However, the same study group found that amygdala–DLPFC connectivity was significantly associated with illness severity, indicating that patients with MDD with reduced connectivity between these regions had a more pervasive and severe course of illness.[58]

Medication status

Antidepressant therapy may normalize patterns of neuronal responding to affective facial stimuli. For example, a recent study by Fu and colleagues[43] examined responding to positive stimuli in patients with MDD compared with matched controls and found reduced activation in subcortical (basal ganglia), limbic (hippocampus) and extrastriate regions among acutely ill patients with MDD; this pattern was attenuated following treatment with fluoxetine. Similarly, Keedwell and colleagues[61] found that severely depressed patients showed increased visual cortex responses to sad faces and reduced neural response in these same regions to happy faces in the early stages of antidepressant treatment. Following continued antidepressant therapy and clinical improvement, these patterns were reversed. Moreover, consistent with prior findings demonstrating subgenual cingulate activity as a marker of treatment response (for example, see Mayberg and colleagues[172] and Nobler and colleagues[173]), reductions in subgenual cingulate activity were associated with reductions in depression scores.[61] Further analysis of data arising from the study by Keedwell and colleagues[61] showed that increased activity in the right visual cortex and subgenual cingulate to sad but not happy facial expressions in the first few weeks of treatment were predictive of a greater clinical recovery.[65] In contrast, enhanced responses to happy and sad stimuli in the ventrolateral prefrontal cortex were associated with a poor clinical outcome. Similarly, Victor and colleagues[73] found that an exaggerated response in the amygdala to masked sad faces and reduced amygdala activity to masked happy faces were reversed following administration of a 4-week treatment regimen of sertraline. These findings indicate that the negative bias toward sad faces improves and a positive bias toward happy faces emerges with antidepressant treatment.

Similar to the effects of antidepressant treatment on neural response to emotional facial expressions, administration of erythropoietin, a novel treatment for psychiatric disorders (for example, see Ehrenreich and colleagues[174]) that exerts neurotrophic and neurorestorative effects, and reduced neural responses in the amygdala and hippocampus to fearful compared with happy faces.[66]

A recent study has also examined the connectivity of the OFC, a key region in the emotion regulation circuit, to other brain areas in patients with MDD. Lisiecka and colleagues[75] found that during a facial emotion identification task, at baseline, an increase in functional coupling between the OFC and motor areas and internally within the right middle OFC was associated with positive response to treatment with antidepressants (mirtazapine and venlafaxine). In contrast, increased connectivity between the OFC and cerebellum was associated with lack of response to antidepressant treatment. The magnitude of response to antidepressant treatment was also positively correlated with functional coupling between the left OFC and the caudate nuclei and thalamus. This study highlights the utility of functional connectivity patterns of regions implicated in the affect regulation circuit as a marker of treatment response.

Overall, these results suggest that conventional antidepressants and novel treatments may dampen hyperactive responses to negative stimuli and enhance the salience of positive stimuli. These findings are also in accordance with the notion that antidepressants may work by remediating the negative bias in information processing found in patients with MDD.[175]

Psychological treatment status

Psychological interventions have also been found to alter patterns of neuronal response to affective stimuli among patients with MDD. Specifically, Fu and colleagues[53] found that hyperactivation in the amygdala and hippocampus in response to sad faces appeared to normalize following 16 weeks of cognitive behavioural therapy (CBT). Moreover, consistent with prior work showing a significant relation between anterior cingulate activity and clinical response to antidepressant medication (for example, see Fu and colleagues[51]), elevated dorsal anterior cingulate activity associated with cognitive control has been shown to be associated with treatment response to CBT.[53,57]

Age

Neuroimaging studies conducted in children and adolescents with MDD also show heightened activation in the amygdala[56,60,74] and OFC[74] in response to emotional facial expressions (for conflicting findings, see Thomas and colleagues[42]).

Comorbidity

The presence of comorbid disorders, including those on the anxiety spectrum,[176,177] may impact patterns of neural activation to affective facial stimuli among patients with MDD. Accordingly, a number of studies reviewed here have excluded patients with comorbid psychiatric diagnoses, including anxiety disorders.[43,50,52,53,55,59,64,74,75] Although other studies have explicitly indicated the inclusion of patients with comorbid anxiety disorders,[60,62,67,68,71] only Suslow and colleagues[71] and Lau and colleagues[60] carried out subanalyses to investigate the impact of comorbidity status, finding no significant differences. Two studies[42,56] directly compared neural activity in patients with a primary diagnosis of an anxiety disorder and patients with a primary diagnosis of MDD. Thomas and colleagues[42] found that during passive viewing of fearful versus neural faces, patients with MDD showed hypoactivation of the right amygdala, whereas hyperactivation of this region was observed in patients with heterogeneous anxiety disorders (generalized anxiety disorder and/or panic disorder). Similar results in the left amygdala were reported by Beesdo and colleagues,[56] but only for fearful compared with happy faces and only when viewed passively.

