CHAPTER 24

Trait Anxiety, Neuroticism, and the Brain Basis of Vulnerability to Affective Disorder

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Studies of the brain basis of "normative" or "healthy" processing of emotionally salient stimuli have flourished over the last two decades. An initial focus on regions implicated in the detection of emotionally salient stimuli (Morris et al., 1996; Whalen et al., 1998) has broadened to include discussion of mechanisms supporting regulatory functions (Bishop, Duncan, Brett, & Lawrence, 2004; Davidson, 2002; Ochsner, Bunge, Gross, & Gabrieli, 2002; Kim, Somerville, Johnstone, Alexander, & Whalen, 2003; Phelps, Delgado, Nearing, & LeDoux, 2004). Running in parallel to this literature, psychiatric imaging studies have described alterations in brain function across a wide range of anxiety and depressive disorders (for reviews and meta-analyses see Etkin & Wager, 2007; Ressler & Mayberg, 2007; Shin & Liberzon, 2010; Stein 2009). The study of the brain mechanisms underlying vulnerability to disorder has, for some reason, fallen outside of the primary spotlight. We argue that work of this nature is critical to bridging studies in healthy volunteer and patient groups and to identifying the pathways through which risk to affective illness is conferred.

Understanding the brain basis of vulnerability to affective disorder goes hand in hand with a focus on individual variation and, in particular, trait differences in the mechanisms supporting the detection and controlled processing of emotional stimuli. How do we study trait differences in vulnerability to anxiety and depressive disorders and try to unpack the brain mechanisms though which these might act? A number of approaches have been adopted, with both shared and unique advantages and limitations.

Studies of the brain basis of vulnerability to affective disorders typically rely on recruiting nonclinical volunteer samples and then regressing scores on self-report measures of trait affect or experience of disorder-related symptomatology against indices of brain function or structure. It is important to remember that this approach is correlational in nature, and hence no conclusions can be drawn about the direction of causality. For example, if we find that, in a student

population, elevated scores on a measure of neuroticism are linked to poor frontal recruitment, this could equally plausibly reflect individuals scoring high on neuroticism being less able to cope with environmental stress, resulting in diminished frontal function; individuals with compromised frontal function being more likely to develop a neurotic personality style; both elevated neuroticism and compromised frontal function stemming from a primary disruption to neurotransmitter function; or all of these factors in combination. There are also important methodological issues pertaining to good practice in conducting correlational analyses of brain activity, which are discussed briefly later in the chapter.

A shared positive feature of studies in this area is that constructs such as trait anxiety or neuroticism can be examined as continuous factors, facilitating exploration of their linear and nonlinear relationships with regional brain activity. This allows for a more complex and potentially accurate picture to be drawn than one that solely uses DSM categorical assessments of the binary presence or absence of a given disease state; the latter "diagnostic" approach faces limitations arising from difficulties in applying categorical cutoffs, high comorbidity between many anxiety and depressive disorders, and poor diagnostic reliability (Brown & Barlow, 2009).

Studies of the brain basis of vulnerability to affective disorder can be categorized according to the measure used to assess individual differences in trait affective style. Arguably there are three main categories. The first involves measures derived from the clinical literature and normed for use in nonclinical populations to assess individuals' tendency to show disorder-related symptomatology, affective and cognitive styles. A prominent example is the Spielberger State Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), widely used in studies of the cognitive correlates of trait anxiety within nonselected student samples. The second

category uses measures taken from the personality literature, such as the Neuroticism scale from either the Eysenck Personality Questionnaire (EPQ; Eysenck & Eysenck, 1975) or the NEO Personality Inventory (Costa & MacCrae, 1992). The third category focuses on genetic markers that differ among individuals (functional polymorphisms with two or more common variants) and that have been linked to differences in affect-related behaviors in humans and other species. In this chapter, we focus on the first two of these categories, commenting only briefly on the third (for further discussion, see Chapter 25). The majority of studies on the brain basis of vulnerability to affective disorder falling within these categories have used measures of trait anxiety (category 1) or neuroticism (category 2). We use these examples to explore the state of the field as it stands and to address outstanding questions for future research.

