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ORIGINAL ARTICLE

Cognitive Deficits in Depression and Functional Specificity of Regional Brain Activity

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Abstract The growing literature on cognitive deficits in depression is considered in light of regional brain activity as well as comorbid anxiety and life stressors. Cognitive impairments associated with depression are reviewed, with an emphasis on various aspects of executive function such as memory, attention, and problem-solving. These deficits are related to patterns of brain activity observed in prefrontal, anterior cingulate, and parietal cortices, as well as in subcortical regions. Evidence for the largely unexplored role of environmental stressors in depression and their impact on cognition and brain function is also examined, and promising avenues of additional research are noted. In addition to promoting interdisciplinary research, systematically assessing variables such as cognitive performance, comorbid anxiety, and relevant stressors may elucidate distinct patterns of brain function and cognition that could inform prevention and intervention.

Keywords Depression · Anxiety · Stress · Executive function · Prefrontal cortex · Anterior cingulate cortex

Introduction

Key features of depression, according to the DSM-IV-TR (American Psychiatric Association, 2000), are feeling down and losing a sense of pleasure from things that were previously enjoyed. Consistent with this emphasis, depression is conventionally viewed as primarily an emotional condition, characterized by a variety of negatively valenced feelings, such as sadness, anhedonia, hopelessness, and worthlessness. Less obvious, but equally disabling, is a constellation of cognitive biases and impairments that

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often accompany the emotional symptoms, including deficits in memory, attention, and problem-solving (Keller, Isaacks, Wesemann, Gergen, & Miller, 1999; Marx, Claridge, & Williams, 1992; Mohanty & Heller, 2002). These biases and impairments are associated with a range of negative affective experiences, from experimentally induced sadness to clinical depression, and have a significant and detrimental impact on many activities of daily living. In addition, these cognitive characteristics have been hypothesized to play a role in the susceptibility to and maintenance of depression (Gibb, Alloy, Abramson, Beevers, & Miller, 2004; Riso et al., 2003; Scher, Ingram, & Segal, 2005).

We and others have argued that the cognitive characteristics associated with depression reflect patterns of activity in specific regions of the brain (Heller & Nitschke, 1997; Henriques & Davidson, 1991; Nitschke, Heller, Etienne, & Miller, 2004; Papousek & Schuelter, 2003). In general, greater activity in a brain region is associated with better performance on the cognitive functions localized to that region, and reduced activity is associated with poorer performance (with some exceptions: for review, see Heller, Nitschke, & Lindsay, 1997). Accordingly, an understanding of the brain regions involved can enhance understanding of the ways in which depression may influence cognition. The present article reviews research on the cognitive characteristics that accompany depression and examines the neural circuitry hypothesized to be associated with them.

Evidence is also reviewed indicating that these patterns of brain activity and their cognitive and emotional correlates are influenced by environmental factors such as child abuse and neglect. Although many studies have investigated abnormal brain function in individuals with depression, very few have investigated the specific environmental factors that may be associated with patterns of abnormal brain function. Repeatedly experiencing stressful life events likely contributes to the manifestation of depression, particularly in individuals with a genetic predisposition (Caspi et al., 2003; Kendler et al., 1995). The brain mechanisms that instantiate this relationship may be inferred from a substantial literature indicating that particular cortical and subcortical brain regions are affected by stressful life events. These findings are discussed in the context of a social agenda supported by neuroscience research that has implications for practice and research in prevention and intervention.

As categorically defined by the DSM-IV-TR, Major Depressive Disorder (MDD) requires the presence of at least five of nine characteristic symptoms, thus allowing for heterogeneity in the presentation of symptoms and in associated functional impairment. There has been extensive debate as to whether depression is best defined as taxonic, dimensional, or both (Angst & Merikangas, 2001; Flett, Vredenburg, & Krames, 1997). Considerable evidence indicates that conceptualizing depression as a dimensional construct is consistent with the variety of cognitive and negative affective experiences that are observed in research and clinical settings (Angst & Merikangas, 2001; Flett et al., 1997; Gibb et al., 2004; Lewinsohn, Solomon, Seely, & Zeiss, 2000; Prisciandaro & Roberts, 2005).

Conceptualizing depression as a dimensional construct fosters the integration of findings from research that has involved participants who experience a range of symptoms (with varying levels of severity) and also a range of negative affective traits and states. Some studies have required participants to meet DSM-IV-TR criteria for mood disorders such as MDD or Dysthymia, whereas others have focused on participants selected on the basis of the presence of subthreshold depressive symptoms. Some research paradigms have experimentally induced negative affect. Across these diverse

approaches, impaired cognitive processes are consistently observed in individuals who experience periods of negatively valenced emotional experience (Burt, Zembar, & Niederehe, 1995; Nitschke et al., 2004; Rogers et al., 2004). Furthermore, there is converging evidence of consistent patterns in at least some cognitive deficits. Moreover, there is some evidence that the severity of depression is associated with the extent of cognitive deficits (for review see Austin, Mitchell, & Goodwin, 2001). Despite the impressive evidence demonstrating an association between particular cognitive impairments and negative affect, the DSM-IV-TR criterion that refers to cognitive function in MDD is very general (''diminished ability to think or concentrate, or indecisiveness, nearly every day''). The present review suggests that it should be possible to generate a set of criteria that would reflect cognitive symptoms more precisely.