Section summary

Taken together, these findings suggest that individuals with MDD demonstrate altered neural responsiveness to both positively and negatively valenced facial stimuli, regardless of whether they are presented inside or outside of conscious awareness. These results may provide a neural mechanism for the negative bias in facial emotion processing in patients with MDD described in a previous section of this review. Specifically, this negative bias in emotion processing may reflect top–down dysfunction in brain areas, such as the DLPFC and

dorsal anterior cingulate cortex, implicated in the cognitive control of attention.[115,116] The above studies demonstrate hypoactivity and reduced levels of connectivity in these regions in patients with MDD. These findings may be interpreted as deficits in the cognitive control of emotion during the processing of emotionally salient stimuli (faces).[49,52,115,116] This negative bias may also stem from deficits in brain areas, such as the amygdala and ventromedial prefrontal cortex function (including the subgenual cingulate), implicated in bottom–up emotion processes.[106,113] Hyperactivity in the amygdala in response to negative facial stimuli has been demonstrated across numerous studies of patients with MDD, and a small number of studies indicate hypoactivity in this region in response to positive facial stimuli. Increased activity in the subgenual cingulate during baseline rest conditions has been consistently reported (for example, see Drevets and Raichle[178] and Mayberg and colleagues[179]), and an emerging body of research suggests that this region is hyperactive during the processing of emotional faces. Elevated activity and altered connectivity of the amgydala and ventromedial regions, such as the subgenual cingulate, may result in the negative processing bias inherent in the disorder.[52] Preliminary evidence suggests that dysfunction in these key emotion processing areas is reversed in the remitted or euthymic state in patients with MDD. These findings suggest that after mood symptoms remit, patients with MDD are able to recruit the DLPFC and dorsal anterior cingulate to suppress activity in the amygdala and related regions and the impact of emotional stimuli, especially negative stimuli. Moreover, preliminary evidence suggests that dysfunction in these key emotion processing regions appears to resolve with antidepressant treatment[51,73] and CBT.[57] Similar to the behavioural literature, the influence of depressive symptom severity and burden of illness variables on neuronal activity during facial emotion processing in patients with MDD remains to be determined. Finally, few studies have examined the impact of comorbidity on patterns of neural activation, with the studies that do exist showing no differences in patterns of neural activity between patients with and without disease comorbidity. Interestingly, patients with a primary diagnosis of MDD show hyperactivation in the amygdala during active facial emotion tasks and, when compared directly, patients with a primary diagnosis of an anxiety disorder also showed hyperactivation of this region; notably, anxiety samples included a heterogeneous range of illness (e.g., generalized anxiety disorder, posttraumatic stress disorder), rendering the results of these studies indeterminate.

Facial emotion processing in patients with bipolar disorder

Several studies report that patients with bipolar disorder experience difficulty decoding facial emotions on facial affect labelling tasks during periods of mania.[180–182] For example, emotion-specific impairments in the identification of sadness,[77] disgust[181] and fear[181] as well as a more generalized deficit in facial emotion recognition have been reported in actively manic patients.[24,180] Increased levels of manic symptoms have been shown to correlate significantly with impaired recognition of sad faces.[181] In a pattern similar to that observed in patients with unipolar illness, studies examining patients with bipolar disorder in a depressed phase of illness reveal a mood congruent bias in emotion perception tasks, including difficulties labelling happy faces[97,102] and a tendency to misinterpret neutral facial stimuli as sad[144,183] and happy faces as angry.[184] Individuals with bipolar depression are also more accurate than patients with MDD and controls when identifying facial expressions of disgust[185] (see Douglas and Porter[183] for conflicting findings). Finally, these patients show a reduction in sensitivity to happy facial expressions[185–187] that is amplified in the presence of more severe depressive symptoms.[186] Hence, whereas mania appears to be associated with a reduction in the ability to recognize negative facial emotions, the presence of depressive symptoms in patients with bipolar disorder appears to result in the overidentification of negative emotion and difficulty recognizing positive affect in faces.