Trait Anxiety and Neuroticism: Indexing Vulnerability to Affective Disorders through Self-Report

The trait subscale of the Spielberger State Trait Anxiety Inventory (Spielberger et al., 1983) is a widely used measure of trait propensity to anxiety. It has been shown to have good concurrent validity, with patients with anxiety disorders (ADs) scoring higher on the STAI trait subscale than controls (Bieling, Antony, & Swinson, 1998). Although fewer studies have examined predictive validity, pretrauma STAI trait scores have been found to predict levels of posttraumatic stress disorder symptomatology after trauma (Weems et al., 2007). However, the STAI has been criticized for having poor discriminative validity, with individuals with major depressive disorder (MDD) also showing elevated scores on the trait subscale (Mathews, Ridgway, & Williamson, 1996). One possibility is that this low discriminant validity reflects a poor choice of anxiety-specific items for the scale. A

second is that there is genuine shared variance underlying vulnerability to both ADs and MDD.

Not only are STAI trait scores elevated in patients with MDD but scores on this and other anxiety scales, such as the Taylor Manifest Anxiety Scale (Taylor, 1953), have also been found to correlate highly with scores on self-report measures of depressive symptomatology; for example, the Beck Depression Inventory (BDI; Beck Ward, Mendelson, Mock, & Erbaugh, 1961) and personality indices of neuroticism (Luteijn & Bouman, 1988). Neuroticism is characterized by a propensity for negative affect (Watson & Clark, 1984). This trait, measured by widely used instruments such as the NEO Personality Inventory and the Eysenck Personality Questionnaire, has emerged over the last century as one of the most widely studied personality traits (Costa & MacCrae, 1992; Eysenck & Eysenck, 1975; John, 1990). The relationship with vulnerability to affective disorder has arguably been investigated more thoroughly for neuroticism than for any other dimension of personality (Brown, 2007; Brown & Rosellini, 2011, Kendler, Gardner, Gatz, & Pedersen, 2007). There is strong evidence to support not only shared variance but also common genetic influences among neuroticism, anxiety disorders, and depressive disorders (Hettema et al., 2008; Kendler et al., 2007).

A likely interpretation of the high correlations observed among indices of anxiety, depression, and neuroticism is that they tap, at least in part, into a common underlying trait (Figure 24.1). According to the popular tripartite model, anxiety and depression not only have a shared component – a propensity to negative affect (which arguably maps on to the construct of neuroticism) – but also unique components of anxious arousal and anhedonia, respectively (Clark & Watson, 1991). This conception has led to the development of the Mood and Anxiety Symptoms Questionnaire (MASQ; Watson & Clark, 1991), which aims to measure both these shared and unique components. Unfortunately the MASQ focuses on "state"
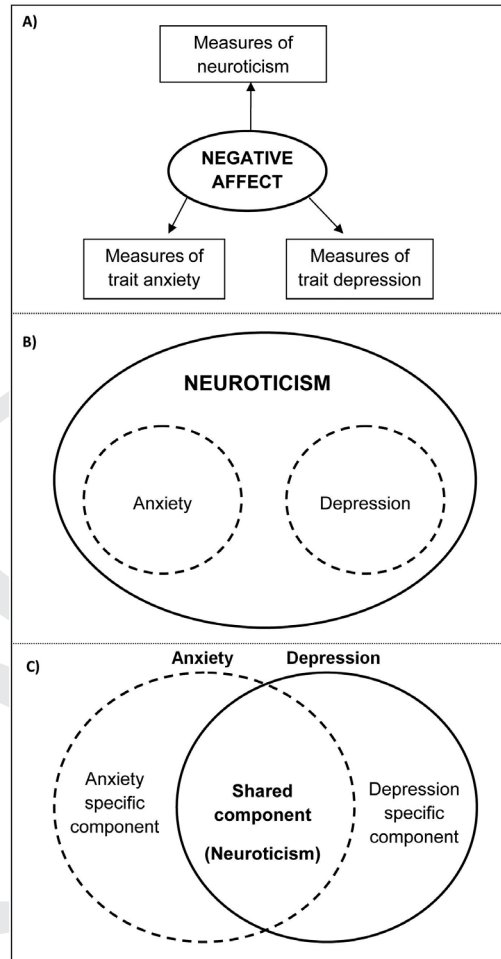

