Neurobiology of Emotion Perception II: Implications for Major Psychiatric Disorders

Mary L. Phillips, Wayne C. Drevets, Scott L. Rauch, and Richard Lane

To date, there has been little investigation of the neurobiological basis of emotion processing abnormalities in psychiatric populations. We have previously discussed two neural systems: 1) a ventral system, including the amygdala, insula, ventral striatum, ventral anterior cingulate gyrus, and prefrontal cortex, for identification of the emotional significance of a stimulus, production of affective states, and automatic regulation of emotional responses; and 2) a dorsal system, including the hippocampus, dorsal anterior cingulate gyrus, and prefrontal cortex, for the effortful regulation of affective states and subsequent behavior. In this critical review, we have examined evidence from studies employing a variety of techniques for distinct patterns of structural and functional abnormalities in these neural systems in schizophrenia, bipolar disorder, and major depressive disorder. In each psychiatric disorder, the pattern of abnormalities may be associated with specific symptoms, including emotional flattening, anhedonia, and persecutory delusions in schizophrenia, prominent mood swings, emotional lability, and distractibility in bipolar disorder during depression and mania, and with depressed mood and anhedonia in major depressive disorder. We suggest that distinct patterns of structural and functional abnormalities in neural systems important for emotion processing are associated with specific symptoms of schizophrenia and bipolar and major depressive disorder.

Key Words: Emotion, neuroanatomy, schizophrenia, bipolar disorder, depression

Introduction

Until recently, there has been little investigation of the neurobiological basis of the abnormalities in emotion processing present in different psychiatric populations. Furthermore, there has been little attempt to compare the severity and nature of these abnormalities across different psychiatric disorders. In a previous review (Phillips et al 2003), we examined the findings from recent animal, human lesion, and functional neuroimaging studies to identify the neural bases of the different neuropsychological processes important to the understanding of normal human emotional behavior. Findings suggest that these processes may be dependent upon the functioning of two neural systems: a ventral system important for the identification of the emotional significance of a stimulus, the production of affective states; and a dorsal system important for executive function, including selective attention, planning, and effortful regulation of affective states (Figure 1). Abnormalities in emotion perception may be associated with abnormal triggering of emotional responses that lead to clinical phenomena unrelated to exteroceptive perception (e.g., depressed or manic mood) that dominate the clinical picture. In this critical review, we have examined the evidence from studies employing a variety of techniques for the presence of specific abnormalities in these systems in major psychiatric illnesses, including schizophrenia, bipolar disorder, and major depressive disorder.

Schizophrenia

Evidence for Impaired Cognitive and Emotion Processing in Schizophrenia

Bleuler (1950) defined schizophrenia as essentially a splitting of thoughts (cognition) from feelings (emotion), and a “flattening of affect” and anhedonia have been recognized as core features of the disorder since its first description. Furthermore, schizophrenic patients often appear to misinterpret social cues and exhibit poor social skills, with symptoms such as persecutory delusions often emerging as misinterpretations of social interactions and events, frequently revolving around a person’s relationship to others and role in society rather than neutral or impersonal themes (Young and Bentall 1995).

One of the most commonly reported neuropsychological impairments in patients with schizophrenia is impaired
executive function, including deficits in performance on tasks of selective attention and working memory (Goldman-Rakic 1994). There is accumulating evidence to indicate that specific abnormalities in emotion identification and emotional behavior are also associated with the poor social function observed in patients with schizophrenia. Impaired recognition of facial (Edwards et al 2001; Feinberg et al 1986; Whittaker et al 2001) and prosodic (Edwards et al 2001) emotion, dysfunctional emotional experience (Flack et al 1998), and a positive correlation between emotion recognition and negative and positive symptomatology (Kohler et al 2000) have been demonstrated in these patients. In one study, however, no impairment in facial expression identification was reported (Flack et al 1997). Other studies have demonstrated an association between emotion identification and more generalized task performance deficits (Kerr and Neale 1993) and between emotion identification deficits and chronicity of illness (Mueser et al 1997).

