Regional brain function, emotion and disorders of emotion

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Significant progress has been made in our understanding of the neural substrates of emotion and its disorders. Neuroimaging methods have been used to characterize the circuitry underlying disorders of emotion. Particular emphasis has been placed on the prefrontal cortex, anterior cingulate, parietal cortex, and the amygdala as critical components of the circuitry that may be dysfunctional in both depression and anxiety.

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Current Opinion in Neurobiology 1999, **9**:228–234

http://biomednet.com/elecref/0959438800900228

 ISSN 0959-4388

Abbreviations

DLPFC	dorsolateral prefrontal cortex
DSM-III-R	Diagnostic and Statistical Manual of the American Psychiatric Association III-R
DSM-IV	Diagnostic and Statistical Manual of the American Psychiatric Association IV
EEG	electroencephalogram
ERP	event-related potential
FDG	fluoro-deoxyglucose
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
HRSD	Hamilton rating scale for depression
OCD	obsessive–compulsive disorder
PET	positron emission tomography
PTSD	posttraumatic stress disorder
rTMS	repetitive transcranial magnetic stimulation
SPECT	single photon emission computed tomography

Introduction

Virtually all forms of psychopathology involve some dysregulation of emotion, and for many forms of psychopathology (e.g. schizophrenia, mood and anxiety disorders), affective dysfunction is a central defining characteristic of the disorder (see [1••] for a review). Over the past several years, rapid developments have been made in characterizing the neural substrates and circuitry of emotion and disorders of emotion, leading to the emergence of affective neuroscience as a scientific specialty [2]. Progress in this area has been facilitated by two major advances. First is the burgeoning literature on animal studies that has characterized in detail some of the key components of the circuitry underlying emotion (see e.g. [3,4]). Second is human functional neuroimaging, which has provided an unprecedented opportunity to examine the same basic emotional circuitry in normal human subjects (see [5••]).

In this review, we focus on recent research on the brain mechanisms underlying emotion-related aspects of mood and anxiety disorders. In addition to hemodynamic neuroimaging (i.e. positron emission tomography [PET] and functional magnetic resonance imaging [fMRI]), we also discuss research using quantitative electrophysiology. Other methods for making inferences about brain–behavior relations, including pharmacological challenge studies and transcranial magnetic stimulation will also be reviewed.

Brain electrical activity measures

New reports of EEG neuroimaging research examining psychopathology have been relatively scarce. The great majority of EEG work during the past two years has examined abnormal sleep EEG profiles in depressed individuals (see e.g. [6]), which has not been informative with regard to the functional neuroanatomy of mood or psychopathology. Similarly, inferences about regional brain activity cannot be drawn from two recent event-related potential (ERP) studies pertinent to psychopathology, because each recorded only from three electrode sites, at least two of which were on the midline [7,8]. The handful of recent studies examining regional brain activity have largely focused on depression and anxiety, consistent with the bulk of the EEG research on psychopathology conducted during the past two decades. Published studies have largely replicated earlier work, while at the same time underscoring two important trends: delineating the separable neural substrates of depression and anxiety, and examining relations between patterns of regional brain function and specific types of cognitive dysfunction.

Depression

Several recent studies have replicated the commonly reported finding of more right than left frontal activity in depression (for reviews, see [1••,9]). In one of the first studies to examine brain activity in depressed individuals with comorbid anxiety, Bruder *et al.* [10] found more right than left anterior activation in a sample of 13 women and 12 men meeting DSM-III-R criteria for major depression and for one or more anxiety disorders. Their sample of 9 women and 10 men with major depression but no comorbid anxiety showed symmetric anterior activation, as did healthy controls. Reid *et al.* [11] found a pattern of right greater than left anterior activation for lateral frontal but not midfrontal sites in a group of women with DSM-III-R major depression, but only for the first 2 min of the 8 min resting baseline protocol. In a separate sample of undergraduate women with Beck Depression Inventory (BDI) scores in the depressed range (i.e. > 15), however, Reid *et al.* [11] did not find asymmetric activity. (See Davidson [12] for a critical review of this work.) In a study of intolerance for odors of common chemicals, Bell *et al.* [13] found that depressed women (DSM-III-R major depression)

without such intolerances had more right than left frontal activation across two sessions, whereas the chemical intolerance group and the healthy controls showed symmetric patterns of frontal brain activity. Gotlib *et al.* [14] found greater right than left frontal activation in current and remitted female depressives (DSM-III-R major depression or dysthymia).