Neuroimaging studies of facial emotion processing in patients with bipolar disorder

Functional neuroimaging studies of facial affect processing in patients with bipolar disorder have revealed mixed findings regarding neural activity in brain regions associated with cognitive and affective processing during facial emotion tasks.

Mood state

In a sample of patients with bipolar disorder with mixed illness states, amygdala activity in response to happy faces was greater in unmedicated patients but lower in medicated patients compared with controls.[80] Moreover, compared with controls, rostral anterior cingulate activation was reduced in unmedicated patients with bipolar disorder, whereas medicated patients with bipolar disorder demonstrated similar levels of rostral anterior cingulate activation.[80] Killgore and colleagues,[88] however, found that a sample of patients with bipolar disorder in varying mood states demonstrated less activation than controls within the putamen, caudate, anterior cingulate gyrus, OFC and superior temporal pole. In addition to the small sample sizes of these studies, heterogeneity within the participant sample in terms of mood state and symptom severity may partially account for these discrepant findings.

In depressed patients with bipolar disorder compared with healthy controls, heightened activation in fronto–striato–thalamic regions, including the superior frontal gyrus, ventral frontal gyrus, precentral gyrus, cingulate, putamen and thalamus, in response to happy faces has been demonstrated.[188] Depressed patients with bipolar disorder have also shown elevated activity in the amygdala[102] and attenuated responses in the OFC and DLPFC to neutral and negative (e.g., angry, fearful, sad) faces.[30] Evidence of greater left amygdala–OFC connectivity in response to sad faces and reduced bilateral connectivity between these same regions in response to happy faces has also been reported in depressed but not euthymic patients with bipolar disorder.[97]

These overall findings of elevated levels of neuronal activation in limbic and emotion-related structures and attenuation of activity in areas subserving primarily executive and cognitive processes are similar to those observed in patients with MDD during the performance of similar tasks (see previous sections). Unlike in patients with MDD, however, there is little

evidence that this pattern remits with the offset of depressive symptoms. In euthymic patients with bipolar disorder compared with healthy controls, studies have demonstrated increased hippocampal activity[82] along with enhanced amygdala activity[76] and diminished DLPFC activation when viewing fearful faces[76,82,86] (see Hassel and colleagues[86] and Robinson and colleagues[90] for conflicting findings). A preliminary study by Surguladze and colleagues[96] reported that euthymic patients with bipolar disorder also show enhanced activity in the mPFC and amygdala in response to happy facial expressions. It is plausible that the discrepant findings in subcortical activations in both actively ill and euthymic patients may stem from failure to account for comorbid disorders. For example, Hassel and colleagues[91] reported significant associations between comorbid symptoms of substance abuse and eating disorders and neural activity in the PFC and subcortical striatal (caudate nucleus, putamen) regions in response to happy and neutral faces.

A number of neuroimaging studies have examined facial affect processing in manic patients. Here, a contrasting pattern of reduced amygdala and subgenual cingulate activation in response to sad but not happy facial expressions has been reported in conjunction with a mood-congruent deficit in recognizing sad facial affect.[77] Chen and colleagues[188] also found that manic patients showed increased activity in the fusiform gyrus in response to sad faces, perhaps leading to enhanced perceptual processing of these stimuli. In that study, a neural response to sad faces was modulated by level of attentional processing. That is, whereas implicit processing of sad faces was associated with enhanced activation in the amygdala, anterior cingulate cortex, lateral temporal cortex and mPFC, explicit processing of sad faces was associated with attenuation of these same regions. Altshuler and colleagues[79] reported increased neural response in the amygdala and reduced orbitofrontal cortex response during an emotion discrimination task. Similar to findings in patients with MDD, Foland and colleagues[84] also found reduced functional connectivity between the ventrolateral prefrontal cortex and the amygdala during a facial emotional labelling task in line with reduced inhibitory frontal control over amygdala reactivity. Interestingly, reduced connectivity between the ventrolateral prefrontal cortex and amygdala was associated with increased manic symptoms. Moreover, consistent with findings in patients with MDD, patients with bipolar disorder in a variety of mood states showed reduced connectivity between the amygdala and anterior cingulate cortex in response to negatively valenced faces.[94]

Severity of depressive or manic symptoms may influence neural response to affective facial stimuli in patients with bipolar disorder, although the evidence is inconsistent. For example, patients with more severe depressive illness show significantly enhanced hippocampal activation when viewing sad faces compared to those with milder symptoms of illness.[99] Moreover, increased depressive symptom severity was associated with lower activation in the medial frontal gyrus in response to angry faces.[98] However, other studies have failed to find significant associations between levels of brain activation and mood state[92,94] or symptom severity in patients with bipolar disorder.[80,81,86,189]

