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ACTIVATION PARADIGMS IN AFFECTIVE AND COGNITIVE NEUROSCIENCE: PROBING THE NEURONAL CIRCUITRY UNDERLYING MOOD AND ANXIETY DISORDERS

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Virtually all forms of psychopathology are associated with disturbances in various aspects of affect and cognition. Although most clinical research has relied on relatively coarse phenomenologic descriptions of symptoms, recent work in neuroimaging with behavioral activation paradigms offers a new and more penetrating look at specific cognitive and affective processes in psychopathology. This new trend is predicated on the view that we must go beyond phenomenology to understand the brain circuitry that is associated with complex mood and anxiety disorders. Advances in our understanding of these conditions will emerge from research that is designed to examine more specific cognitive and affective processing abnormalities. This work holds promise in revealing additional targets for therapeutic intervention, both behavioral and pharmacologic. It also will be important in helping to expose the heterogeneity of these disorders and in offering more meaningful ways in which to parse various subtypes. Finally, by examining the impact of particular therapeutic interventions on functional brain activity elicited in the context of activation paradigms, a better understanding of the impact of these interventions on specific subcomponents of the brain circuitry underlying affect and cognition is likely to emerge.

In this chapter, some key elements of the circuitry that is most relevant to understanding mood and anxiety disorders are first reviewed. The role of individual differences in the functional activity of this circuitry is then considered. The next section reviews key approaches and findings of activation paradigms that have been used in this area. The chapter concludes with a summary and a discussion of future trends in this rapidly developing area.

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CIRCUITRY OF AFFECT AND COGNITION IN MOOD AND ANXIETY DISORDERS

The review presented in this section of the key components of the circuitry underlying aspects of emotion and cognition that are most relevant to mood and anxiety disorders is gleaned mostly from studies of lesions experimentally produced in animals, the human lesion literature, and neuroimaging studies in normal humans. The review focuses on various territories of the prefrontal cortex, amygdala, hippocampus, and anterior cingulate cortex. Collectively, these studies provide important clues regarding the types of activation paradigms that are most promising for use in patients with mood and anxiety disorders to probe the underlying circuitry of affect and cognition. Research in which activation paradigms with neuroimaging are applied in patients with mood and anxiety disorders is reviewed in a subsequent section.

Prefrontal Cortex

A large corpus of data at both the animal and human levels implicates various sectors of the prefrontal cortex (PFC) in both cognition and emotion. The PFC is not a homogeneous zone of tissue; rather, it has been differentiated on the basis of both cytoarchitectonic and functional considerations. The three subdivisions of the primate PFC that have been consistently distinguished are the dorsolateral, ventromedial, and orbitofrontal sectors of the PFC. In addition, it appears that important functional differences exist between the left and right sides within some of these sectors.

The role of the PFC in cognitive control has recently been reviewed (1), so it is not extensively considered here other than to underscore that a major function of the PFC in general is ''to extract information about the regularities

across experiences and so impart rules that can be used to guide thought and action'' (1). One of the principal roles of the PFC is to represent goal-relevant information, a key component of both complex thought and emotion. As many studies at the nonhuman primate level have now documented, reward-related information plays a key role in modulating the activity of PFC neurons. Activity in both lateral and ventromedial zones of the PFC is associated with the identity and size of expected rewards (2). This component of PFC activity is likely governed by a dopaminergic input from the ventral tegmental area of the midbrain (see ref. 1 for review). Our notion of the role of the PFC in pre-goal attainment positive affect is based on this corpus of research, which is discussed below (3,4).