Other findings have suggested a greater differential impairment in negative affect recognition (Bell et al 1997), the superior ability of paranoid compared with nonparanoid patients in negative affect identification (Kline et al 1992), and a positive association between the severity of psychotic symptoms and the ability to recognize unpleasant odors (Crespo-Facorro et al 2001). Furthermore, when examined case by case, although no universal emotional identification deficits were demonstrated in schizophrenic patients (Evangeli and Broks 2000), emotions thought to rely on intact amygdala function (particularly fear) were most consistently affected. Additionally, schizophrenic patients with persecutory delusions were reported as demonstrating specific abnormalities in their viewing strategies for social scenes depicting ambiguous rather than overtly threatening information (Phillips et al 2000). It is therefore possible that schizophrenic patients identify stimuli that are ambiguous in their emotional content as more emotive and threatening than stimuli that depict overt fear or threat.

A strong association has been reported in schizophrenia between social outcome and the ability to accurately recognize emotions displayed by others (Green et al 2000). Impairments in the ability to monitor the source of willed intentions, so that self- and nonself-originated intentions become indistinguishable, and deficient understanding of the behavior and intentions of others (theory of mind;
Abnormal neural circuitry in schizophrenia, involving dysfunctional prefrontal–thalamic and temporolimbic or cerebellar connections, has been emphasized by previous authors (Andreasen et al 1998; Weinberger 1997). A disruption in connectivity between nodes in prefrontal cortex, the thalamus, and the cerebellum has been associated with “cognitive dysmetria,” a difficulty in prioritizing, processing, coordinating, and responding to information, which may account for many of the diverse symptoms of schizophrenia (Andreasen et al 1998).

Many studies have reported in schizophrenic patients structural and functional abnormalities in dorsolateral prefrontal cortex and dorsal anterior cingulate gyrus, regions important for selective attention and planning and implicated in the previous review (Phillips et al 2003) in the effortful regulation of affective states and emotional behavior. Neupathologic findings indicate reduced cortical neuronal size and reduced glial cell density in frontal cortex (Benes et al 1991; Rajkowska et al 1998). Although there are inconsistent findings regarding the presence of volume reductions within the prefrontal (Goldman-Rakic and Selemon 1997; Lawrie and Abukmeil 1998; Pearlson and Marsh 1999; Wright et al 2000) and, more specifically, dorsolateral prefrontal cortex in patients with schizophrenia (Zaffante et al 2001), several studies have demonstrated reduced blood flow and reduced activation of dorsal prefrontal cortex and dorsal anterior cingulate gyrus in these patients during the performance of tasks of executive function (Andreasen et al 1997; Carter et al 1998; Goldman-Rakic and Selemon 1997; Hazlett et al 2000; Haznedar et al 1997).

These neuropsychological and structural and functional neuroanatomic abnormalities within dorsal prefrontal cortical regions have been associated in particular with psychomotor poverty syndrome and negative symptoms (Heckers et al 1999; Liddle and Morris 1991). Interestingly, the reduced activation within the dorsal anterior cingulate gyrus observed during performance of a paced verbal fluency task in unmedicated schizophrenic patients has been demonstrated to be reversed after challenge with apomorphine, a dopamine agonist (Fletcher et al 1996). This finding suggests that the pattern of hypofrontal activity observed in schizophrenic patients during performance of executive tasks may be a result of dysfunctional dopaminergic activity, although this matter requires further clarification.