Figure 24.1. Anxiety, neuroticism and depression: overlapping constructs? Three alternate models. (A). Self-report measures of anxiety, depression, and neuroticism could potentially all be tapping the same single underlying trait. (B). Alternatively, anxiety and depression might be separate components of the broader trait of neuroticism. In keeping with this perspective, the NEO-PI-R includes anxiety and depression as subfactors, or "facets," of neuroticism (Costa & McCrae; 1995). (C). A third theoretical stance, represented by Clark and Watson's (1991) tripartite model, asserts that anxiety and depression not only have a shared component of negative affect or general distress (potentially corresponding to the construct of neuroticism) but also unique components of "anxious arousal" (autonomic hyperactivity) and "anhedonic depression" (low positive affect).

or current mood levels and not on trait differences between individuals. Indeed, the scarcity of trait measures of the propensity to anxiety and depression poses a major difficulty for researchers aiming to investigate the brain basis of these tendencies. Not only the MASQ but also the major depressive inventories – including both the BDI and the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff 1977) – focus on current levels of symptomatology. This may explain why several imaging studies have used neuroticism as a proxy for vulnerability to depression, but doing so inevitably hinders attempts to disentangle the extent to which neuroticism, trait anxiety, and trait depression involve disruption to common or unique mechanisms at either a cognitive or systems (regional brain structure and function) level of analysis.

Studying Affective Trait-Related Differences in Cognitive and Brain Function: Lessons from the Last Decade

Over the last 10 years, much progress has been made in using neuroimaging techniques to study individual differences in neurocognitive function; recent challenges and developments set the stage for equivalent progress over the next decade. In the early 2000s, neuroimaging studies of personality led to a conceptual shift in the approach to the investigation of human brain function. These studies argued that individual variation need not simply be treated as a source of noise in group studies of "normative" neurocognitive function but that between-subject differences could be studied in their own right by examining associations between traits such as extraversion or neuroticism and regional brain function (for a review see Canli, 2004).

Although these studies were groundbreaking in advancing the investigation of individual differences in neurocognitive function, as with many first steps in a new field, several of these studies have since been

subject to criticism (Vul, Harris, Winkielman, & Pashler, 2009). However, many of the issues raised – pertaining to whole-brain correlational analyses, insufficient correction for multiple comparisons, and biased selection of regions of interest – can be avoided if investigations of differences in regional brain function associated with personality indices or trait affective style are constrained to ones that specifically test theories derived from the cognitive or social psychological literature. An elegant argument for this approach was initially made by Kosslyn et al. (2002). In this article, Kosslyn and colleagues take the proposal put forward by Underwood (1975) – that naturally occurring individual differences can be used to test psychological theories and to reveal the structure of psychological processes, potentially providing greater insights than group-based methods – and argue that the same logic can be applied to the use of individual differences to investigate the biological mechanisms that underpin cognitive processes. The authors make the case that there is natural variation around every central tendency, that individuals may differ in the efficiency and recruitment of mechanisms (which can be studied at various levels including both regional brain activation and cognitive processing), and that pooling information across individuals may be uninformative or misleading. They also point out that the main dangers of unguided correlational studies can be avoided by theoretically grounding the study design and the analysis and interpretation of results, with alternate theoretical explanations of observed correlations being used to generate further hypotheses than can in turn be tested. In the sections that follow, we illustrate how the approach proposed by Kosslyn and colleagues can be applied, using the example of studies that have investigated the brain basis of the association between trait anxiety and attentional capture by threat. In addition, we explore if we can ascertain whether neuroticism shows a similar, potentially common, relationship to the function of these mechanisms.
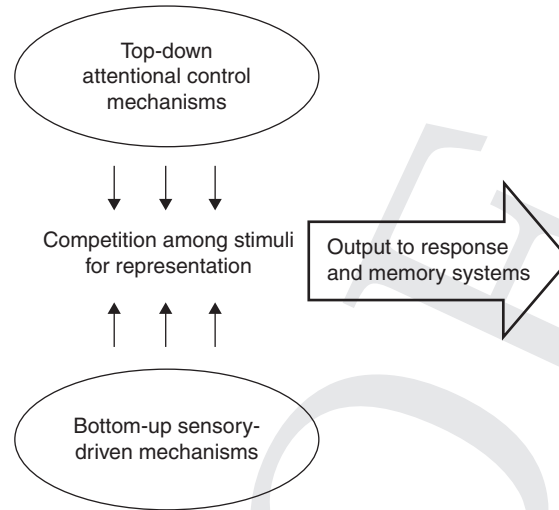
Figure 24.2. According to the biased-competition model of selective attention (Desimone & Duncan, 1995; Kastner & Ungerleider, 2000), top-down attentional control mechanisms, which favor task-relevant stimuli, and bottom-up sensory-driven mechanisms, sensitive to stimulus salience, jointly determine which stimuli are selected for further processing. Adapted from Bishop (2008) and Kastner and Ungerleider (2000), with permission.
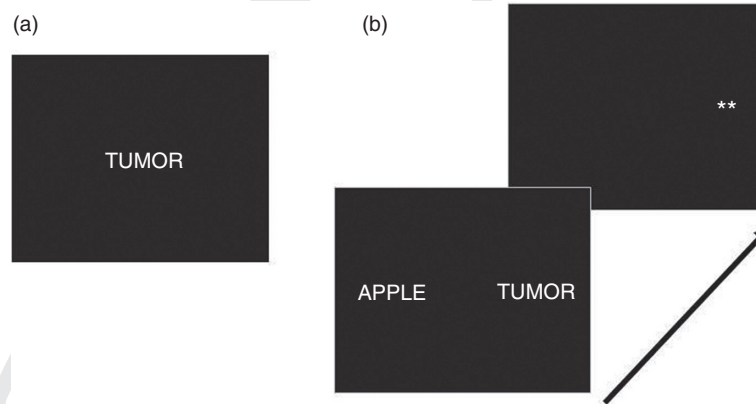