The case for the differential importance of left and right PFC sectors in emotional processing was first made systematically in a series of studies of patients with unilateral cortical damage (5–7). Each of these studies compared the mood of patients with unilateral left or right-sided brain damage and found a greater incidence of depressive symptoms following left-sided damage. In most cases, the damage was fairly gross and likely included more than one sector of the PFC and often other brain regions as well. The general interpretation that has been placed on these studies is that depressive symptoms are increased following left-sided anterior PFC damage because this brain territory participates in certain forms of positive affect, particularly pre-goal attainment positive affect; damage leads to deficits in the capacity to generate this form of positive affect, a hallmark feature of depression (8). It should be noted that not all studies support this conclusion. In a recent metaanalysis of lesion studies, Carson et al. (9) failed to find support for this hypothesis. Davidson (10) has previously reviewed many of these studies and has addressed a number of critical methodologic and conceptual concerns in this literature. The most important of these issues is that according to the diathesis stress model of anterior activation asymmetry proposed by Davidson and colleagues (11–13), individual differences in anterior activation asymmetry, whether lesion-induced or functional, represent a diathesis. As such, they alter the probability that specific forms of emotional reactions will occur in response to the requisite environmental challenge. In the absence of such a challenge, the pattern of asymmetric activation will simply reflect a propensity but will not necessarily culminate in differences in mood or symptoms. In a recent study of mood sequelae in patients with unilateral lesions with the largest sample size to date ($n = 193$), Morris et al. (14) found that among stroke patients, it was only in those with small lesions that the relation between left PFC damage and depressive symptoms was observed. It is likely that larger lesions intrude on other brain territories and mask the relation between left PFC damage and depression.

A growing corpus of evidence in normal intact humans is consistent with the findings derived from the lesion studies. Davidson and colleagues have reported that induced positive and negative affective states shift the asymmetry in prefrontal brain electrical activity in lawful ways. For example, film-induced negative affect increases relative right-sided prefrontal and anterior temporal activation (15), whereas induced positive affect elicits an opposite pattern of asymmetric activation. This general pattern has been replicated by others using similar measures (16,17). In positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies, with considerably better spatial resolution, similar PFC activations have been reported, although many important methodologic details must be considered in interpreting the findings (see ref. 4 for review). The most important of these is considered in a later section. In addition, a body of evidence supports the conclusion that individual differences in baseline levels of asymmetric activation in these brain regions are lawfully related to variations in dispositional affective style (18).

The ventromedial PFC has been implicated in the anticipation of future positive and negative affective consequences. Bechara and colleagues (19) have reported that patients with bilateral lesions of the ventromedial PFC have difficulty anticipating future positive or negative consequences, although immediately available rewards and punishments do influence their behavior. Such patients show decreased levels of electrodermal activity in anticipation of a risky choice in comparison with controls, whereas controls exhibit such autonomic change before they explicitly know that a choice is risky (20–22).

The findings from the lesion method when effects of small unilateral lesions are examined and from neuroimaging studies in normal subjects and patients with anxiety disorders converge on the conclusion that increases in right-sided activation in various sectors of the PFC are associated with increased negative affect. Less evidence is available for the domain of positive affect, in part because positive affect is much harder to elicit in the laboratory and because of the negativity bias (23,24). This latter phenomenon refers to the general tendency of organisms to react more strongly to negative than to positive stimuli, perhaps as a consequence of evolutionary pressures to avoid harm. The findings of Bechara et al. (19) on the effects of ventromedial PFC lesions on the anticipation of future positive *and* negative affective consequences are based on studies of patients with bilateral lesions. It will be of interest in the future to examine patients with unilateral ventromedial lesions to ascertain whether valence-dependent asymmetric effects are also present, although most lesions in this PFC territory are bilateral.

Systematic studies designed to disentangle the specific role played by various sectors of the PFC in emotion are lacking, although a growing corpus of work illustrates the functional differentiation among different sectors of the PFC in different aspects of cognitive control (25). Many theoretical accounts of emotion assign it an important role

in guiding action and organizing behavior toward the acquisition of motivationally significant goals (26,27). This process requires that the organism have some means of representing affect in the absence of immediately present rewards and punishments and other affective incentives. Such a process may be conceptualized as a form of affective working memory. It is likely that the PFC plays a key role in this process (28). Damage to certain sectors of the PFC impairs an individual's capacity to anticipate future affective outcomes and consequently results in an inability to behave in an adaptive fashion. Such damage is not likely to disrupt an individual's response to immediate cues for reward and punishment, only the anticipation before and maintenance after an affective cue has been presented. This proposal can be tested with current neuroimaging methods (e.g., fMRI) but has not yet been rigorously evaluated. With regard to the different functional roles of the dorsolateral, orbitofrontal, and ventromedial sectors of the PFC, Davidson and Irwin (4) suggested on the basis of both human and animal studies that the ventromedial sector is most likely involved in the representation of elementary positive and negative affective states in the absence of immediately present incentives. The orbitofrontal sector has most firmly been linked to rapid learning and unlearning of stimulus-incentive associations and has been particularly implicated in reversal learning (29). As such, the orbitofrontal sector is likely key to understanding aspects of emotion regulation (30). One critical component of emotion regulation is the relearning of stimulus-incentive associations that may have been previously maladaptive, a process likely requiring the orbitofrontal cortex. The dorsolateral sector is most directly involved in the representation of goal states toward which more elementary positive and negative states are directed.