With regard to medial temporal lobe structures, including the amygdala and hippocampus, there have been several reports of abnormal neuronal cell integrity (Falk and Bogerts 1986; Nasrallah et al 1994) and volume reductions (Altshuler et al 2000; Heckers 2001; Lawrie and Abukmeil 1998; Nelson et al 1998; Shenton et al 1992; Wright et al 2000) in these regions, an association between amygdalar lesions and psychotic symptoms (Fudge et al 1998), and an inverse correlation between left amygdalar volumes and thought disorder and between left anterior and posterior hippocampal volumes and positive and negative symptom scores, respectively (Rajarethinam et al 2002). Although there have been inconsistent findings of no differences in amygdalar (e.g., Altshuler et al 2000; Chance et al 2002) or hippocampal (Laasko et al 2001) volumes between patients and control subjects, volumetric abnormalities in these regions have been demonstrated in first-degree relatives (Seidman et al 1999). Although there have been inconsistent findings regarding thalamic size in patients with schizophrenia (Andreasen et al 1990; Gur et al 1998), in a recent meta-analysis, a significant, small-to-moderate effect size was demonstrated for thalamic size reduction in these patients compared with nonpsychiatric and nonneurologic control subjects (Konick and Friedman 2001). Other studies have reported decreased insular size in schizophrenic patients (Crespo-Facorro et al 2000; Wright et al 2000). The relative contribution of medication to these structural neural abnormalities in schizophrenic patients remains to be clarified.

Hippocampal dysfunction has been reported in schizophrenic patients, with increased activity at rest (e.g., Medoff et al 2001) but decreased hippocampal activity during memory task performance (e.g., Benes and Berretta 2000; Heckers and Konrad 2002). There have been few studies examining neural responses to emotional stimuli in these patients, however. The delusions and hallucinations of reality distortion syndrome have been associated with a specific pattern of abnormal cerebral flow involving overactivity of the left medial temporal lobe (Liddle et al...
1992). Studies have demonstrated, however, that schizotypic patients fail to activate the amygdala in response to fearful facial expressions (Phillips et al 1999), aversive scenes (Taylor et al 2002), and during sad mood induction (Schneider et al 1998). Schizophrenic patients also show decreased amygdalar activation during facial emotion discrimination (Gur et al 2002), although they may show amygdalar activation in response to happy faces (Kosaka et al 2002).

Additionally, regional cerebral blood flow to the anterior insula, nucleus accumbens, and parahippocampal gyrus failed to increase in response to unpleasant odors in a group of schizophrenic patients, despite their subjective experience of these stimuli as unpleasant (Crespo-Facorro et al 2001). In schizophrenic patients with prominent persecutory delusions, however, amygdalar activation has been reported in response to ambiguous emotive stimuli comprising fearful faces and neutral sounds, but not to overtly fearful stimuli, comprising fearful faces and fearful sounds (Parker et al, unpublished data).

These findings suggest an impaired response of the amygdala, anterior insula, and ventral striatum, regions important for the identification of the emotional significance of a stimulus, to overt displays of emotions, and particularly fear, in schizophrenic patients. Findings also suggest an enhanced amygdalar response to ambiguous stimuli, however. One possibility is that there is a lowering of the threshold at which these regions respond to ambiguous stimuli but an attenuation of their responses to overt displays of emotion, although this requires further study.

Is There an Abnormal Functional Neuroanatomy of Emotion Processing in Schizophrenia?

Findings indicate that the misinterpretation of others’ intentions and positive symptoms, such as persecutory delusions, emotional flattening or anhedonia, and the poor social functioning evident in patients with schizophrenia, may be related to impaired recognition of emotion. Additionally, there may be a tendency for ambiguous stimuli to be misinterpreted as threatening, particularly in patients with prominent persecutory delusions. Studies employing neuroimaging techniques have demonstrated in schizophrenic patients structural and functional abnormalities within ventral and dorsal neural systems important for emotion processing, although inconsistent findings have been noted.

How are these emotion processing and structural and functional neurobiological abnormalities associated with symptoms in schizophrenic patients? Structural and functional abnormalities in regions important for the appraisal and identification of positive and negative emotional stimuli and production of affective states, including the amygdala, anterior insula, and ventral striatum, may result in a restriction of the range of positive and negative emotions identifiable. They may also be associated with a misinterpretation as threatening of nontargeting and ambiguous stimuli and with a decreased range of subsequent affective states and behaviors. Specific negative symptoms, including emotional flattening and anhedonia, positive symptoms, including persecutory delusions, and impaired social function could arise from these abnormalities in emotion processing. Structural and functional abnormalities in the hippocampus and dorsal prefrontal cortical regions, resulting in impairments in reasoning, contextual processing, and effortful regulation of affective states, may then perpetuate these abnormalities and symptoms (Figure 2).