Illness burden

A limited number of studies have examined the relation between burden of illness variables and neural activity during affective facial processing in patients with bipolar disorder. Recent work has demonstrated significant associations between an earlier illness onset and both amygdala hyperactivity[86] and decreased activity within the DLPFC.[76] A greater illness burden was associated with reduced functional connectivity between the amygdala and OFC in response to sad faces in a mixed sample of patients in depressed and remitted mood states.[97] Foland and colleagues[84] also found that reduced connectivity between the ventrolateral prefrontal cortex and amygdala was associated with number of previous manic episodes and illness duration in manic patients. It should be noted, however, that Blumberg and colleagues[80] did not find any significant associations between level of brain activation and variables such as illness duration or age at onset of illness. Critically, however, patients with bipolar disorder with a longer illness duration and earlier age at illness onset were found to have greater dorsal prefrontal cortex and reduced amygdala activity in response to negatively valenced faces, suggesting an ameliorating effect of a greater illness burden on neural response.[91,102]

Medication status

As in patients with MDD, administration of pharmacologic agents may alter the neural circuits underlying the perception and recognition of facial emotion in patients with bipolar disorder. Specifically, 2 recent studies report that patients with bipolar disorder treated with 12 weeks of lamotrigine monotherapy demonstrated "normalized" (increased) activations within the neural circuitry involved in facial affect processing (e.g., medial frontal cortex, precentral and anterior cingulate gyri, middle temporal gyrus) in response to angry[85] and sad faces.[87]

Age

Finally, neuroimaging studies conducted in adolescents with bipolar disorder similarly showed enhanced activations in subcortical limbic regions and hypoactivation in prefrontal regions in response to emotional faces.[30,190,191] These findings have been shown in euthymic youth with bipolar disorder (for example, see Pavuluri and colleagues,[83] Rich and colleagues[89] and Pavuluri and colleagues[93]) and heterogeneous samples[81,92,95,98] of patients in a variety of mood states. Finally, compared with controls, youth with bipolar disorder demonstrate reduced connectivity between the amygdala and neural regions that are thought to be involved in facial expression processing and emotional stimuli (posterior cingulate/precuneus, fusiform gyrus/parahippocampal gyrus).[89]

Comorbidity

Preliminary evidence indicates that comorbid symptoms, and in particular the presence of an anxiety, eating or substance abuse disorder, may alter patterns of neuronal activation during recognition of emotional faces in patients with bipolar disorder, highlighting the need for future studies to consider the presence of comorbidities in their analyses.[86,91] Specifically,

Hassel and colleagues[86] found that, in comparison to patients with bipolar disorder without comorbidities, those with a comorbid diagnosis of any of these disorders showed a trend toward increased activity in the left striatum in response to mildly happy faces during a sex discrimination task. Higher scores on the eating disorder spectrum were also associated with increased activity in the right ventral putamen during identification of intensely happy faces by patients with bipolar disorder.[91] Two emotion identification studies[89,90] explicitly included Axis I comorbidities with subanalyses indicating no differences in patterns of neural activity (see the section discussing mood state during facial emotion processing in patients with bipolar disorder) after removal of patients with comorbidities. Several studies excluded patients with comorbid conditions.[30,80,82,84,85,87,187]

Section summary

These neuroimaging findings support theories proposing abnormally increased activity in subcortical and limbic emotion processing regions (e.g., amygdala) and reduced response in prefrontal cortical emotion regulation regions in patients with bipolar disorder.[108] These dysfunctional patterns of neural activity and connectivity are observed in both manic and depressed patients with bipolar disorder (for example, see Foland and colleagues[84] and Almeida and colleagues[101]). However, in contrast to patients with MDD, evidence suggests that in patients with bipolar disorder, alterations in regions implicated in emotion appraisal, generation and regulation may not normalize with remission of mood symptoms.[76,82,96] These findings, however, were not consistently observed in euthymic patients with bipolar disorder.[86,90] Preliminary research indicates that treatment with a mood stabilizer (lamotrigine) may mitigate dysfunction in neuronal regions involved in the generation and regulation of emotion,[85,87] a similar pattern observed after depressive symptoms remit.[192] Finally, early evidence of differences in connectivity patterns between the amygdala and OFC in response to displays of facial emotion in patients with bipolar depression may be a potential biomarker that is not present in those with unipolar depression.[102] Preliminary evidence indicates that comorbid symptoms, and in particular the presence of anxiety, eating disorder and substance abuse symptoms, may contribute to observed patterns of dysfunction in neural circuits involved in mood regulation in patients with bipolar disorder, highlighting the need for future studies to consider comorbidities in their analyses.[86,91] Relatively small sample sizes and variable emotion processing paradigms employed in these studies may also have contributed to discrepant findings observed in subcortical regions, such as the amygdala, across mood states.