Amygdala

A large corpus of research at the animal (mostly rodent) level has established the importance of the amygdala in emotional processes (31–33). Because many reviews of the animal literature have appeared recently, a detailed description of these studies is not presented here. LeDoux and colleagues have marshaled a large corpus of compelling evidence to suggest that the amygdala is necessary to establish conditioned fear. Whether the amygdala is necessary to express that fear following learning and whether the amygdala is the actual locus where learned information is stored is still a matter of some controversy (34,35). The classic view of amygdala damage in nonhuman primates (resulting in major affective disturbances as expressed in the Kluver–Bucy syndrome, in which the animal exhibits an abnormal approach, hyperorality and hypersexuality, and little fear) is now thought to be a function of damage elsewhere in the medial temporal lobe. When very selective excitotoxic lesions of the amygdala are made that preserve fibers of passage, nothing resembling the Kluver–Bucy syndrome is observed (36). This diverse array of findings suggests a more limited role for the amygdala in certain forms of emotional learning, although the human data imply a more heterogeneous contribution.

Although the number of patients with discrete lesions of the amygdala is small, they have provided unique information about the role of this structure in emotional processing. A number of studies have now reported specific impairments in the recognition of facial expressions of fear in patients with restricted amygdala damage (37–40). Recognition of facial signs of other emotions have been found to be intact. In a study that required subjects to make judgments about the trustworthiness and approachability of unfamiliar adults based on facial photographs, patients with bilateral amygdala damage judged the unfamiliar persons to be more approachable and trustworthy than did control subjects (41). Recognition of vocalic signs of fear and anger was found to be impaired in a patient with bilateral amygdala damage (42), which suggests that this deficit is not restricted to facial expressions. Other researchers demonstrated an impairment of aversive autonomic conditioning in a patient with amygdala damage despite the fact that the patient demonstrated normal declarative knowledge of the conditioning contingencies (43). Collectively, these findings from patients with selective bilateral destruction of the amygdala suggest specific impairments on tasks that tap aspects of negative emotion processing. Most of the studies have focused on perception; the data clearly show the amygdala to be important in recognizing cues of threat or danger. The conditioning data also indicate that the amygdala may be necessary for acquiring new implicit autonomic learning of stimulus–punishment contingencies. In one of the few studies to examine the role of the amygdala in the expression of already learned emotional responses, Angrilli and colleagues (44) described a patient with a benign tumor of the right amygdala who underwent an emotion-modulated startle study. Among control subjects, they observed the well-known effect of startle potentiation during the presentation of aversive stimuli. In the patient with right amygdala damage, no startle potentiation was observed in response to aversive versus neutral stimuli. These findings suggest that the amygdala may be necessary for the expression of an already learned negative affect.

Hippocampus and Anterior Cingulate Cortex

In this section, the contributions of the hippocampus and anterior cingulate cortex (ACC) to emotion and cognition are briefly mentioned. A more extensive discussion of the contributions of this circuit to emotional and cognitive processing can be found in several recent reviews (4,45–47).

The hippocampus has been implicated in various aspects of memory (47), particularly declarative memory of the sort we experience when we consciously recall an earlier episode. The contribution of the hippocampus to emotion and affec-