Bipolar Disorder

Evidence for Impaired Cognitive and Emotion Processing in Bipolar Disorder

Many of the symptoms experienced by patients with bipolar disorder, including irritability, distractibility, and emotional lability, would appear to be associated with abnormalities in emotion processing, including the experience of emotions of inappropriately high intensity in relation to the context in which they occur, and an inability to regulate mood. Impaired performance on cognitive tasks, including those of selective attention and working memory, has been demonstrated in manic (Bulbena and Berrios 1993; Bearden et al 2001) and depressed bipolar patients (Borkowska and Rybakowski 2001) and also within remitted patients (Wilder-Willis et al 2001). Other studies have reported relatively spared (Clark et al 2002; Paradiso et al 1997; van Gorp et al 1998) or little generalized impairment (Sapin et al 1987) in remitted patients on these tasks.

Studies have reported in bipolar patients impaired recognition of happy and sad facial expressions (Rubinow and Post 1992), increased biases toward the identification of stimuli as emotional rather than neutral, and particularly negative, in depressed bipolar patients (Gur et al 1992; Lyon et al 1999; Murphy et al 1999), and in manic patients, increased negative and positive biases (Lyon et al 1999; Murphy et al 1999). In euthymic bipolar patients, enhanced disgust (Harmer et al 2002), and impaired fearful facial expression identification (Yurgelun-Todd et al 2000) have been demonstrated. Other studies have indicated that the performance of schizophrenic patients on these tasks is more impaired than that of bipolar patients (Addington and Addington 1998). Despite these findings, there has been little examination of performance on these tasks at different phases of illness in bipolar
disorder. It has therefore been difficult to determine whether the cognitive and emotional processing abnormalities demonstrated by bipolar patients represent state or trait effects.

**Evidence for Structural and Functional Neuroanatomic Abnormalities in Regions Important for Emotion Processing in Patients with Bipolar Disorder**

Findings from neuropathologic studies have indicated decreased glial cell number and density and reduced neuronal cell density in prefrontal cortex (Rajkowska et al 2001), reduced glial cell number and density in the subgenual anterior cingulate gyrus (Ongur et al 1998; Rajkowska 2002), and entorhinal and hippocampal changes, including a reduction and dysgenesis of various neuronal cell lines (Benes et al 1998) in bipolar disorder. Studies employing structural neuroimaging techniques have demonstrated reductions in prefrontal and subgenual cingulate cortical volumes (Drevets et al 1997; Hirayasu et al 1999; Lopez-Larson et al 2002), reductions asymmetry, and increases in right and left temporal lobe volumes (Altshuler et al 2000; Harvey et al 1994), and, predominantly, increases in amygdalar volumes (Altshuler et al 1998; Strakowski et al 1999). There have been additional reports of increased caudate volume (Aylward et al 1994) but inconsistent findings regarding thalamic volumes (Caetano et al 2001; Dasari et al 1999; Strakowski et al 1999). These studies have been unable to distinguish between abnormalities caused by and/or associated with the depressive, euthymic, and manic phases of the disorder.

Although long-term use of lithium has been associated with increase in volume of the subgenual cingulate gyrus (Harrison 2002; Manji et al 2000), the effect of medication on the development of these structural neural abnormalities remains unclear.

In depressed bipolar patients, compared with healthy volunteers, executive task performance and at-rest studies have demonstrated reduced metabolism in dorsolateral and dorsomedial prefrontal cortical regions (Baxter et al 1989; Ketter et al 2001) but increased metabolism within the right amygdala and thalamus (Ketter et al 2001). Reduced prefrontal and caudate metabolism to aversive stimulation (Buchsbaum et al 1986) and inconsistent findings of decreased (Drevets et al 1997) but also increased (Kruger et al, unpublished data) blood flow in rostral/ventral and subgenual anterior cingulate gyrus have been demonstrated during rest and sad mood induction, respectively.