Studies comparing patients with unipolar and bipolar depression

A small number of neuroimaging studies comparing individuals with unipolar versus bipolar depression while performing facial affective processing tasks suggest that different pathophysiologic mechanisms may distinguish these 2 types of depression. Almeida and colleagues[101] found that recurrent MDD was associated with a top–down negative connectivity between the orbitomedial prefrontal cortex and amygdala in response to positive (happy) faces, suggesting a top–down prefrontal "inhibition" of amygdala activity in response to positive facial expressions. Moreover, in patients with MDD, the greater the medication load, the more positive (less abnormal) the effective connectivity between these 2 regions. In contrast, bipolar depression was associated with a bottom–up disconnectivity between the amygdala and orbitomedial prefrontal cortex, suggesting reduced inhibitory control over amygdala reactivity in patients with this disorder. Patients with bipolar depression have also shown enhanced activation in the amygdala in response to neutral and sad faces compared with controls, patients with remitted bipolar disorder and patients with MDD.[102] Finally, Lawrence and colleagues[99] also found enhanced levels of activity in limbic and emotion-related structures in patients with bipolar disorder compared with MDD. Specifically, these authors reported that a heterogeneous sample of euthymic and depressed patients with bipolar disorder showed greater activations in subcortical and ventral prefrontal regions in response to positive and negative facial expressions compared with patients with unipolar depression and controls. Overall, these data suggest that patients with bipolar depression may be biased toward negative mood–congruent facial expressions, whereas those with unipolar depression have an attentional bias away from positive expressions.[102]

Influence of facial emotion processing paradigms

It should be noted that studies investigating facial emotion comprehension in patients with mood disorders employ diverse methods, such as attention bias,[49,52,71,73] emotion identification,[30,49,52,55,59,62,64,66–69,71–76,79,82,84,85,87,89–91,93,97,98,101,103,133,185,193–195] sex identification[44,45,47,50,51,53,57,64,86,91,92,94,96] and passive viewing paradigms,[41,42,54,56,58,60,61,63,66,80,81,83,88,89,95,196] when utilizing fMRI to uncover the neural mechanisms underlying emotion processing. During passive viewing paradigms, patients with bipolar disorder and those with MDD demonstrate hypoactivity in the DLPFC and OFC and hyperactivity in the amygdala and anterior cingulate (subgenual and pregenual), although evidence is less consistent for subcortical regions such as the amygdala and paralimbic regions.[41,54,60,63,80,83,95,194] During sex identification tasks, again patients with bipolar disorder and those with MDD demonstrate elevated amygdala responses[47,51,92,96] and reduced connectivity between the amygdala and anterior cingulate cortex.[50,94] In contrast, preliminary evidence suggests that during sex identification paradigms, patients with MDD show increases in the subgenual anterior cingulate[45] and OFC,[70] whereas those with bipolar disorder demonstrate less activity in the DLPFC[91] and greater activity in the mPFC.[96]

Facial emotion identification paradigms have converged on several neural regions found to be consistently altered in patients with mood disorders. On average, neural activity is most commonly decreased in the DLPFC[30,59,68,76] and increased in the left amygdala,[55,74,76,79,98,99] the fusiform gyrus[82,93,98] and the inferior frontal gyrus[82,90,98] in patients with mood disorders. Interestingly, however, whereas hippocampal and parahippocampal activity is generally increased in patients with bipolar disorder,[82,87,98,99] the same regions show decreased

activity in those with MDD.[72,99] Disturbances in the connectivity between the OFC and the amygdala and cerebellum have also been apparent during identification of emotional faces in patients with MDD[75,101] and those with bipolar disorder.[97,101] Attention bias paradigms utilizing fMRI have only been carried out in MDD samples, with amygdala hyperactivity emerging as the primary finding. Taken together, these different paradigms tend to converge on a pattern of decreased activation in prefrontal cortical regions associated with emotion regulation and cognitive control (e.g., DLPFC) and increased activation in prefrontal, limbic and subcortical regions associated with affective processing.