tive style has only recently begun to be gleaned from the available corpus of animal studies on its role in context-dependent memory (48). This literature has generally supported a role for the hippocampus in the learning of context. For example, when an animal is exposed to a procedure in which a discrete cue is paired with an aversive outcome, in addition to learning the specific cue–punishment contingency, the animal learns to associate the context in which the learning occurs with the aversive outcome. Lesions to the hippocampus abolish this context-dependent form of memory but have no effect on learning of the cue–punishment contingency. The fact that the hippocampus has a very high density of glucocorticoid receptors and participates in the regulation of the hypothalamic–pituitary–adrenal axis is particularly germane to the importance of this structure in regulating emotion. Basic research at the animal level has demonstrated the powerful impact of glucocorticoids on hippocampal neurons (32,49). Data indicate that the exogenous administration of hydrocortisone to humans impairs explicit memory that is presumably hippocampus-dependent (50), although other data that suggest that in more moderate amounts, cortisol may facilitate memory (Abercrombie, *unpublished doctoral dissertation,* Department of Psychology, University of Wisconsin at Madison, 2000). A number of investigators using MRI-based measures have reported that hippocampal volume is significantly decreased in patients with several stress-related disorders, including posttraumatic stress disorder (PTSD) (51) and depression (52,53), although several failures to replicate these findings have also been reported (54). In the studies in which hippocampal atrophy has been found, the implication is that excessively high levels of cortisol associated with the stress-related disorder cause hippocampal cell death and result in the hippocampal atrophy seen on MRI. Although virtually all these studies have focused on the effects of hippocampal changes on cognitive function, particularly declarative memory, we have proposed that the hippocampus also plays a key role in the context modulation of emotional behavior (55). Moreover, we have suggested that it is in the affective realm that the impact of hippocampal involvement in psychopathology may be most apparent, and that in persons with compromised hippocampal function, the normal context-regulatory role of this brain region is impaired, so that they consequently display emotional behavior in inappropriate contexts. This argument holds that what may be particularly abnormal in disorders such as PTSD and depression is not the display of "abnormal emotion" but rather the display of perfectly normal emotion in inappropriate contexts. For example, in the case of PTSD, extreme fear and anxiety were likely very adaptive in the original traumatic context. This extreme emotional response probably plays an important role in facilitating an organism's withdrawal from a threatening situation. However, in PTSD, this response is elicited in inappropriate situations. The patient with PTSD behaves like the animal with a hippocampal lesion in failing to modulate emotional responses in a context-appropriate manner. These suggestions are only inferential at the present time. Neuroimaging studies are needed to document the role of the hippocampus in this process in normal and disordered populations. In addition, further study is needed to understand how and why the hippocampus may preferentially extract and process information about context. Finally, some research (56) indicates that other structures with direct connections to the hippocampus (e.g., the bed nucleus of the stria terminalis) play a role similar to that of the hippocampus. More work is needed to understand the differential contributions of the various components of this circuitry.

Many studies that have used neuroimaging methods to probe patterns of brain activation during the arousal of emotion have reported that the ACC activates in response to emotion. Several investigators (45,57) have recently distinguished between cognitive and affective subdivisions of the ACC based on where activations lie in response to tasks that are purely cognitive versus those that include aspects of emotion. The various tasks used to make these inferences are described in a subsequent section. Based on the model of Carter et al. (58) of the role of the ACC in conflict monitoring in the cognitive domain, we have proposed that the affective subdivision of the ACC may play a similar role in emotion (4). When emotion is elicited in the laboratory, something of a conflict arises because social norms dictate certain rules for participant behavior that do not usually include the display of strong emotion. Thus, the very process of activating emotion in the unfamiliar context of a laboratory environment might activate the ACC. Carter et al. (58) have suggested that ACC activation results in a call for further processing by other brain circuits to address the conflict that has been detected. In most individuals, automatic mechanisms of emotion regulation are likely invoked to dampen strong emotion that may be activated in the laboratory. The initial call for the processes of emotional regulation may result from ACC activation.

PROBING THE NEURAL CIRCUITRY OF AFFECT AND COGNITION IN PATIENTS WITH MOOD AND ANXIETY DISORDERS: CONCEPTUAL AND METHODOLOGIC CONUNDRA

In this section, some of the key conceptual and methodologic issues in the use of activation paradigms to probe dysfunctions in the underlying neural circuitry of cognition and affect in patients with mood and anxiety disorders are considered. Issues specific to the study of dysfunctions in the circuitry of emotion in children are considered in a recent review by Davidson and Slagter (59). A key issue that is often neglected in the design of activation studies is the specification of how deficits in the process that is being

studied may account for the symptoms of the disorder. For example, many of the early PET studies in patients with various types of psychopathology used easy continuous performance tasks in which behavioral differences between groups were not expected to occur, or they used unilateral somatosensory stimulation (see ref. 60 for review of early studies). Just what the hypothesized relation was between abnormalities in activation patterns in response to such tasks and symptoms of the disorder being studied was most often not specified in these earlier studies. The better the conceptual link between task performance and symptomatology, the more useful an activation paradigm will be for revealing the underlying deficits in the disorder in question. Several examples of strong conceptual connections between specific task-related deficits and symptomatology in both the cognitive and affective domains are available and can be consulted by the interested reader (see ref. 61 for an example in the cognitive domain and ref. 30 for an example in the affective domain).