Figure 24.3. Two widely used paradigms in the attention to threat literature. (A) In the Emotional Stroop task, participants are asked to name the font color of a word (here green/gray), ignoring its meaning, which can be either threat-related or neutral in valence. High trait anxious subjects show RT slowing for threat-related words. (B) In the dot probe task, participants are presented with two words, followed by a "probe" (the two asterisks presented here) in the location of one of the words. They are typically asked either to indicate when the probe appears or to specify its orientation. On key trials, one word is threat- related, and the other is neutral. High trait anxious individuals show RT speeding when the location of the probe was previously occupied by a threat word (as in the example here), suggesting that attention was allocated to the location of the threat word.

Trait Anxiety, Neuroticism, and Threat-Related Biases in Selective Attention: Cognitive Models and Findings

Both AD patients and high trait anxious participants show elevated attentional capture by threat-related stimuli (Mathews & Mackintosh, 1998). According to biased competition models of selective attention, attentional competition is influenced both by "bottom-up" sensory mechanisms that prioritize the processing of salient stimuli and by "top-down" attentional control mechanisms that support the processing of task-relevant stimuli (Figure 24.2; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Stimulus valence – the extent to which a given stimulus is threat or reward related – is an important dimension of stimulus salience. A number of selective attention tasks have been adapted to examine how stimulus valence, especially threat-relatedness, influences attentional competition. Two notable examples are the Emotional Stroop and probe detection tasks (Figure 24.3). In the Emotional Stroop task, participants name the ink color of a stimulus word while ignoring its semantic content. On this task, high trait anxious individuals show slower color naming of threat-related words than emotionally neutral words; in low trait anxious individuals this slowing is reduced or absent (Richards & Millwood, 1989). In the probe detection task, participants are presented with two words or pictures (e.g., faces) followed by a single dot or pair of dots in the position previously occupied by one of the two stimuli. Here, high trait anxious individuals are faster to detect the presence of a single dot or to determine the orientation of a pair of dots, when the dot probe is presented in the position previously occupied by a threat-related stimulus (Macleod & Mathews, 1988).

These findings have informed cognitive models of anxiety that extend the biased competition model of selective attention to specifically deal with attentional capture by threat-related stimuli (Mathews & Mackintosh, 1998; Mogg & Bradley, 1998). These models typically propose that anxiety acts by amplifying the signal from a bottom-up preattentive threat detection mechanism that biases attentional competition in favor of threat-related stimuli. When these stimuli are distracters (non-task-relevant), this is held to interfere with the processing of target stimuli, as indexed by slowed reaction times (RTs) and/or elevated error rates. These models have not, in the most part, argued for disrupted top-down or controlled processing of threat-related stimuli in anxiety.