New evidence supports previous work documenting diminished right parietal activity and compromised right posterior brain function in depression (for reviews, see [9,15]). For the depressed group without comorbid anxiety described above, Bruder *et al.* [10] found more left than right posterior activation. The depression group with comorbid anxiety, however, showed the opposite asymmetry — as Heller and Nitschke [16•] predicted for anxiety — whereas the control group was characterized by symmetric parietal activity. Similarly, Reid *et al.* [11] found that the large parietal asymmetry favoring the right hemisphere in healthy controls was significantly reduced in the clinically depressed group. Further substantiation for this parietal effect in depression has been provided by Henriques and Davidson [17] in the first known study to measure brain activity during psychometrically matched verbal and spatial tasks in depressed and nondepressed subjects. Analysis of the behavioral data supported their hypothesis of selective impairment on the spatial compared with the verbal task in depressed subjects. EEG measurement during task performance confirmed that the depressed subjects' impaired performance on the spatial task was significantly predicted by decreased right parietal activation. Nondepressed controls showed significantly greater right-sided parietal activation compared with depressed subjects during spatial task performance.

Anxiety

In a sample of spider-phobic women, increased fear of spiders was associated with more right than left parietal activity [18]. However, there were no group effects comparing the phobics to nonphobic controls. In a nonclinical sample, subjects with more right than left frontal activation reported increases in phasic state anxiety following exercise, whereas those with the opposite asymmetry reported decreases in state anxiety following exercise [19].

In separate samples selected on the basis of extreme anxiety and depression scores, Heller *et al.* [20] and Nitschke *et al.* [21] used different experimental designs to test whether anxious apprehension (worry) was associated with increased left hemisphere activation and anxious arousal (panic) with increased right hemisphere activation. Both studies found that measures of brain activity distinguished anxious apprehension from anxious arousal. In sum, the EEG findings for anxiety are consistent with earlier work stressing the importance of carefully measuring and controlling for comorbidity with depression [16•] and of distinguishing between different types of anxiety [22].

Hemodynamic imaging: PET, SPECT and fMRI studies of mood and anxiety disorders

Functional connectivity

Several recent studies have examined functional connectivity among brain regions. As opposed to the typical investigation of differences in average regional cerebral measures, the analysis of functional connectivity reveals functional relations among brain regions and the potential group differences therein. A range of techniques, from computation of zero-order correlations among regions to more sophisticated multivariate techniques, has been developed, and some have been applied in studies of psychopathology [23]. One recent study using fluorodeoxyglucose (FDG)-PET examined differences in correlations among brain regions between control subjects and three patient groups (depression, obsessive–compulsive disorder [OCD], and schizophrenia). Each group showed differences in functional connectivity relative to the controls, and all three patient groups displayed reduced coupling (i.e. the correlation of regional metabolic rate) between the left and right frontal lobes compared with controls [24]. Furthermore, the reduction in frontal coupling was not observed in remitted depressives, suggesting that the frontal decoupling in depression may be a related to the depressive state rather than to a vulnerability marker.