The use of tasks that require active performance on the part of subjects poses a host of methodologic issues that are crucial for studies of psychopathology. One of the most important of these is matching the difficulty of an experimental task with that of a control task. This is an issue with a long history in experimental research in psychopathology (62), although the neuroimaging field has yet to appreciate its significance fully. When performance on two tasks is compared between groups, it is imperative that the difficulty of the two tasks be matched. If one task is more difficult than the other task in normal subjects, than a differential deficit on one versus the other task may be a consequence of differences in task difficulty and not specific to the processes that are putatively required for performance of the task. Chapman and Chapman (62) have provided many examples of such artifactual group differences that are products of variation in task performance rather than reflections of differential deficit. It is therefore essential in neuroimaging studies for activation tasks to be matched in this way. If the tasks that are being compared in imaging studies are not matched, then any difference found in activation between tasks may arise as a consequence of differences in the difficulty level of the tasks. Unfortunately, the neuroimaging literature is replete with task comparisons for tasks that do indeed differ in the level of difficulty and thus are particularly problematic for comparisons between groups. The challenge is to design control conditions that are matched to the experimental conditions in regard to basic stimulus and response components, in addition to task difficulty. In one of the few studies to have addressed this potential source of confound, Barch et al. (63), using fMRI, found that the sustained PFC increases in working memory tasks were a function of specific task requirements when they compared such tasks to control tasks that were matched in level of difficulty but did not require working memory.

In studies with patients, investigators frequently wish to examine changes over time with treatment. In this way, effects that may be specifically associated with the symptoms of the disorder can be disentangled from those associated with vulnerability to the disorder. The latter class of effects may also arise as a consequence of scarring—effects produced by having once had the disorder. In experimental designs that require subjects to be scanned and administered tasks on two or more occasions, it is imperative to have data on the test–retest stability of the effects in question. If the effects do not show stability over time, it becomes difficult to interpret group differences in change over time in task activations. We have strongly advocated the psychometric assessment of both psychophysiologic (64) and neuroimaging (65) measures. Such assessments can turn up important surprises. Resting regional glucose metabolism measured with PET is frequently used to assess baseline differences in regional brain activation in various forms of psychopathology. Using MRI coregistration and regions of interest, we recently examined the test–retest stability across a 6-month period of such baseline measures of glucose metabolism in subcortical regions implicated in affective processing. We found that all the regions we examined showed good test–retest stability, including the left and right hippocampus, left and right anterior caudate region, left and right thalamus, and the left amygdala, but not the right amygdala (65). The right amygdala apparently varied over time, in part because metabolic rate in this region was more affected by the stress of the first scan in comparison with activation elsewhere.

Emotional pictures are frequently used to provoke changes in affect in imaging studies (66). When these pictures are used to compare patients and controls over time, it is again important to establish that the effects produced are stable over time in normal subjects. We used startle to probe the test–retest stability of the potentiation produced by negative pictures and the attenuation produced by positive pictures, and we found poor stability when the same pictures were used on both occasions. It was only when different pictures were used, matched on valence and arousal characteristics to the original set, that we found better stability (64). These data underscore the importance of not assuming that effects will be stable over time and the utility of actually measuring the test–retest stability of both task performance and activation changes in normal subjects before conducting a longitudinal study of changes in patients.