In manic patients compared with healthy volunteers, studies have demonstrated decreases in prefrontal (O’Connell et al 1995) and ventromedial prefrontal (orbitofrontal) cortical activity (Blumberg et al 1999) and increases in dorsal anterior cingulate gyril (Blumberg et al 2000; Goodwin et al 1997; Rubinsztein et al 2001) and ventral striatal (Blumberg et al 2000; O’Connell et al 1995) activity during performance of executive tasks, gambling, and at rest, with dorsal anterior cingulate gyril activity correlating positively with mania ratings (Goodwin et al 1997; Rubinsztein et al 2001) but also increasing more during easy versus difficult decision making (Rubinsztein et al 2001). The latter suggests that dorsal anterior cingulate gyril activation in manic patients is negatively correlated with task difficulty, although this requires clarification. Overall, this pattern of results may reflect a tendency in patients who are able to perform these tasks successfully to attempt to regulate in an effortful manner inappropriate affective states and behaviors resulting from increased sensitivity to emotionally salient environmental information. Future studies examining neural responses both to emotional stimuli and during cognitive task performance in a single group of manic patients may help to clarify the neural basis of the impairment in the regulation of emotional behavior and mood, and the relationship between this and cognitive task performance in these patients.

There have been conflicting findings regarding basotemporal regions, including the amygdala, in manic patients at rest (Gyulai et al 1997; O’Connell et al 1995). No study has examined neural responses to emotional stimuli in these patients. Neuroleptic medication levels have been positively correlated with mean regional cerebral blood flow at rest (Silfverskiold and Risberg 1989) and prefrontal cortical activation during decision-making in manic patients (Rubinsztein et al 2001), although the effect of medication on cerebral activity in these patients requires further study.

In the few studies examining neural correlates of task performance in euthymic patients, findings indicate fewer functional neuroanatomic abnormalities compared with symptomatic patients during executive task performance (Baxter et al 1989; Blumberg et al 1999, 2000). Additionally, increased amygdalar and reduced prefrontal cortical activation has been reported to facial expressions of fear (Yurgelun-Todd et al 2000).

Differences in functional neuroimaging techniques, medication status, and in the type of cognitive task performed by patients during scanning procedures may have contributed to the discrepancies in some of the findings from these studies. The results indicate, however, that structural and functional abnormalities in prefrontal cortex, the subgenual anterior cingulate gyrus, the amygdala, and ventral striatum are present in patients with bipolar disorder, and functional abnormalities exist in these structures in manic and depressed phases of illness.
Is There an Abnormal Functional Neuroanatomy of Emotion Processing in Bipolar Disorder?

The evidence to date indicates that although bipolar patients demonstrate abnormalities in executive function, they are less impaired than schizophrenic patients in the identification of emotional stimuli. In bipolar patients, there are reports of structural abnormalities in neural regions important for emotion processing; within the amygdala, important for the identification of the emotional significance of a stimulus; within the subgenual region of the anterior cingulate gyrus and orbitofrontal cortex, important for the production of affective states; and within dorsolateral prefrontal cortical regions, important for the performance of non-emotional, cognitive tasks and implicated in the effortful regulation of affective states and emotional behavior.

How are these emotion processing and structural and functional neurobiological abnormalities associated with symptoms in bipolar patients? It may be speculated that the findings in bipolar patients of enlarged rather than decreased amygdalar volumes and enhanced rather than reduced activity within the amygdala, subgenual cingulate gyrus, and ventral striatum, together with reduced prefrontal cortical volumes and metabolism, indicate an oversensitive but dysfunctional neural system for identification of emotional significance and production of affective states, and an impaired system for the effortful regulation of the subsequent emotional behavior. Specific symptoms of both the depressed and manic phases of illness in bipolar disorder, including prominent mood swings, emotional lability, and distractibility, may then be associated with these abnormalities in emotion processing (Figure 3). To date, however, no information is available regarding the functional neuroanatomy of the switch process to and from euthymia or between mania and depression.