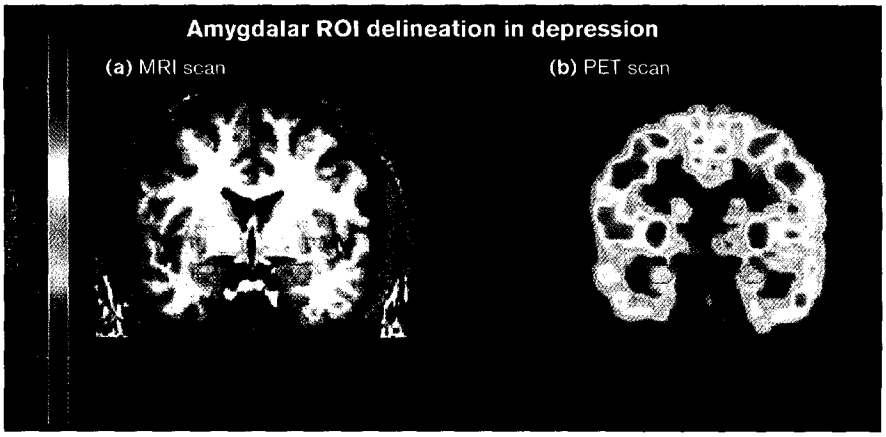
Using a variation of these techniques, we [25] found that depressives and controls differ in their pattern of correlations between frontal and amygdalar metabolic rate. Correlations between frontal and averaged amygdalar metabolic rate were negative for both groups, but controls showed more left-sided negative correlations whereas depressives showed more right-sided negative correlations, possibly suggesting greater left-sided inhibition of amygdala activity in the controls.

Related to these studies of functional connectivity are two recent studies from our lab [26,27] examining the relation of cortical EEG alpha power and PET-derived metabolic rate measurements in the thalamus. We found that whole-head alpha power is negatively correlated with thalamic metabolic rate, a finding that is consistent with the hypothesis that the thalamus serves as a neuronal oscillator of cortical alpha [26]. When examining this relation separately for depressed patients and controls, we found that only the controls show the inverse relation between thalamic metabolic rate and alpha power, possibly indicating a deficit in thalamocortical connectivity in depressives [27].

Regional blood flow and metabolism: group differences and correlations with clinical indices

Drevets *et al.* [28••] found a brain region, the subgenual prefrontal cortex, that consistently showed reduced blood flow or metabolism across several samples of depressed patients (three samples of bipolar patients who were in the depressive phase and one sample of unipolar depressives) compared to controls. They found that the reduced activity in the subgenual cortex, the region of the frontal

Figure 1

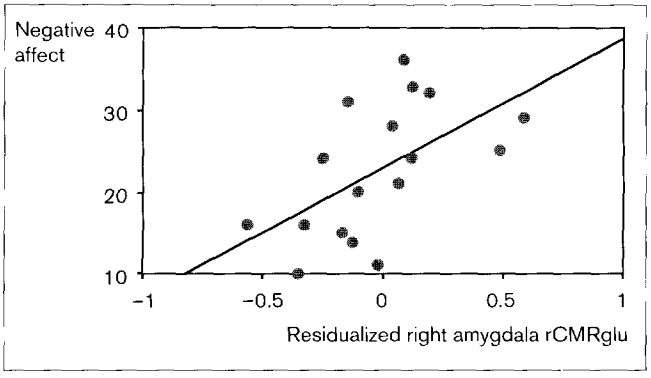


Measurement of metabolic rate in the right amygdala of a depressed patient. **(a)** MRI scan. **(b)** PET scan. This figure illustrates PET–MRI co-registration and amygdala region of interest (ROI) delineation, and it presents representative image planes in the coronal orientation for one subject. The PET image plane is presented besides its corresponding co-registered MRI plane. Glucose metabolism data extracted using these MR-defined ROI's was then used for the correlational analysis depicted in Figure 2. Adapted from Abercrombie *et al.* [31•].

lobes ventral to the genu of the corpus callosum, was partly but not wholly accounted for by reduced volume of this area in the depressed groups. Four of the bipolar patients were re-tested in the manic phase and showed increased activity compared with activity during the depressed state in this region. These findings suggest that abnormal activation in this region varies depending on the mood state.

Amygdala activity has previously been found to be increased in depression and during symptom provocation in posttraumatic stress disorder (PTSD) [29,30]. Consistent with these findings, we [31•] recently found that metabolic rate in the right amygdala predicts negative affect in depressed patients (see Figures 1 and 2), though there were no overall differences in amygdala metabolism between depressed patients and nondepressed controls.