At present, fMRI studies may not be optimized to detect potential differences in patterns of neural activation between patients with MDD and those with bipolar disorder during social cognitive tasks. Critically, to date, few studies have included separate groups with MDD and with bipolar disorder and have directly compared patterns of neural activation between these groups; most studies included relatively small samples of patients with MDD or bipolar disorder. Moreover, as neuroimaging studies are inherently under temporal constraint, a decreased number of trials may be used to shorten the scan duration, consequently decreasing the statistical power during between- and within-group comparisons.

Task complexity is another issue that may contribute to the inconsistency seen during facial emotion recognition. Some fMRI studies[69,84] appear to employ emotion recognition tasks that are not difficult or cognitively challenging (for example, see Haldane and colleagues[85] and Wilbertz and colleagues[163]). The goal of these studies was generally to elicit activation from specific brain regions of interest and not necessarily to investigate performance differences in emotion recognition and discrimination.[84] Whereas it is beneficial to increase the number of emotions examined for identification to improve ecologic validity, this type of complexity may engage supplementary neural regions (primarily related to ToM) that may be hard to disentangle from neural regions that are predominantly affected in the identification of basic emotions.[197] As is generally seen in the neuroimaging literature of emotion identification, although patients with mood disorders may perform comparably to controls on behavioural measures, the neural processing of that information is extensively altered (for example, see Frodl and colleagues[64] and Yurgelun-Todd and colleagues[76]). Another shortfall of the comparison of results within the emotion identification paradigm is the number and types of emotions presented. For example, whereas some studies present only angry and neutral faces, others only present angry and happy faces, making it difficult to yield firm conclusions regarding potential emotion-specific recognition deficits.

Affective prosody recognition in patients with mood disorders

Neural correlates of affective prosody recognition

Recognition of emotional prosody is thought to draw on multiple processing resources mediated by a complex neural network found primarily in the right superior temporal region.[198,199] Wildgruber and colleagues[199] recently proposed a neuroanatomical model implicating right-sided primary and association audition areas in the temporal lobe in the perception and extraction of auditory information,[200–202] whereas posterior regions of the right superior temporal sulcus are thought to be involved in representing the meaning of the acoustic sequences.[196,201] In contrast, evaluative aspects of affective prosody identification are believed to be mediated by the bilateral inferior frontal cortex;[200,202,203] this has been reviewed by Wildgruber and colleagues[199] and Adolphs and colleagues.[204]

Affective prosody recognition in patients with bipolar disorder

Preliminary evidence indicates that individuals with mood disorders experience difficulty in the recognition of affective prosody. In a pattern similar to the results reported for identification of facial emotion, a bias toward interpreting neutral prosodic emotions (i.e., surprise) as negative,[152,205] and difficulty identifying both positively valenced[206,207] and negatively valenced[206,207] emotional tones (for contradictory findings, see Uekermann and colleagues[208]) have been reported in homogeneous samples of acutely depressed patients. Similar findings of impaired recognition of positively[206] and of negatively valenced[206,209] tones have been reported in both actively ill and euthymic[209] patients with bipolar disorder (for contradictory findings, see Harmer[175]).

Neuroimaging studies of affective prosody recognition in patients with bipolar disorder

Despite these preliminary behavioural findings, the neural correlates of altered affective prosody recognition in patients with mood disorders remain relatively unexplored. One preliminary study by Mitchell and colleagues[78] compared the neural responses of controls and patients with schizophrenia and bipolar disorder to recorded scenarios presented in happy, sad and neutral intonations. Patients were scanned while passively listening to affective prosody stimuli and while actively attending to the emotional intonation of each phrase. During the passive listening task, compared with controls, the bipolar group demonstrated less activation in the amygdala, uncus, bilateral superior temporal gyrus and right inferior frontal gyrus in response to pure emotional prosody and greater activation of the left superior temporal gyrus in response to unfiltered emotional prosody. The lack of activation found in the right-sided prefrontal and temporal areas implicated in affective prosody recognition (see the section discussing neural correlates of affective processing recognition) suggests a reduced neural capacity to process this type of emotional stimuli.[78]

Mood state, illness burden, medication status, age

The influence of mood state, illness burden, medication status and age on neural response during affective prosodic processing remains to be investigated.