It is important to note that a variety of factors that contribute to variability in symptom presentation can also influence the manifestation of cognitive impairment in depressive disorders, including age, presence of psychotic features or mania, subtype of depression, severity, and medication status (Austin et al., 2001; Mohanty & Heller, 2002; Porter, Gallagher, Thompson, & Young, 2003; Purcell, Maruff, Kyrios, & Pantelis, 1997). These factors may all influence brain mechanisms that mediate cognitive performance and ultimately should be taken into account to construct detailed profiles of likely impairments. The present article focuses on brain mechanisms associated with unipolar depression and relies on theoretical perspectives that emphasize common deficits in certain functions (e.g., executive function) across age and etiology (Heller, 1990; Heller, Etienne, & Miller, 1995; Heller & Nitschke, 1997; Heller, Koven, & Miller, 2003).

Cognitive characteristics associated with depression have been linked to patterns of brain activity in specific regions of the brain. Brain activity can be measured in a variety of ways, and different approaches have been pursued in the investigation of depression. Fruitful approaches include utilizing lesion or stroke data or EEG, MEG, fMRI, PET, and neuropsychological testing. Converging evidence suggests that there is a bilateral decrease in prefrontal cortex (PFC) activity in depression (Heller & Nitschke, 1997). Superimposed on this decrease is an asymmetry with the right more active than the left hemisphere (Henriques & Davidson, 1991; for review, see Coan & Allen, 2004). In addition, there appears to be a decrease in activity in right posterior cortex (Deldin, Keller, Gergen, & Miller, 2000; Heller, Nitschke, Etienne, & Miller, 1997; Henriques & Davidson, 1990; Keller et al., 2000) and in dorsal anterior cingulate cortex (ACC) (Pizzagalli et al., 2001) and an increase in the activity of the limbic system (Mayberg, Keightley, Mahurin, & Brannan, 2004; Mayberg & Fossati, in press).

Depression and cognition

Numerous empirical and review articles have investigated the link between brain activity and cognitive function in depression. In general, depression has been associated with difficulties in memory, attention, and problem-solving, all of which depend heavily on aspects of executive function that have been associated with PFC activity. Researchers have observed that depression is associated with a general reduction in the ability to perform cognitive tasks, and several theories argue that cognitive resources are depleted in depression (Mathews & MacLeod, 1994). Instead of a reduction in capacity, Hertel and colleagues provided evidence that individuals with depression have difficulties initiating efficient cognitive strategies but perform normally if cued or primed in advance

(Hertel, 1994; Hertel & Gerstle, 2003; Hertel & Hardin, 1990; Hertel & Rude, 1991). These findings suggest that the fundamental problem is one of strategic deployment of processing resources, rather than the extent of effort put forth, consistent with the idea that the fundamental deficit lies in the domain of executive function, for which PFC is prominent.

Executive function

Executive function is known to depend on anterior regions of the brain (Banich, 1997; Heller & Nitschke, 1997) and encompasses judgment, planning, abstract thinking, metacognition (''thinking about thinking''), cognitive flexibility (e.g., choice of strategy), inhibition, verbal fluency, initiative, and the ability to direct behavior in a goal-directed manner. Examples include the ability to shift response set and modify strategies in task performance (Cicerone, Lazar, & Shapiro, 1983), the evaluation of a situation and the use of cues and extra information in the environment to guide behavior (Alivisatos & Milner, 1989), and the ability to monitor behavior or performance accurately (Luria, 1966).

In a review of studies that investigated performance on various facets of executive function in depression, Rogers et al. (2004) identified consistent impairments across domains of executive function. People with depression performed more poorly on tests of verbal fluency, planning (e.g., as measured by the Tower of London test), inhibition (e.g., as measured by the Stroop Color-Word test), and almost universally on set-shifting (e.g., as measured by the Wisconsin Card Sort test). However, according to Rogers et al. (2004), the impairments did not appear to follow a clear pattern with regard to subtype of depression, severity, or medication status. Several factors may make it difficult to discover consistent patterns. Multiple strategies can be used to perform the neuropsychological tests that are typically used to measure executive function (e.g., Elfgren & Risberg, 1998). Furthermore, studies may vary in severity, subtype, and medication status of depressed participants, and each of these may be differentially related to cognitive function and associated patterns of brain activity. Specific patterns of function and dysfunction may emerge more reliably when depression is subtyped on the basis of homogenous symptoms, severity, and medication status. An important issue that has been a focus of our research, not identified by Rogers et al. (2004), is the considerable but variable comorbidity of depression with anxiety.

Of critical importance, very few studies measure and report the amount of comorbid anxiety in their samples. We have repeatedly demonstrated that different types of anxiety and depression are associated with different patterns of brain activity, in conjunction with different physiological and psychological manifestations (Heller et al., 1995; Heller et al., 1997; Heller et al., 2003; Keller et al., 2000; Nitschke, Heller, Palmieri, & Miller, 1999).

The presence of comorbid anxiety has been shown in some cases essentially to cancel out the effects of depression on neuropsychological performance (Heller et al., 1995) or to have a nonadditive effect (Keller et al., 2000). The failure to separate anxiety types and depression experimentally or statistically (see Keller et al., 2000; Miller & Chapman, 2001) makes it impossible to determine whether observed patterns of performance or physiology are specific to depression, or a particular type of depression, regardless of the range or severity of psychopathology in the samples. Thus, comorbid anxiety may account for a considerable portion of the cross-study variability in reported executive function impairments in individuals with depression. We have suggested (e.g., Nitschke,

Heller, & Miller, 2000; Nitschke et al., 2004) that, when the noise introduced by unassessed, comorbid anxiety is successfully addressed, executive function impairments specific to depression can account for many of the cognitive deficits that have been identified in the domains of memory, attention, and problem-solving.