Figure 2



Scatter plot of correlation in depressed subjects (N = 17; $r(15) = 0.56$, $p < 0.02$) between dispositional negative affect (assessed with the Positive and Negative Affect Schedule [PANAS] Negative Affect Scale-Trait Version [62]) and glucose metabolism in the right amygdala (residualized for global metabolic rate). rCMRglu, regional cerebral metabolic rate for glucose. Adapted from Abercrombie *et al.* [31•].

A recent single photon emission computed tomography (SPECT) study examined brain regions associated with negative symptoms in depression [32]. The investigators found that blood flow in the left dorsolateral prefrontal cortex and the left anterior temporal cortex is negatively correlated with severity of negative symptoms, suggesting that these cortical zones play a role in generating positive affect, motivation and goal-setting, and that their inactivity leads to negative symptomatology.

Several studies from Dolan's group in London [33–35] have assessed regional blood flow in relation to performance on cognitive tasks during depressed mood in normal subjects and in unipolar depressives. They found that depressed subjects fail to show the normal task-related increases in blood flow in regions of the frontal cortex, cingulate cortex, basal ganglia, or thalamus.

The other primary region to emerge in the PET literature on depression during the past two years is the anterior cingulate. Hirono *et al.* [36] have recently reported a strong association between depression in Alzheimer's disease and decreased activity in the left anterior cingulate gyrus. In a clinical trial conducted by Buchsbaum *et al.* ([37]; also see below), the anterior cingulate gyrus was the only region that showed a relation with change in HRSD scores following treatment with the antidepressant sertraline, with increased metabolic rate associated with clinical improvement. Further implicating a role for the anterior cingulate in the treatment and remission of depression, Mayberg *et al.* [38] found that treatment responders showed more anterior cingulate activity than controls, whereas nonresponders showed less.

Metabolic rate in relation to treatment and to tryptophan depletion

Research examining the treatment and remission of depression provides further support for altered frontal lobe function. For patients diagnosed with DSM-III-R major depression, Buchsbaum *et al.* [37] found that a 10-week, placebo-controlled trial of sertraline resulted in metabolic

rate increases in the bilateral middle frontal gyri and the medial frontal lobe.

Short-term depletion of tryptophan (which reduces the presynaptic availability of serotonin) often results in a relapse of depressive symptoms in remitted depressives. Bremner *et al.* [39•] examined cerebral metabolic rate using PET during tryptophan depletion and placebo. They compared subjects who showed a depletion-induced relapse in symptoms to those without relapse, and found that tryptophan depletion resulted in decreases in regional metabolism in the dorsolateral prefrontal cortex, thalamus, and orbitofrontal cortex in patients who relapsed but not in patients without relapse. Furthermore, patients who relapsed compared to those who did not showed higher baseline (i.e. placebo) metabolism in several areas (including the dorsolateral prefrontal cortex, orbitofrontal cortex, hippocampus, and amygdala), suggesting that increased basal activity in these structures increases vulnerability to depressive relapse.

Regional neurochemistry

Several studies have examined the distribution of dopamine and serotonin receptors in depressive patients, both before and during treatment (e.g. [40,41]). One recent study used SPECT and the dopamine D_2 receptor antagonist iodobenzamide to examine dopamine D_2 receptor density in unipolar depressives before and during treatment with selective serotonin reuptake inhibitors (SSRIs) [42]. They found an increase in dopamine D_2 receptor binding during treatment in the striatum and anterior cingulate in treatment responders but not in nonresponders. They also found that the increase in dopamine D_2 receptor binding in these areas was correlated with an improvement in depression rating scores. These data are consistent with other findings in normals showing dopaminergic effects of serotonergic modulation [43].

PET studies of anxiety

Unlike studies of depression, where consistent differences between depressed and nondepressed individuals have been observed in baseline regional brain function, most studies of patients with anxiety have provoked anxiety. In various groups of patients with anxiety disorder, symptom provocation paradigms consistently activate the amygdala. PET studies have indicated that right amygdala blood flow is increased in two separate samples of PTSD patients [30,44]. These results are consistent with the findings of several fMRI studies measuring amygdala activation in patients suffering from anxiety (see below).