Theory of mind in patients with mood disorders

Neural correlates of ToM

Theory of mind refers to the ability to infer the mental states

of other individuals, including their beliefs, desires and intentions, to explain or predict human behaviour.[210] Recent theoretical models propose that ToM draws on both cognitive (e.g., understanding another's perspective) and affective (e.g., emotional response to feeling states of others) processing resources.[211,212]

Neuroimaging and behavioural studies of ToM implicate a core network of neural regions that serve diverse functions, and include cognitive (e.g., DLPFC[19,213,214]), affective (e.g., mPFC,[215–219] anterior paracingulate cortex[220,221]) and memory systems (e.g., posterior cingulate, temporal poles;[220] for a review, see McKinnon and colleagues[222]). Moreover, neuroimaging evidence also implicates the posterior superior temporal sulcus, which is involved in biological motion perception,[223,224] including socially relevant directional cues such as the eye gaze of others,[225,226] and the adjacent temporoparietal junction, which is involved in the attribution of beliefs to others,[227] as critical for ToM ability.[7,228,229]

Theory of mind ability in patients with mood disorders

Theory of mind ability in patients with mood disorders remains an underexplored area of research[230] despite recent findings that impaired ToM ability may be associated with poor clinical and functional outcome in these patients.[231] A small number of studies conducted in actively depressed patients with MDD suggest that these patients show impairments on ToM tasks that involve decoding mental states from available information, such as facial expressions, tone of voice, gestures and reasoning[232–234] (for contradictory findings, see Wolkenstein and colleagues[235]) and tasks that involve reasoning about mental states by combining contextual information and prior knowledge about an individual or situation to understand behaviour[236] (for contradictory results in patients with varying levels of symptom severity, see Wilbertz and colleagues[163]). Similar findings have been reported for patients with active and subsyndromal symptoms of bipolar disorder.[164,237] Importantly, these deficits appear to persist into the euthymic state in patients with MDD[238] and with bipolar disorder,[10,239,240] particularly for those ToM tasks that place high demands on cognitive processing resources (e.g., working memory, executive functioning; for an extended discussion of this issue, see McKinnon and colleagues[237]).

Neuroimaging findings: ToM

Mood state

To date, studies examining the neural correlates of ToM processing in patients with mood disorders have been confined to investigations of patients with bipolar disorder; 2 preliminary investigations have examined euthymic patients with bipolar disorder. Malhi and colleagues[82] instructed patients with bipolar disorder and matched controls to observe computer-animated ToM stimuli depicting complex mental states, such as bluffing, persuading, surprising and mocking. Patients performed more poorly than controls on this task. These authors also found that, compared with controls, patients with bipolar disorder demonstrated a diminished pattern of activation in the supramarginal, angular and middle temporal gyri. These regions have been shown previously to have strong functional connectivity with the temporoparietal junction and superior temporal sulcus,[241] regions thought to be crucial to ToM. Moreover, the patient sample showed a reduced neural response in the insula and bilateral inferior frontal gyri during viewing of these stimuli. These regions are strongly implicated in the mirror neuron system involved in decoding the actions and intentions of others.[242]

In a separate study, Kim and colleagues[105] examined the performance of euthymic patients with bipolar disorder on a social cognitive task that involved inferring the reason for the expressed emotion of a virtual human (avatar) based on emotional cues (facial expression of avatar and verbal description of experience). Similar to the findings of Malhi and colleagues,[104] euthymic patients with bipolar disorder showed hypoactivation in mirror neuron system regions, such as the right inferior frontal gyrus, right insula and right premotor cortex, during happy and angry emotional conditions.[105] Moreover, although the bipolar disorder group performed comparably to controls on the social cognitive task, they showed significantly delayed response times during the emotional conditions.

Medication status

Kim and colleagues[105] found that neither the number of medications nor medication dosage influenced neuronal activation during ToM performance.

Illness burden, age

The effect of illness burden and age on neuronal activation during ToM performance in patients with mood disorders remains an underexplored area of research.