Memory

People with depression show various memory deficits, such as problems with autobiographical remembering (Williams & Broadbent, 1986; Williams & Dritschel, 1988; Williams & Scott, 1988), episodic memory recall (Cabeza, Locantore, & Anderson, 2003), and working memory (Elliott et al., 1996). A meta-analysis synthesizing 147 recall and recognition studies in clinically depressed and nondepressed samples revealed a significant, stable association between depression and memory impairment (Burt et al., 1995). Furthermore, the review showed that memory impairment in depression is linked to particular aspects of memory. Specifically, depression is associated with deficits on explicit but not implicit memory tasks. It is also associated with a tendency to remember negative material better than positive material.

Heller and Nitschke (1997) argued that deficits in executive function may account in large part for the observed impairments in memory. Individuals with depression often demonstrate difficulties initiating cognitive strategies that enhance their ability to process and remember information (Ellis, 1991; Ellis & Ashbrook, 1988; Hertel & Rude, 1991). Many studies have shown that depressed individuals are more likely to show deficits on effortful or controlled tasks such as recall of information than on recognition tasks or tests of implicit memory (Denny & Hunt, 1992; Hertel & Hardin, 1990; Hertel & Milan, 1994; Ilsley, Moffoot, & O'Carroll, 1995; Roy-Byrne, Weingartner, Bierer, Thompson, & Post, 1986). As mentioned above, Hertel (1994) proposed that attentional resources are sufficient in depression but that the initiative to control them is missing. This model is strongly supported by studies showing that use of attentional control strategies such as focusing attention on the task and monitoring relevance of the past can result in improvement of memory deficits in depression (Hertel, 1994). Similarly, Weingartner, Cohen, Murphy, Martello, and Gerdt (1981) reported that depressed individuals failed to use encoding operations that are useful in reorganizing input to facilitate later recall. Related to this finding, Nitschke et al. (2004) found that bilateral prefrontal activation preceding the presentation of a sad narrative predicted better recall of the narrative content in controls, but not in a group with high scores on depression measures. This may indicate an impairment that is associated with diminished initiative in allocating attentional resources for using strategies that improve memory (Hertel & Hardin, 1990) or problems with sustained attention (Burt et al., 1995). The failure to efficiently encode information has also been observed in individuals during a period of remission from MDD (Weiland-Fiedler et al., 2004). In addition to problems with executive function, it is plausible that the lack of engagement in effortful memory strategies is associated with a lack of motivation to employ strategic encoding processes (Burt et al., 1995).

Attention

Impaired attention has been considered to be one of the cardinal features of clinical depression. Decreased concentration is part of the cognitive criterion for a diagnosis of depression in the DSM-IV-TR. In a thorough review of the attention literature in

depression, Mialet, Pope, and Yurgelun-Todd (1996) reported that impairment was consistently observed on tasks such as simple and choice reaction time (Cornell, Suarez, & Berent, 1984), the Digit Symbol Subtest (Austin et al., 1992), the Continuous Performance Task (Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989), and sustained attention tasks (Mialet et al., 1996). Additionally, it appears that problems with attention continue while depression is in remission. Weiland-Fiedler et al. (2004) reported prominent, ongoing problems with sustained attention in individuals with MDD after the major depressive episode remitted.

As with memory, many of the attentional deficits in depression may have their roots in fundamental impairments in executive function. Individuals with depression often show an impaired ability to suppress external and internal distractors, resulting in inappropriate allocation of resources. The increased interference seen on attentional tasks requiring distractor inhibition such as the color-word Stroop task (Raskin, Friedman, & DeMascio, 1982; Trichard et al., 1995) led Lemelin, Baruch, Vincent, Everett, and Vincent (1997) to hypothesize that there is a difficulty in inhibiting distractors in depression. Support was provided for this hypothesis by a study using a negative priming paradigm that demonstrated that depressed patients had reduced ability to inhibit features of a distractor (MacQueen, Tipper, Young, Joffe, & Levitt, 2000). Inhibition of distractors on the color-word Stroop task has been shown to be dependent on PFC (e.g., Compton et al., 2003).

Despite the claim that attentional biases are more common in anxious individuals and memory biases more common in depressed individuals (Dalgleish & Watts, 1990; Matthews & MacLeod, 1994), a number of studies have reported an attentional bias for negatively valenced stimuli in depression. Studies have shown that both depressed nonpatients and clinically depressed patients took longer to name the colors of tachistoscopically presented, depression-relevant words than neutral words (Gotlib & Cane, 1987; Gotlib & McCann, 1984). Furthermore, this bias was not evident after symptom recovery. Depressed individuals were also slower on a reaction time task when the distractor words were negative than when they were positive or neutral (Ingram, Bernet, & McLaughlin, 1994; McCabe & Gotlib, 1993). Similarly, depressed individuals are faster to detect a dot that replaces negative stimuli (e.g., words and emotion faces) than a dot that replaces positive stimuli (Gotlib, Krasnoperova, Neubauer Yue & Joorman, 2004; Mathews, Ridgeway, & Williamson, 1996). However, a number of studies have failed to find an association between depression and attentional bias to negative stimuli (Clark, Teasdale, Broadbent, & Marti, 1983; Mogg, Bradley, Williams, & Matthews, 1993; Mogg, Millar, & Bradley, 2000). Due to substantial comorbidity between depression and anxiety, observed attentional biases may be due to accompanying (but often unassessed) anxiety rather than to depression (Heller et al., 1997, 2003; Nitschke et al., 1999).