Right-sided activation in various areas of the prefrontal cortex is a general characteristic of anxiety when symptoms are provoked in patients with several different anxiety disorders (e.g. OCD, simple phobia and PTSD) [45]. Stapleton *et al.* [46] have shown that subjects with high levels of anxiety have larger asymmetry in favor of the right hemisphere during a second (but not first) PET session using FDG compared with those showing low levels of anxiety, particularly in various territories of the prefrontal cortex and the temporal cortex. In one of the first studies to use [^{11}C]flumazenil and PET to examine $GABA_A$–benzodiazepine receptor binding in patients with panic disorders, Malizia *et al.* [47••] reported a reduction of receptor binding throughout the brain in patients that was particularly dramatic in right orbitofrontal and right insular cortex.

fMRI studies of mood and anxiety disorders

The literature on the use of fMRI to study basic emotional processes in normal individuals (see [48] for a review) is burgeoning. This work has built on animal research that provided a framework for understanding the neural circuitry of basic emotional processes (see e.g. [3]). However, there are few studies that have combined fMRI in psychiatric populations with paradigms to elicit emotion in an effort to understand emotional deficit or dysregulation symptoms in psychopathology.

Breiter *et al.* [49•] used fMRI to examine the effects of cocaine on human brain activity and emotion in cocaine-dependent subjects. In a double-blind study using cocaine (0.6 mg/kg) and saline infusions, Breiter *et al.* [49•] imaged the entire brain for 5 min before and 13 min after each infusion. Seventeen subjects completed two scanning sessions where they were injected with one of the substances in a randomized order. Subjects used rating scales to indicate rush, high, low, and craving. Measures taken that confirm the effect of cocaine infusion include self report (no subjects reported effects from the saline infusion), increases in heart rate and mean blood pressure, and measurement of cocaine plasma concentrations, which reached maximum approximately 7 min after infusion. At the time of onset of subjective measures of euphoria, increases in fMRI signal were found in brain circuitry implicated in reward (i.e. the nucleus accumbens/subcallosal cortex, basal forebrain, and the ventral tegmentum) and the caudate, putamen, thalamus, medial temporal and paralimbic regions (i.e. the hippocampus, parahippocampal gyrus, cingulate, cortex, and insula), brainstem (pons), and neocortical regions, such as the lateral prefrontal cortex, lateral temporal cortex, parietal cortex, and occipital cortex. The saline condition, in contrast, produced few regions of fMRI signal increase. Craving measures were correlated with the nucleus accumbens/subcallosal cortex and right parahippocampus; a negative correlation with craving was also noted in the amygdala.

Using fMRI, Birbaumer *et al.* [50] explored the activation of the amygdala of social phobics relative to healthy controls, as they were exposed to slides of neutral faces and aversive odor stimuli. All the subjects in this study were male; seven were diagnosed with DSM-IV social phobia and five were age-, gender-, and education-matched healthy controls. All subjects were presented with neutral faces, which do not lead to amygdala activation in nonpsychopathological humans [51], and aversive odors, which are significantly associated with amygdala activation compared to a 'no odorant' control condition [52]. Birbaumer *et al.* [50]

compared activation in the thalamus and the amygdala between groups. For both groups, odors elicited more bilateral activation in the amygdala but not in the thalamus. In contrast, social phobics responded with significantly more bilateral amygdala activation to the faces than the controls. However, no regional activation difference between the two groups in response to the neutral faces was found for the thalamus. Interestingly, although the social phobics showed significant amygdala activation, their subjective ratings of the faces were not different than the controls.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) has recently received attention as a potential treatment for depression (for a review, see [53]) and mania [54]. This technique permits a relatively focal, non-invasive alteration in regional brain activation by applying an externally imposed strong magnetic field near the head. Certain stimulation parameters lead to inhibition of underlying neuronal activity, whereas other forms of stimulation lead to excitation.