The final issue I wish to raise here pertains to studies in which emotion is provoked by specific task manipulations, such as pleasant and unpleasant pictures, guided imagery, monetary rewards and punishments, and symptom provocation with the use of actual feared objects, pictures of objects, or imagined objects. When such paradigms are used, it is imperative for the investigator to verify independently the presence of the intended affective state. Ideally, such verification should include more than self-report measures. For example, peripheral biological indices (e.g., emotion-modu-

lated startle, electrodermal activity) can often be effective when utilized in imaging studies to provide an independent index of the effects of the intended emotion. Moreover, when such measures are used, correlations between activations produced by the task in question and changes in the peripheral biological index can be computed and are often revealing. For example, Furmark et al. (67) found that subjects showing larger conditioned electrodermal changes in a classic conditioning task showed greater increases in blood flow in the right amygdala during conditioning.

ACTIVATION STUDIES IN PATIENTS WITH MOOD AND ANXIETY DISORDERS

Most of the extant imaging studies of patients with mood disorders have been performed with PET while the subjects are in a baseline state. These findings have been recently reviewed elsewhere (68). Recent studies using these methods have reported associations between the severity of particular symptom clusters and patterns of regional blood flow or metabolism (69–71). These studies have underscored the importance of differentiating among various symptoms of depression and illustrate the lawful relations that can be gleaned by examining associations between specific symptoms and patterns of regional brain activity. The few studies using activation paradigms that have been conducted in patients with mood disorders have utilized complex cognitive tasks designed to activate the PFC and ACC. Several studies from Dolan's group (72–74) assessed the relationship of regional blood flow to performance on complex planning tasks during depressed mood in normal subjects and unipolar depressives. Depressed subjects failed to show normal task-related increases in blood flow in regions of the PFC, ACC, basal ganglia, and thalamus.

Several reports have been published of deficits in task performance in depressed patients in which tasks were used that have been extensively studied in previous neuroimaging or neuropsychological research. For example, Merriam et al. (75) studied Wisconsin Card Sorting performance in a large group of patients with major depression who had been without medication for at least 28 days. They found significant deficits on various indices of the Wisconsin Card Sorting task in these patients in comparison with controls. Moreover, patients with more severe depression, reflected in the Hamilton Depression Scale, performed more poorly. Merriam et al. (75) interpreted their data as consistent with suggestions of a dysfunction in prefrontal function in depression.

Other investigators have suggested that in addition to prefrontal deficits, right-sided parietal dysfunction can also contribute to specific symptoms of depression (76). Henriques and Davidson (77), using extremely carefully psychometrically matched verbal and spatial tasks chosen to reflect left- and right-sided posterior cortical function, found a selective deficit on the spatial cognitive task (dot localization) in depressed subjects in comparison with controls. Moreover, in this study, measures of brain electric activity paralleled the performance data and revealed deficits in activation in the right posterior scalp.

We have begun using positive and negative emotional pictures to probe affective processing in depressed patients and controls and to examine changes over time with treatment (see ref. 78 for early preliminary findings). In more recent work with this same paradigm, we have found that patients show a reduction in MR signal intensity in the amygdala in response to negative versus neutral pictures with treatment, whereas controls tested at the same points in time do not. Moreover, the magnitude of MR signal change in the amygdala predicts treatment response (55).

A unique strategy used in research on mood disorders is the short-term depletion of tryptophan among remitted depressed patients maintained on selective serotonin reuptake inhibitors. The depletion of tryptophan, which reduces the presynaptic availability of serotonin, often results in depressive relapse. Thus, this method can be powerfully harnessed to examine activation patterns during the production of depressive relapse in mood-disordered patients. Bremner at al. (79) examined regional metabolic rate with PET during tryptophan depletion and placebo. When they compared subjects who showed a depletion-induced relapse in symptoms with those without relapse, they found that tryptophan depletion resulted in decreases in regional metabolism in the dorsolateral PFC, thalamus, and orbitofrontal cortex in patients who relapsed, but not in patients without relapse. Furthermore, patients who relapsed had a higher baseline (i.e., placebo) metabolism in several areas, including the dorsolateral PFC, orbitofrontal cortex, hippocampus, and amygdala, than those who did not relapse, which possibly suggests that increased basal activity in these structures increases vulnerability to depressive relapse.

We are currently using a task designed to elicit anticipatory positive affect, a form of positive affect that, as noted earlier in this article, is probably implemented at least in part in the dorsolateral PFC. We have hypothesized that this form of positive affect is abnormally decreased in patients with depression (80,81). The task we designed is a computerized "lottery" task in which subjects are required to choose digits that may or may not match the digits displayed by a computer after a 10-second delay during which the digits spin like a slot machine. We have found reliable attenuation of startle magnitude at selected points in time during this task (82), and we are now studying a variant of this task in the scanner with fMRI in both normal persons and patients with depression.