Major Depressive Disorder

Evidence for Impaired Cognitive and Emotion Processing in Major Depressive Disorder

Studies have reported impaired executive function in patients with major depressive disorder (Elliott 1998; Murphy et al 2001), with positive correlations with depression severity (Smith 1994) and illness duration (Borkowska and Rybakowski 2001), and studies have suggested either no difference (Goldberg et al 1993; Sweeney et al 2000) or fewer impairments in these compared with depressed bipolar patients (Borkowska and Rybakowski 2001; Wolfe et al 1987). Studies have also demonstrated a persistence of impairments in euthymic patients with major depressive disorder (Austin et al 2001) and more severe impairment in these than in euthymic bipolar patients (Paradiso et al 1997).

Other studies have reported in patients with major depressive disorder generalized and specific impairments in the identification of emotional stimuli (Rubinow and Post 1992), negative emotional biases (Bradley et al 1996; Murphy et al 1999; Williams et al 1996), and negative or reduced positive attentional biases during facial expression identification (David and Cutting 1990; Gur et al 1992; Surguladze et al, in press).

Evidence for Structural and Functional Neuroanatomic Abnormalities in Regions Important for Emotion Processing in Patients with Major Depressive Disorder

Similar neuropathologic abnormalities have been demonstrated in patients with major depressive disorder and those with bipolar disorder. Findings from postmortem studies have indicated reduced density and number of glial cells in the amygdala (Bowley et al 2002), the subgenual anterior cingulate gyrus and orbitofrontal cortex (Cotter et al 2001; Drevets et al 1998; Ongur et al 1998), and the dorsolateral prefrontal cortex (Rajkowska et al 1999, 2001), and reduced neuronal cell density in the ventrolateral and dorsolateral prefrontal cortex (Rajkowska et al 1999, 2001), in patients with major depression. Neuropathologic abnormalities have also been reported in these patients in the entorhinal cortex (Bernstein et al 1998).

Studies employing structural neuroimaging methods have demonstrated in patients with major depressive disorder volume reductions in the prefrontal cortex (Coffey et al 1993; Goodwin et al 1997), including the orbitofrontal cortex (Bremner et al 2002), and the subgenual region of the anterior cingulate gyrus (Botteron et al 2002; Drevets et al 1997), as well as the hippocampus (Bremner et al 2000; Sheline et al 1999), the putamen (Husain et al 1991), the caudate nucleus (Krishnan et al 1992), and the amygdala (Sheline et al 1998). Discrepant findings of no significant volume reductions in the hippocampus and amygdala (Ashtari et al 1999; Pantel et al 1997) and striatal structures (Lenze and Sheline 1999) may be due to differences in medication status of patients, acquisition paradigms, and image resolution (Sheline 2000).

Studies employing functional neuroimaging techniques have consistently demonstrated in patients during a major depressive episode reductions in metabolism and blood flow within dorsomedial and dorsolateral prefrontal cortices (Baxter et al 1989; Bench et al 1993; Buchsbaum et al 1997; Soares and Mann 1997) but increased metabolism and blood flow within the ventrolateral prefrontal cortex (Drevets et al 1992). Reduced ventromedial prefrontal
cortical activity to feedback on planning and guessing tasks (Elliot et al 1998) but no functional impairment in this region during gambling (Rubinsztein et al 2001) have also been reported. Increased activity within rostral anterior cingulate gyrus and orbitofrontal cortical activity to negative emotional stimuli during an affective go-no-go task (Elliot et al 2002), and decreased activity within these regions (Buchsbaum et al 1997; Drevets et al 1997) has been demonstrated. Subsequent reports, however, have demonstrated that if the reduction in subgenual cingulate gyral volumes in patients with major depressive disorder is corrected, then the effect is a relative increase rather than decrease in activity within this region (Drevets 1999, 2000).

Increased blood flow within the amygdala (Drevets et al 1992), thalamus (Drevets et al 1992), and ventral limbic regions, including the anterior insula and ventral striatum (Mayberg et al 1999), and a positive correlation between amygdalar metabolism and the severity of depressed mood (Abercrombie et al 1998; Drevets et al 1992) have been reported in patients with major depressive disorder. Additionally in these patients, studies have reported to masked presentation of fearful faces increased activation within the left amygdala, which then normalizes after treatment with antidepressant medication (Sheline et al 2001), and decreased attenuation of the amygdalar response to negative words (Siegle et al 2002). Interestingly, there are compatible findings in healthy volunteers during the induction of sad mood of increased regional cerebral blood flow within the insula and subgenual anterior cingulate gyrus, and decreased regional cerebral blood flow within the dorsomedial prefrontal cortex (Mayberg et al 1999).