In one of the first double-blind studies to examine the effects of rTMS in depressed patients, Pascual-Leone *et al.* [55] used fast left dorsolateral prefrontal cortex (DLPFC) rTMS for 25 days and found marked antidepressant effects in psychotic depression. Eleven of 17 patients showed a HRSD decline of greater than 50%. George *et al.* [56] used a double-blind, sham-controlled, single-crossover study to investigate the effects of daily fast left DLPFC rTMS on 12 medication-resistant depressed outpatients. In comparison to the sham treatment, there was a greater improvement with 10 days of active rTMS. A more significant treatment effect was found by Klein *et al.* [57], who randomized 71 depressed outpatients to 2 weeks of active or sham slow rTMS over right prefrontal cortex (producing inhibition). In the active group, 41% of the rTMS-treated patients responded with at least a 50% drop in HRSD. This is in contrast to the 17% of the sham-treated patients who responded with at least a 50% drop in HRSD. Another dramatic decrease in depressive symptomatology was found by Figiel *et al.* [58], who used fast left DLPFC rTMS for 56 largely medication-resistant depressed patients who had been referred for electroconvulsive treatment. After five days of treatment, 42% responded (> 50% decrease in HRSD scores) to the treatment.

Although these results are promising, rTMS studies are hampered by inconsistent TMS parameters that make it difficult to compare findings (see [53] for a review). Most of the extant data, however, are consistent with the prefrontal valence model articulated by Davidson and colleagues (e.g. [48]) and others (e.g. [59–61]).

Conclusions

There has been a substantial amount of research activity over the past year in the neurobiology of affect and emotional disorders. Both the electrophysiological and neuroimaging literature continue to highlight the importance of abnormalities in various territories of the prefrontal cortex for disorders of emotion. Decreases in both left and bilateral prefrontal activation have been found to accompany depression. Davidson [1••] has previously suggested that different regions of the left and right prefrontal cortex implement approach and withdrawal-related emotion, respectively, and that decreased activation in these regions might reflect deficits in these emotion processing systems. While an individual with specific decreases in activation in regions of left prefrontal cortex would be expected to show deficits in approach-related behavior and emotion, an individual with bilateral decreases would be hypothesized to be more anhedonic and show blunted positive and negative emotion. The role of regions of both right prefrontal and right parietal cortex in anxiety has also been highlighted in the electrophysiological and neuroimaging literatures. It has been hypothesized that the right prefrontal activation associated with certain forms of anxiety might be indexing the increased vigilance that is characteristic of these states [1••] while the right parietal activation might index the increase in arousal that typifies anxiety [16•].

New neuroimaging studies suggest that patterns of functional connectivity may differ between depressed patients and controls. Interhemispheric, cortical–limbic and thalamocortical connectivity have all been found to be different in depressed patients compared to controls. Just which specific features of depression are associated with each of these different patterns of functional connectivity must be disentangled in future research. A promising strategy exemplified in other neuroimaging studies has been to search for relations between specific patterns of regional blood flow or metabolism and the severity of specific symptoms. For example, in our own work, we [31•] found that depressed patients with greater metabolic rate in the right amygdala reported more severe negative affect. Among the most exciting new developments in neuroimaging studies in this area has been the study of regional neurochemical effects using PET. In patients with panic disorder, Malizia *et al.* [47••] have reported a reduction in benzodiazepine receptor binding that is particularly dramatic in the right orbitofrontal cortex. These neuroreceptor studies need to be combined with functional activation studies in the same patients to better understand the functional consequences of the receptor differences observed. Finally, rTMS provides a method by which relatively localized regional activation changes in cortex can be specifically manipulated and the effects on mood studied. Particularly when rTMS is combined with functional imaging, we can begin to test causal hypotheses about the role of activation in specific circuits on emotion and its disorders. We expect that progress in affective neuroscience will continue to accelerate.

Acknowledgements

We thank Christine Larson, Wil Irwin, and other members of the Laboratory for Affective Neuroscience for their comments and assistance, Jenny Fleischman for assistance in the library, and Michele Albert for help in manuscript preparation. This work was supported in part by

National Institute of Mental Health (NIMH) grants MH43454, MH40747, Research Scientist Award K05-MH00875, and P50-MH52354 to the Wisconsin Center for Affective Science (RJ Davidson, Director), by a National Alliance for Research on Schizophrenia and Depression (NARSAD) Established Investigator Award, and by a grant from the John D and Catherine T MacArthur Foundation.

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