Event-related brain potential (ERP) studies have also demonstrated deficits in attentional processing in depression, and evidence suggests that the abnormalities are not as simple as a lack of motivation or a failure to perform the task. For example, N2b, an ERP measure of selective attention, was enhanced in nonpatients with dysthymia and anhedonia (Fernandes et al., 1999; Giese-Davis, Miller, & Knight, 1993) and in patients with major depression (Keller et al., 1999). Due to substantial comorbidity of anxiety and depression, Mohanty et al. (2000) used self-report scales that have been shown to distinguish among anxiety, depression, and negative affect (Nitschke, Heller, Imig, McDonald, & Miller, 2001) to determine which among these is involved in the attentional deficit measured by N2b enhancement. Results indicated that it was negative

affect, not something specific to depression or anxiety, that carried the N2b enhancement.

Problem-solving

Difficulties in problem-solving have been commonly reported in individuals with depression. Clore, Schwarz, and Conway (1994) observed that individuals who experience sad affect have problems generating novel responses. Related to these findings, Conway and Giannopoulous (1993) showed that, during an information processing task, individuals with depression utilized a smaller amount of available information and failed to manipulate information efficiently. Individuals with depression have also been reported to use less effective problem-solving strategies, evidenced by difficulties developing alternative solutions, and foreseeing potential obstacles when solving hypothetical personal problems (Marx et al., 1992). Again, these findings can largely be accounted for by deficits in executive function.

Visuospatial function

Depression has been associated with deficits in aspects of cognitive function that have been associated with posterior right-hemisphere cognitive specializations (for review, see Heller et al., 1997). Individuals with depression show impaired performance on right-hemisphere tasks such as judgment of emotional faces, line orientation, three-dimensional constructional praxis, spatial association learning, and subtests of the WAIS-R performance scale (Asthana, Mandal, Khurana, & Haque-Nizamie, 1998; Flor-Henry, 1976; Keller et al., 2000; Silberman & Weingartner, 1986). Furthermore, severity of depression has been found to correlate with performance on tests of visuospatial function such as spatial span, pattern recognition, and delayed matching (Elliott et al., 1996).

Emotional reactivity

Beyond these deficits in visuospatial processing and in executive functions that impair memory, attention, and problem-solving, depression has been associated with abnormalities in a variety of functions mediated by subcortical regions that may not be characterized as cognitive processes per se but that do have a significant and far-reaching impact on cognitive performance. These include, for example, reactivity to potential threat stimuli, which is likely to be mediated in part by activity in amygdala (Bradley, Cuthbert, & Lang, 1999; Garavan, Pendergrass, Ross, Stein, & Risinger, 2001; LeDoux, 1998, 2000).

Neural correlates of cognition in depression

Prefrontal cortical function

Important aspects of executive function are implemented in PFC, which is often implicated as a hypoactive region in individuals with depression. Given that a majority of studies have shown that increased activity in a brain region is associated with better performance on tasks specialized to that region (for review, see Heller et al., 1997), we

and others have argued that reduced PFC activity can account for the deficits in executive functions seen in depression (Heller & Nitschke, 1997; Rogers et al., 2004).

A consistent finding in depression has been a decrease in activity in PFC, particularly in the dorsolateral, ventrolateral, and ventromedial areas (but see reports of normal and hyperactivity in Brody et al., 2001 and Drevets et al. 1992, and evidence that patients with relatively active rostral ACC show better recovery according to Mayberg & Fossati, in press, and Pizzagalli et al., 2001). In the hemodynamic neuroimaging literature, the findings are generally bilateral, but EEG studies have often reported an asymmetry in favor of relatively greater right- than left-hemisphere activity. In recent work, we have argued that the lack of findings in favor of prefrontal asymmetries in the hemodynamic neuroimaging literature is an artifact of the pervasive use of inappropriate analytic strategies that are not sensitive to the presence of asymmetries (Herrington et al., 2005; Herrington, Koven, Miller, & Heller, 2006). Integrating these two literatures, we hypothesized that depression is generally characterized by a pattern of bilateral decrease in activity with a superimposed asymmetry (for reviews, see Heller & Nitschke, 1997; Herrington et al., 2005; Nitschke et al., 2004). We have emphasized the role of dorsolateral PFC in the cognitive deficits reviewed above. However, we and others have suggested that different regions within PFC may be involved depending on the degree of comorbid anxiety and the specific symptom presentation (Brody et al., 2001; Heller et al., 2003; Rogers et al., 2004).

A recent fMRI study demonstrates that the bilateral decrease and superimposed asymmetry in frontal activity can be found when manipulating emotional valence even in a nonclinical sample. Using a variant of the color-word Stroop paradigm involving emotional words, Herrington et al. (2005) found a bilateral decrease in dorsolateral PFC activity for unpleasant compared to pleasant words. Furthermore, having faster overt responses for unpleasant than for pleasant words was associated with greater bilateral DLPFC decrease. Given that the emotional Stroop task requires inhibiting word meaning in favor of word ink color, these data suggest that emotional valence and executive function can be tightly coupled, even when the valence manipulation is relatively mild and task-irrelevant. Furthermore, within this same frontal region, greater left than right DLPFC activity was found for pleasant than for unpleasant words. This asymmetry parallels numerous EEG studies comparing depressed and nondepressed individuals (Davidson, 2004), although it was the first fMRI replication of it using a direct, robust test of asymmetry. These fMRI data clearly demonstrate the coupling of emotional valence to executive function and prefrontal activity, but more focused research is needed to examine the respective roles of left and right frontal cortex in specific executive functions and how these roles may be related to affect.