Recovery from a major depressive episode after successful treatment has been associated predominantly with increased metabolism and blood flow within dorsomedial and dorsolateral prefrontal cortices (Baxter et al 1989; Brody et al 1999; Buchsbaum et al 1997; Kennedy et al 2001; Mayberg et al 1999, 2000) and the dorsal anterior cingulate gyrus (Kennedy et al 2001). Studies examining the effect of pharmacologic and interpersonal therapies on prefrontal activity in patients with major depressive disorder have either failed to demonstrate increased prefrontal blood flow (Martin et al 2001) or have reported decreased prefrontal metabolism (Brody et al 2001) after these treatments.

Other changes reported after treatment include reduced metabolism in the ventral/subgenual cingulate gyrus (Drevets et al 2002; Mayberg et al 1999, 2000) and in other regions important for the generation of emotional states, including the thalamus, ventral striatum, and insula (Mayberg et al 1999, 2000; Nobler et al 1994; Smith et al 1999). Within the hippocampus, increased metabolism has been associated with 1-week treatment with fluoxetine, whereas decreased metabolism has been associated with a response to 6 weeks of treatment with this medication (Mayberg et al 2000).

There are discrepant findings regarding the role of the pregenual/rostral anterior cingulate gyrus in major depression. Although there are reports of increased activity in this region during depressive episodes (Drevets 1999), metabolism has been demonstrated to be abnormally decreased in this region in depressed patients who had poor responses to treatment (Mayberg et al 1997). Furthermore, although a response to medication at 6 weeks of treatment with selective serotonin reuptake inhibitor medication is associated with decreased regional cerebral blood flow in the subgenual anterior cingulate gyrus (Mayberg et al 1999, 2000), this is also associated with increased regional cerebral blood flow in the pregenual anterior cingulate gyrus (rostral region of Brodmann Area 24; Mayberg et al 1999, 2000). Decreased regional cerebral blood flow within this region has also been demonstrated in healthy volunteers during the induction of sad mood (Mayberg et al 1999).

There are also inconsistent findings regarding changes in activity within the ventrolateral prefrontal cortex on recovery from a major depressive episode (Brody et al 1999, 2001; Drevets et al 1992; Nobler et al 1994). It has been suggested that whereas pharmacologic interventions may have a direct effect in reducing activity within regions important for the generation of emotional states, including the limbic structures described above, resulting in a “relaxation” of activity within the ventrolateral prefrontal cortex, nonpharmacologic interventions may serve to increase activity within the ventrolateral prefrontal cortex to enhance the role of this structure in the regulation of emotional behavior (Drevets 2000).

Despite some of the inconsistencies in these findings, taken together they suggest a reciprocal functional relationship between a ventral neural system, implicated in the production of both normal and abnormal affective states, and a dorsal neural system, implicated in the performance of cognitive tasks and the effortful regulation of affective states (Mayberg et al 1999). The specific nature of the roles of the pregenual anterior cingulate gyrus and ventrolateral prefrontal cortex in the induction of sad mood, as well as in the generation of and recovery from depression, requires further clarification.

Conclusion: Is There an Abnormal Functional Neuroanatomy Underlying Major Depressive Disorder?