Conclusion

Alterations in social cognitive functioning in patients with mood disorders are likely related to alterations in patterns of neuronal activation observed during performance of these tasks. Functional neuroimaging studies of facial emotion processing in patients with MDD and those with bipolar disorder implicate altered interactions between subcortical, limbic and ventral prefrontal regions associated with emotion identification and production, and dorsal anterior cingulate cortex and dorsolateral prefrontal regions associated with emotion regulation and higher cognitive functions, which may vary with the emotional valence (i.e., positive, negative) of affective stimuli. Taken together, these results point toward an overall lack of inhibition by higher-order cognitive structures on limbic and emotion-related structures during social cognitive processing in patients with mood disorders that is consistent across different social cognitive tasks, including recognition of emotion in faces and prosody, as well as ToM. Critically, our review of the primary body of literature in this area concerning facial emotion processing suggests that whereas this pattern is likely to return to levels of activation seen in healthy controls following symptom remission in patients with MDD, patients with bipolar disorder do not show this normalization of function despite recovery (for exceptions

following treatment with a mood stabilizer, see Hassel and colleagues[86] and Robinson and colleagues[90]). Interestingly, consistent with the results of mood provocation studies (for a review, see Ressler and Mayberg[243]), very preliminary evidence indicates that psychotropic medications and CBT may exert different effects on the neural networks involved in affective recognition. Specifically, whereas treatment with psychotropic medication appears to attenuate levels of activation in prefrontal and subcortical regions involved in affective processing, CBT appears to increase levels of neural activation in regions associated with emotion regulation and higher-order cognitive processing. It will be critical for future studies to examine the effect of different medication classes and psychologic treatments on social cognitive function in patients with mood disorders.

A number of other key methodologic and demographic variables may further moderate patterns of neuronal activation during social cognitive processing in patients with mood disorders. Specifically, patients with a lower burden of illness (i.e., fewer disease episodes or shorter duration of illness) may be less likely to show alteration in the circuitry underlying social cognitive processing in the early stages of illness. Findings concerning the impact of symptom severity among actively ill patients have been less consistent and, on average, have failed to reveal a relation between severity of active illness and patterns of neural activation; these findings may be challenged with the inclusion of larger samples of patients with groups ranging in symptom severity. Finally, the inclusion of heterogeneous samples of patients with comorbid diagnoses, particularly anxiety disorders, may limit the interpretability of findings. Future studies may seek to directly compare patients with mood disorders and a single anxiety disorder, such as PTSD, which is well known to impact the neural circuitry involved in cognitive and affective processing. Finally, social cognitive tasks that place high demands on cognitive processing resources (e.g., executive functioning, working memory) may engage higher-order cognitive regions to a greater extent than those social cognitive tasks having lower-order processing demands; these tasks may prove particularly challenging to patients with a more severe burden of illness and elevated level of symptom severity.

A nascent literature suggests that youth with MDD and with bipolar disorder show impaired performance on tests of facial emotion processing, a finding underscored by studies demonstrating early alterations in the neuronal circuitry underlying social cognitive processing in these samples. Social reasoning abilities, such as emotion comprehension, ToM, and empathy, undergo an extended development from early childhood to adolescence.[7,244,245] Adolescence, a period of time characterized by marked changes in social relationships with peers and family,[246,247] is also associated with increased vulnerability to depression and bipolar disorder.[248–250] It is possible that any alterations in social cognitive processes and their neuronal underpinnings during this period of development may contribute to the early onset of mood disorders. Alternatively, the development of psychiatric morbidity during adolescence could alter or delay the development of social cognitive abilities and the development of neuronal circuits mediating these processes. A better understanding of social cognition in patients with mood disorders and of factors that may influence social cognitive functioning could improve early intervention efforts aimed at reducing the peak morbidity and mortality observed in youth.

The study of social cognitive processing in patients with mood disorders is still in an early stage of discovery, where many outstanding questions remain concerning: for example, the influence of medications, course of illness variables and cognitive status on task performance and patterns of neuronal activation. Given the heterogeneous profile of these disorders in terms of symptom severity, chronicity, recurrence, comorbidities and treatment status, it will be important for future studies to incorporate larger sample sizes to take into account the influence of these variables on social cognitive processing. In particular, small sample sizes in fMRI paradigms may have constrained the ability to detect performance differences among groups (for example, see Canli and colleagues,[44] Chen and colleagues,[48] Schaefer and colleagues,[100] Gotlib and colleagues,[134] Gilboa-Schechtman and colleagues[156] and Bediou and colleagues[251]). Longitudinal studies, for example, will be necessary to determine whether social cognitive deficits are trait markers of vulnerability for patients with mood disorders. Investigations recruiting individuals at risk for mood disorders will also address this issue. Future studies may also determine whether known alterations in neuronal structure (e.g., reduced hippocampal volume) in patients with MDD and with bipolar disorder are associated with altered patterns of social cognitive performance across multiple social cognitive domains, including emotion recognition, ToM, empathy and moral reasoning. An enhanced understanding of social cognition in patients with mood disorders may contribute to new advances in the treatment of these illnesses.

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