Left PFC has been implicated in studies of semantic memory recall (Levine et al., 1998), verbal memory (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994), and word retrieval (Rösler, Heil, & Henninghausen, 1995). These studies all involved manipulating verbal information, which is quite important for autobiographical recall and contextualizing autobiographical memories within a narrative framework. However, Cabeza et al. (2003) argued that, regardless of stimulus type (verbal or nonverbal), an important factor in understanding the role of left PFC is the proportion of production versus monitoring operations in a given task. They suggested that left PFC is more engaged with semantically guided information production processes than is the right hemisphere. The right hemisphere, in their view, is more involved in monitoring and veridical checking processes. Accordingly, Cabeza et al. (2003) provided PET data showing left PFC more active during recall tasks than during recognition tasks and right

PFC more active during recognition tasks than during recall tasks. These results are consistent with their hypothesis, since recall tasks are thought to involve self-initiated search and word-production processes, whereas recognition tasks generally involve monitoring and evaluating stimuli. Cabeza al. (2003) suggested that the production-monitoring hypothesis is congruent with the notion that the left hemisphere is responsible for creating inferences and interpolating available information to make generalizations, whereas processes implemented in the right hemisphere are often more literal in interpretation of information.

Consistent with Nolde, Johnson, and Raye (1998) and Cabeza et al. (2003), Buckner and Wheeler (2001) hypothesized that frontal cortex initiates monitoring of information during recall and is also responsible for the implementation of the memory recall process. This notion was echoed by Fletcher, Frith, and Rugg (1997), who highlighted the role of PFC both in adoption and maintenance of retrieval strategies and in verifying or monitoring the products of retrieval.

On a broad conceptual level, then, left PFC appears to be associated with the capacity to construct meaning and generate inferences that extend beyond the information presented. Meta-cognitive processes such as strategizing, initiation, and self-cuing contribute to the production of novel information and appear to be left-specialized (e.g., Banich, 2004; Nolde et al., 1998). These specializations are consistent with both theory and data indicating that individuals with depression show general deficits in initiative and in strategic use of information as a result of a failure to activate left PFC (e.g., Heller & Nitschke, 1997; Nitschke et al., 2004).

Not only are the executive processes specifically associated with left PFC dysfunctional in depression, it appears that executive processes associated with right PFC are also impaired. However, less is known about the distinct functions associated with this region of the brain. Recent neuroimaging findings have demonstrated an important role for right PFC in inhibitory control (Aron, Robbins, & Poldrack, 2004; Fassbender et al., 2004; Garavan, Ross, & Stein, 1999). For example, this region appears to be involved in the suppression of unwanted memories (Anderson et al., 2004), a finding with particular relevance to depression, where negative information is more readily recalled than positive, in contrast to nondepressed people (DeMonbreun & Craighead, 1977; Gotlib, 1983). In addition, Nitschke et al. (2000) highlighted a special role for this region in a threat-response network, consistent with the emphasis of others on the role of right PFC in withdrawal processes (e.g., Davidson, 1992). Nolde et al. (1998) theorized that right PFC is involved in tasks such as refreshing activated information, shifting among concepts, and identifying relationships among concepts (also see Heller, 1994). Although few studies have specifically investigated the relationship between reduced activity in this region and performance on regionally specialized tasks in depressed people, it may be predicted that they will display deficits in these domains.

Anterior cingulate cortical function

Depression has also been associated with changes in activity in ACC (for review, see Mayberg & Fossati, in press; Rogers et al., 2004; Ebert & Ebmeier, 1996). ACC is believed to be involved primarily in action-oriented evaluation processes such as monitoring for the occurrence of conflict within the attentional network (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998; MacDonald, Cohen, Stenger, & Carter, 2000; Milham et al., 2001). Researchers have subdivided ACC functionally into rostral and dorsal subdivisions. The dorsal subdivision has been shown to play an

important role in a variety of cognitive functions, including response selection, competition monitoring, error detection, and working memory. Reduced activity in depression has been particularly localized to dorsal ACC (Pizzagalli et al., 2001). In contrast, the rostral subdivision (sometimes referred to as the emotional or affective subdivision) is involved in the assessment of the salience of emotional information as well as the regulation of emotional responses. There is considerable research indicating that this subdivision is activated by affect-related tasks, during both emotional processing in normal controls and symptom provocation in psychiatric disorders (see Bush, Luu, & Posner, 2000, for review). For this subdivision of ACC, studies have found that higher activation in depression predicts positive treatment response (e.g., Mayberg et al., 1997; Pizzagalli et al., 2001; Wu et al., 1999). Mayberg and colleagues have suggested that a dorsal brain system including dorsolateral PFC, dorsal ACC, inferior parietal lobe, and striatum controls the cognitive symptoms of depression. A ventral system that includes the hypothalamic-pituitary-adrenal (HPA) axis, insula, rostral ACC, and brainstem is hypothesized to be involved in vegetative and somatic symptoms. The increased rostral ACC activity in depression and its relationship to improvement has been interpreted as an adaptive, compensatory mechanism in response to being depressed that increases the likelihood of remission (Pizzagalli et al., 2001). Of note, recent data from our laboratory (Engels et al., in press) revealed a deficit in rostral ACC responses associated with anxious apprehension and anxious arousal (psychometrically distinct types of anxiety that we have found to show different patterns of brain activity, e.g., Nitschke et al., 2000). In addition, other research has indicated less rostral ACC activity in individuals with high anxiety levels (Bishop, Duncan, Brett, & Lawrence, 2004), so it remains to be seen whether ACC dysfunction is specific to depression.