Findings indicate impaired executive and emotional processing in patients with major depression. These impairments appear to be less severe than those observed in
bipolar patients and may involve a bias toward the identification of emotional information as negative or sad. Studies have demonstrated structural abnormalities, and predominantly volume reductions, within many of the regions implicated in emotion processing: within the amygdala and ventral striatum, important for the identification of the emotional significance of stimuli; within the subgenual cingulate gyrus, important for the production of affective states and behavior; and within prefrontal cortical regions and hippocampus, implicated in the effortful regulation of this behavior. Studies have also demonstrated in patients during a major depressive episode increased activity within regions important for the identification of emotional stimuli and generation of emotional behavior, including the subgenual cingulate gyrus, ventrolateral prefrontal cortex, the amygdala, anterior insula, ventral striatum, and thalamus, and decreased activity within regions implicated in the effortful regulation of emotional behavior, including dorsomedial and dorsolateral prefrontal cortices. This pattern of activity reverses after recovery from a depressive episode, with increased activity within dorsomedial and dorsolateral prefrontal cortices and decreased activity within the subgenual cingulate gyrus, hippocampus, thalamus, ventral striatum, and insula.

How are these structural and functional neurobiological abnormalities associated with the symptoms of patients with major depression? In these patients, volume reductions within regions such as the amygdala, important for the identification of the emotional significance of a stimulus and production of affective states, may result in a restriction of the range of emotions identifiable and experienced, as in patients with schizophrenia. In patients with major depression, however, reports suggest increased rather than decreased function within these regions during episodes of illness. The combination of these structural and functional abnormalities may therefore result in a restricted emotional range, but with a bias toward the predominant role of the amygdala in the identification of negative rather than positive emotions. Thus, rather than identify and experience a reduced range of emotions...
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*aThis pattern of activity reverses after recovery from a depressive episode, with increased activity within dorsomedial and dorsolateral prefrontal cortices, and decreases within the subgenual cingulate gyrus, hippocampus, thalamus, ventral striatum, and insula.
together with a bias toward the identification of all emotionally salient stimuli as threatening, as in patients with schizophrenia, or rather than demonstrate a lowered threshold for the identification of emotional significance and production of affective states, as in patients with bipolar disorder, patients with major depression may experience an increased tendency to identify stimuli as emotional and experience affective states, but within a predominantly negative context. This may then result in the production of depressed mood and anhedonia. The structural and functional impairments in dorsolateral and dorsomedial prefrontal cortices apparent in these patients, and associated impairments in executive function and effortful regulation of affective states and behavior, may then perpetuate the depressed mood and anhedonia (Figure 4).

A Neuroanatomic Explanation of Abnormalities in Emotion Perception in Schizophrenia and Affective Disorders

To date, few studies have aimed to examine the nature of the functional and structural neuroanatomic abnormalities associated with the presence of symptoms in psychiatric disorders. In this critical review, we have examined the evidence for the presence of specific abnormalities in ventral and dorsal neural systems implicated in emotion processing in schizophrenia, bipolar disorder, and major depressive disorder. We have suggested that different patterns of structural and functional abnormalities, particularly within the ventral system, exist within these disorders and are responsible for the generation of specific symptoms (Table 1). In particular, we have speculated that in schizophrenia, the pattern of structural and functional neural abnormalities in ventral and dorsal systems is associated with a restriction of the range of positive and negative emotions identifiable and a misinterpretation of all emotional stimuli as threatening, which may, in turn, result in specific negative and positive symptoms characteristic of the disorder, including emotional flattening, anhedonia, and persecutory delusions, and impaired social function. In bipolar disorder, we suggest that the pattern of abnormalities is associated with an oversensitive but dysfunctional neural system for identification of emotional significance and production of affective states, together with impaired regulation of subsequent emotional behaviors, resulting in prominent mood swings, emotional lability, and distractibility. In major depressive disorder, we suggest that the pattern of reduced volume but increased rather than decreased function within components of the ventral system during depressed episodes indicates a bias of this system toward the identification specifically of negative rather than emotional material per se, resulting in depressed mood and anhedonia, rather than the restricted range of affective states observed in schizophrenia or the emotional lability in bipolar disorder.

Future studies should aim to examine more closely the effects of different treatments on functional and structural neuroanatomic abnormalities in these and other psychiatric populations. Studies employing imaging paradigms and methods of analysis examining more closely functional relationships between neural regions important for emotion processing, and those combining neuroimaging with electrophysiologic, neurochemical, and genetic approaches, will help to clarify further the nature of the distinguishing neurobiological features of each of these disorders.

References