Many more studies have been performed in patients with various anxiety disorders (see ref. 83 for recent review). In general, most studies that have used either symptom provocation or other procedures designed to activate the amygdala have found greater activation in this region in response to

such stimuli in anxious patients than in controls. For example, in two studies using script-driven imagery and PET to assess regional blood flow, increased activation was found in the amygdala of patients with PTSD (84,85). In a more recent study comparing patients with PTSD and controls, Rauch et al. (86) reported an increased activation of the amygdala in the PTSD patients in response to masked facial expressions of fear versus masked expressions of happiness.

Right-sided activation in various territories of the PFC has been found as a general characteristic of anxiety when symptoms are provoked in patients with several different anxiety disorders (e.g., obsessive-compulsive disorder, simple phobia, and PTSD) (87). In a series of studies that used PET to measure regional cerebral blood flow, Fredrikson and colleagues (88; see ref. 89 for review) reported increases in secondary visual associative regions in patients with snake phobia in response to the presentation of phobia-relevant visual stimuli (e.g., pictures of snakes) versus control visual stimuli. Interestingly, in a separate group of patients with arachnophobia, this pattern did not change after the administrative of diazepam when the subjects were rescanned (90). Using fMRI, Birbaumer et al. (91) explored activation of the amygdala of patients with social phobia relative to that in healthy controls as they were exposed to slides of neutral faces and aversive odor stimuli. The subjects in this study were all male; seven had been given a DSM-IV diagnosis of social phobia and five were healthy controls matched for age, sex, and education. Neutral faces, which do not lead to amygdala activation in nonpsychopathologic humans (92), and aversive odors, which are significantly associated with amygdala activation in comparison with a no-odorant control condition (93), were presented to all the subjects. Birbaumer et al. (91) compared activation in the thalamus and amygdala in the two groups. In both groups, odors elicited greater bilateral activation in the amygdala than in the thalamus. In contrast, the social phobics responded to the faces with significantly greater bilateral amygdala activation than did the controls. However, no difference in regional activation of the thalamus was found between the two groups in response to the neutral faces. Interestingly, although significant amygdala activation was noted in the social phobics, their subjective ratings of the faces did not differ from those of the controls.

SUMMARY AND CONCLUSIONS

This chapter began with discussion of some key components of the circuitry underlying affect and cognition that are most relevant to an understanding of affective and cognitive dysfunction in patients with mood and anxiety disorders. Emphasis was placed on the PFC, amygdala, hippocampus, and ACC. Next, some important conceptual and methodologic problems that plague research in this area were considered. The relevance of the task chosen in activation studies to the underlying symptoms of the disorder should be made explicit in this type of research. Several psychometric problems were then considered, including the issues of matching experimental and control tasks according to level of difficulty and of establishing the reliability of tasks before using them in longitudinal studies of patients in whom changes produced by treatment are being examined. Finally, in studies of emotion, the importance of independent verification of elicitation of the intended emotion was emphasized.

Recent activation studies in patients with mood and anxiety disorders were reviewed. It should be apparent from this review that studies using this strategy are currently lacking despite its obvious importance in revealing the abnormalities in circuitry that underlie basic cognitive and affective processes. It is imperative that the next generation of clinical investigators be trained in the methods and techniques of affective and cognitive neuroscience, the area where such activation paradigms are typically first developed.

It is also imperative that the results of burgeoning research on cognitive and affective information-processing deficits in mood and anxiety disorders (see ref. 94 for review) be used to develop new tasks that can be applied with neuroimaging to probe the circuitry associated with specific types of processing anomalies. For example, an extensive corpus of literature has now documented biases in forms of explicit memory in depression and biases in attention in various types of anxiety disorders. This information can be used to design activation paradigms that are more closely linked to the various hypothesized underlying information-processing deficits. Such research should help to uncover abnormalities in the circuitry underlying the processing of emotion and cognition in patients with mood and anxiety disorders, and should also provide new targets for novel therapeutic approaches.

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