Posterior right-hemisphere function

In addition to evidence implicating the role of the PFC in depression, posterior right-hemisphere disturbances are thought to be associated with cognitive impairments in depression. Some EEG studies have shown evidence of decreased brain activity over right posterior cortex, consistent with relatively poor performance on neuropsychological tests of face processing and other posterior right-hemisphere specialized tasks (Deldin et al. 2000; Henriques & Davidson, 1990; Keller et al., 2000; Heller et al., 1997). These findings have not been consistently replicated (for review see Heller, 1990). However, as noted above, the right posterior region has also been implicated in anxiety. Our neuropsychological model of emotion and psychopathology predicts, and data indicate, that the direction of activation in this region is opposite for depression and anxiety (for review, see Heller, 1993; Heller et al., 2003). Confirmation of this model for posterior regions has been provided by several studies with clinical and nonclinical samples (Bruder et al., 1997; Keller et al., 2000). Therefore, inconsistent results regarding activity in this region for individuals with depression may reflect un-assessed comorbid anxiety.

Research has indicated that posterior regions of the right hemisphere are involved in facial processing, and individuals with depression often experience impairments processing facial information (for review, see Deveney & Deldin, 2004). Individuals with depression showed a reduction in the N200 component of the ERP recorded over the right posterior cortex in response to facial stimuli but not to words (Deldin et al., 2000). This result may be interpreted as a failure to efficiently activate the right posterior cortex in response to facial stimuli. Difficulties processing facial stimuli and

understanding nonverbal facial cues may be related to social skill problems that are sometimes observed in people with depression (Deveney & Deldin, 2004).

Subcortical function

In addition to prefrontal and parietal cortical regions, subcortical regions such as the amygdala and hippocampus have been implicated in depression (Abercrombie et al., 1998; Drevets et al., 1992; Mayberg et al., 2004; Mayberg & Fossati, in press). Both structures are functionally interconnected with PFC and are thought to be associated with aspects of motivation and emotional processing (e.g., Davis, 1997; LeDoux, 1995; Mayberg et al., 2004). Problems with cognitive and emotional regulatory processes in depression may be related to impaired cortical and subcortical function as well as dysfunctional circuitry among various brain regions. In particular, it has been argued that decreased cortical activity is associated with increased activity in limbic regions (Anand et al., 2005; Mayberg & Fossati, in press). These findings extend to orbitofrontal cortex (for review, see Rogers et al., 2004), a component of the limbic system (Barbas, 1995). The general pattern of decreased dorsolateral PFC and increased amygdala, orbitofrontal, and rostral ACC activity in depression is consistent with a reduction in cognitive control and executive function and a concomitant exaggerated response to threat.

Animal and human studies using a wide range of techniques provide support for the role of amygdala in responding to emotional stimuli. The amygdala is considered to play an important role in processing negatively valenced information (Abercrombie et al., 1998; Davis & Whalen, 2001; Garavan et al., 2001; Whalen, 1998) and is also recruited in the evaluation of internal and external stimuli in terms of their motivational and emotional significance (e.g., Cahill, Roozendaal, & McGaugh, 1997; Davidson & Irwin, 1999; Lang, Davis, & Öhman, 2000; LeDoux, 1995). Because of numerous pathways from sensory areas to amygdala and from amygdala to cortex and brainstem, the amygdala is strategically placed for monitoring the environment for salient stimuli and modifying behavior accordingly (Anderson & Phelps, 2001; Davis, 1997; Kapp, Whalen, Supple, & Pascoe, 1992; LeDoux, 1996). Additionally, amygdala involvement has been demonstrated in response to visual presentations of threatening words, pictures, fearful vocalizations, unpleasant olfactory and gustatory stimuli, and in memory for emotional information and in the enhanced perception of emotionally salient information (for review see Phillips, Drevets, Rauch, & Lane, 2003).

Although it is well established that the amygdala is involved in processing emotional information generally, very few studies have investigated how the amygdala is related to cognition in individuals with depression. The majority of studies investigating the amygdala and depression have focused on volume and atrophy of the amygdala (e.g., Caetano et al., 2004; Frodl et al., 2003; Hastings, Parsey, Oquendo, Arango, & Mann, 2004; Sheline, Gado, & Price, 1998) without assessing associated cognitive function. However, Siegel, Steinhauer, Thase, Stenger, and Carter (2002) reported a more sustained amygdala response to negative information in a depressed sample than in nondepressed controls. This finding is consistent with the notion that decreased activity in the PFC is associated with a disinhibition of activity in limbic regions, leading to exaggerated, or less regulated, emotional responses.

Whereas the amygdala is central to emotional evaluation of fear and threat-related sensory stimuli, the hippocampus mediates contextual aspects of emotional evaluation (Grace, 2000; Grace & Moore, 1998; Kim & Fanselow, 1992; Phillips & LeDoux, 1992, 1994). The hippocampus is involved in various forms of associative learning. It is

thought to play a selective role in memory, with involvement in relational or declarative memory as opposed to nondeclarative and procedural memory such as skills and habits, simple conditioning, and priming (Cohen, 1997; Eichenbaum, Otto, & Cohen, 1992, 1994; Squire, 1992). Declarative memory relies on the binding of different elements of an event. Patients with hippocampal damage fail to exhibit long-term memory of relations among the constituent elements of scenes (Ryan, Althoff, Whitlow, & Cohen, 2000; Ryan & Cohen, 2004). Magnetoencephalography has recently demonstrated a specific hippocampal deficit in relational binding in schizophrenia (Hanlon et al., 2005). Electrophysiological studies in animals show that neuronal activity in hippocampus encodes relationships among important cues and objects in the environment (O'Keefe & Speakman, 1987). Anatomical and physiological research indicates that the hippocampus possesses the connections and neural mechanisms required to support relational binding (Cohen, 1997). Due to inputs from and projections to various neocortical and limbic regions, hippocampus is in a key position to receive and bind information about stimuli present in the environment, the spatial and temporal relations among them, and the events in which they play significant roles.

Given that individuals with depression often demonstrate considerable memory impairment (Cabeza et al., 2003; Elliot et al., 1996; Williams & Broadbent, 1986; Williams & Dritschel, 1988), many researchers have investigated hippocampal abnormalities in individuals with depression, with an emphasis on hippocampal volume (e.g., Bremner et al., 2000; Hastings et al., 2004; Sheline, Wang, Gado, Csernansky, & Vannier, 1996; Vythilingam et al., 2004). Results from this research are inconsistent, reporting both smaller and normal volumes (for review see Vythilingam et al., 2004). Similar to investigations of the amygdala, little has been done to investigate how hippocampal function is related to cognitive ability in depression. Vythilingam et al. (2004) replicated the phenomenon of memory impairment (specifically, verbal memory impairment) in individuals with MDD but reported normal hippocampal volume for MDD participants without a history of childhood abuse or other comorbid axis I disorders. Their study showed an improvement in memory following fluoxetine treatment, which led the authors to infer that functional changes likely occurred in the hippocampus despite no evidence for structural changes. More research at the intersection of affective and cognitive neuroscience is clearly needed to understand the relationship between regional subcortical structural volume, function, and cognition in individuals with depression.

The emphasis in the present review is on the functional specificity of regional brain activity in depression. However, as Mayberg has highlighted (e.g., Mayberg et al., 2004, in press), it is clear that the brain regions that have been identified as important in depression are all components of an integrated network that mediates both cognitive/emotional and physiological phenomena and that has many degrees of freedom for abnormal operation. The diverse configurations of symptoms that the DSM-IV-TR permits within a given diagnostic category may arise from diverse patterns of psychological and physiological processes. Understanding depressive cognition, its psychological mechanisms, and it biological implementation in detail will require the interpretation of regionally specific anomalies in the context of that network.

Depression, cognitive neuroscience, and environmental influences

Depression is often presaged by negative life stressors, and the recurrent experience of stressors fosters an increased vulnerability to depression, especially in individuals with a

genetic predisposition (Caspi et al., 2003; Hollon, 1995; Kendler et al., 1995; Kessler, 1997). Individuals with clinically significant depression show different configurations of symptoms that likely reflect distinct past experiences. Varied combinations of psychosocial environmental factors may contribute to different pathways to depression, and these pathways may have distinct etiologies (Kaufman, Plotsky, Nemeroff, & Charney, 2000). Research that investigates the relationship between childhood experiences and adult mental health indicates that negative stressors such as disruptions in parenting (e.g., parental death or divorce), abuse, neglect, poor attachment, and high levels of familial conflict may create vulnerabilities to physical and mental health problems that emerge during adulthood (Gutman & Nemeroff, 2003; Luecken & Lemery, 2004; Heim & Nemeroff, 1999).

Some stressors, such as childhood abuse, have been correlated with the frequency of symptoms, the severity of depression, and the early onset of depression (Gutman & Nemeroff, 2003; Heim & Nemeroff, 1999). An emerging body of research investigates how childhood stressors are associated with observed changes in brain function and related cognitive and affective problems. Stressors experienced during childhood may be associated with abnormal long-term changes in neurotransmitter systems and related brain regions and functions (Heim, Owens, Plotsky, & Nemeroff, 1997; Kaufman et al., 2000; Teicher et al., 2003). Abnormal activity and structure in PFC and subcortical regions such as hippocampus and amygdala have been associated with the occurrence of environmental stressors (Teicher et al., 2003; Vythilingam et al., 2002). The brain regions affected by life stressors, therefore, substantially overlap with those implicated in depression. Investigating how environmental stressors contribute to the development of depression from an affective neuroscience perspective provides additional insight into etiological factors that may relate to abnormal brain functioning associated with depression.

Prefrontal cortical function and stress

A number of researchers have implicated PFC in response to childhood stressors (Kaufman et al., 2000; Teicher et al., 2003). High levels of stress are associated with a reduction of rostral ACC activity (Arnsten, 1998; Lawrence & Grasby, 2001; Shin et al., 2001). Other research suggests that the lateralization of brain function is susceptible to early environmental stressors (Teicher et al., 2003). Teicher and his colleagues have argued that traumatic events such as abuse and neglect are associated with problematic development of the left hemisphere (Teicher, Andersen et al., 2004; Teicher, Dumont et al., 2004). Teicher, Andersen et al. (2004) reported that children with a history of abuse demonstrated electrophysiological abnormalities in the left hemisphere relative to children without a history of abuse. Neuropsychological testing corroborated impaired left-hemisphere function. MRI studies have suggested volume reductions in some left-hemisphere subcortical brain structures in individuals with a history of abuse (Bremner et al., 1997). As previously mentioned, left PFC is implicated in depression, and left prefrontal disturbances are associated with a pattern of executive function impairments specific to depression. Most studies investigating left-hemisphere activity and associated neuropsychological impairments have not assessed history of childhood abuse and other environmental stressors. It is likely that in many cases left-hemisphere abnormalities in depression are correlated with the experience of early environmental stressors that precede the development of depressive symptoms.

Subcortical regions, endocrine function, and stress

In addition to PFC, many of the subcortical regions associated with depression are implicated in responses to stress. These regions have been related to endocrine function and the release of neurotransmitters and hormones in response to environmental stressors and are thought to be associated with the pathophysiology of mood disorders (Heim et al., 2000; Heim & Nemeroff, 2001). Stress can have enduring effects on early brain development, when neural systems are highly responsive to environmental modifications that can permanently alter set points or wiring (Luecken & Lemery, 2004).

The HPA-axis and associated corticotrophin-releasing factor (CRF) are implicated in the response to stress in humans and animals. One of the most robust findings in biological psychiatry is that people with depression have increased HPA-axis activity and thus hypersecrete cortisol (Heim & Nemeroff, 1999; Gutman & Nemeroff, 2003; Young, Abelson, & Cameron, 2004). PFC, amygdala, and hippocampus are all areas where CRF receptors are located (Fuchs and Flugge, 2003; Gutman & Nemeroff, 2003; McEwen, 2000).

Onset of depression is frequently preceded by environmental stressors (Kessler, 1997). Early childhood stress may be associated with an impairment in the ability to regulate cognition and associated affective experiences in the face of stress. For example, individuals raised in a particularly stressful environment may be more likely to appraise subsequent ambiguous situations as threatening (Chen & Matthews, 2003), preferentially recruiting some brain structures (e.g., right hemisphere regions involved in threat monitoring) and suppressing others (PFC regions involved in executive function). McEwen (2000) hypothesized that individuals who are more reactive to stress will be repeatedly exposed to more cortisol, leading to a progression of neuronal structural changes that could have deleterious effects on cognition such as atrophy and permanent neuronal loss. In support of McEwen's (2000) conjecture, MRI studies of hippocampus volume have indicated that atrophy correlates with duration of depression (Kaufman et al., 2000; but see McNally, 2003).

Stress, brain function, and cognition

Research documenting the association between stress, brain function, and cognitive impairment is sparse outside of the human-factors literature. Vythilingam et al. (2002) found that depressed women with a history of childhood abuse had reduced hippocampal volume in comparison to depressed women without a history of childhood abuse. If individuals with and without abuse have different psychological and biological profiles within the same mood disorder, it would appear imperative to assess childhood abuse history in such work.

The diathesis-stress framework presented here sets an agenda for further research investigating the relationship of stress to brain development and function and its concomitant impact upon cognitive processes. However, such research presents certain challenges. Reports of childhood stress may be inaccurate for a variety of reasons. Additionally, individuals with depression often show memory deficits (Cabeza et al., 2003; Elliott et al., 1996). Of particular relevance, studies of autobiographical memory have indicated that individuals with depression often lack specificity in their reports of autobiographical events (Williams & Broadbent, 1986; Williams & Dritschel, 1988). Moreover, the experience of a depressed mood has been associated with the tendency to

report more past stressful events (Cohen, Towbes, & Flocco, 1988). Reports of the timing of stressors and onset of depression may be especially unreliable. Finally, Kessler (1997) highlighted the contextual nature of research investigating environmental stressors. He noted that individuals experience the world differently, and thus the meaning of a given event may differ across people. Of course, numerous other issues such as type of stressor, duration of stressor, number of co-occurring stressors, age during onset of stressor(s), and genetic factors contribute to different behavioral and physiological outcomes.

It is increasingly becoming appreciated that not everyone who experiences negative childhood stressors will develop problems later in life. Childhood stress creates a vulnerability to the development of affective disorders, but there are protective factors that compensate for the vulnerability. The developing brain is characterized by a significant degree of plasticity, and it continues to develop and change throughout adulthood. For example, Kaufman et al. (2000) suggested that subsequent caregiving involving positive support and attachment can moderate the effects of early stress. The role of stress in risk for depression and its impact on cognition and relevant brain mechanisms clearly warrants more research.

Conclusion

Depression is associated with myriad factors contributing to diverse etiologies and manifestations, including contributions from stress and consequences for brain plasticity and cognitive performance. Despite the number of possible configurations of genetic load, environmental stressors, protective factors, and measurement error, stress and depression appear to affect similar brain regions and functions involving cortical and subcortical structures such as PFC, amygdala, and hippocampus. Echoing McEwen (2000), research is needed to better understand how the endocrine system functions in relation to brain activity in depression and how this is manifested in cognitive problems.

The present review has emphasized conventional but underestimated issues of diagnostic heterogeneity and comorbidity as barriers to discovery of consistent patterns of relationships among specific cognitive deficits and specific regional brain activity differences in depression. Less conventionally, it should also be noted that affective neuroscience, relatively young as an identified subdiscipline, has been strikingly neglectful of potential environmental stress as a mediator or moderator of relationships among depression, brain structure and function, and cognition. A critical payoff for studies investigating cognition, stress, and associated brain function in depression will be translation of findings into effective prevention and intervention programs. Such programs will surely encompass multiple systemic levels, including community, school/workplace, and home, rather than focusing on a decontextualized individual. There is every reason to think that affective neuroscience research will eventually inform work at all of these levels and profoundly enhance psychological and physical welfare. Conversely, it may prove crucial to include direct brain measures in some community prevention and intervention studies. A convergence of these diverse perspectives and their respective methods will contribute to explaining and ameliorating depression.

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