A number of studies have used variants of the probe detection task to examine whether attentional biases are also associated with elevated neuroticism ("N") scores. These have produced rather mixed results. Reed and Derryberry (1995) found evidence for a correlation between N scores and attentional bias toward negative trait adjectives previously rated as self-applicable. However, this correlation was only observed at one of three alternate adjective-probe stimulus-onset asynchronies (500 ms, not 250 ms or 750 ms). In addition, Chan, Goodwin, and Harmer (2007) and Rijsdijk et al. (2009) failed to find any relationship between neuroticism and performance on probe detection tasks using social threat words and subliminally presented threat-related faces, respectively. Differences among these studies in the choice of stimuli, stimulus onset asynchrony SOA, and neuroticism scale (EPQ versus NEO) further complicate interpretation of these findings.

Interestingly, the limited evidence for an association between neuroticism and attentional bias toward negatively valenced stimuli parallels similarly mixed findings within the subclinical depression literature. Here, two studies using the Emotional Stroop task have reported increased RT slowing for color naming of negatively valenced words as a function of scores on the Beck Depression Inventory (BDI). These effects were strongest in participants with elevated BDI scores at two time points a year apart (Williams & Nulty, 1986) and were not found when a depressed mood was induced in par-

ticipants with low BDI scores (Gotlib & McCann, 1984), potentially suggesting the role of an enduring trait conferring vulnerability to depression, rather than simply state affect. Other studies have found no relationship between individual differences in subclinical levels of depression and attentional bias toward negative or threat-related stimuli across both the Emotional Stroop and probe detection tasks (Bradley, Mogg, Falla, & Hamilton, 1998; Gotlib, MacLachan, & Katz, 1988; Hill & Dutton, 1989; Hill & Knowles, 1991; Macleod & Hagan, 1992).

One possibility is that a partial correlate of depression scores, such as trait anxiety levels, rather than depression itself, might be responsible for the intermittently reported attentional interference effects. A similar argument can be made for neuroticism. The NEO measure of neuroticism comprises different subfacets, one of which is especially related to anxiety and another to depression (Costa & MacCrae, 1992; see also Figure 24.1). Variability among studies in the items that high-N participants endorse might explain the occasional but inconsistent findings of attentional biases reported by studies using this measure.

It is also possible that multiple mechanisms contribute to attentional capture by threat stimuli – with trait anxiety, neuroticism, and depression potentially sharing a common relationship with one of these mechanisms but differing in their association with others. The most obvious candidate mechanisms are those involved in bottom-up responsivity to threat versus top-down attentional control. Investigation of the brain basis of these mechanisms opens up a new door for examining how different trait characteristics are linked to the function of these component processes. Specifically, it is possible to build on what is known about the function of different brain regions to explore whether trait anxiety is associated with increased activation of brain mechanisms involved in processing stimulus threat value, with impoverished recruitment of brain mechanisms involved in attentional control, or with altered function of both processes. We can also explore

whether neuroticism is linked to a similar pattern of task-specific hyperactivity and hypo-recruitment. Studies that have begun to address this question are reviewed next.

From Networks to Modules and Back Again

The late 1930s through to the early 1950s saw the advent of theories that proposed that networks of brain regions including areas such as the hippocampus, cingulate gyrus, amygdala, and orbital frontal cortex were responsible for emotional processing (MacLean 1949; Papez, 1937). Support for the "Papez circuit" and "limbic system" was countered by criticisms that these accounts were more descriptive than functional and lacked a clear rationale for inclusion of certain regions and the exclusion of others (for more extensive discussion of these criticisms, see Chapter 9 in Gazzaniga Ivry, & Mangun, 2009; Early neuroimaging studies of emotion conducted in the late 1990s and early 2000s took a more modular approach. Much research was focused on the amygdala and its role in the detection or evaluation of threat (Morris et al., 1996; Vuilleumier, Armony, Driver, & Dolan, 2001; Whalen et al., 1998, 2004) Indeed, a number of studies from the later part of this era used scan parameters that focused data acquisition on a narrow slab of slices covering the amygdala but omitting much of the rest of the brain.

In contrast, within the last 5 to 10 years, there has been an increasing focus on the interplay of regions involved in the evaluation of threat stimuli with those that enable the regulation of emotional state and physiological fear responses, the (re)appraisal of stimuli, and the control of attentional focus (Bishop, Duncan, Brett, & Lawrence, 2004a; Kim et al., 2003; Ochsner et al., 2002; Phelps et al., 2004). This focus has been accompanied by a shift from examining brain regions in isolation and toward conceptualizing regions as nodes within interconnected networks, the activation of which varies with task engagement and may be meaningful even at "rest" (Deco, Jirso, &

McIntosh, 2011). Neuroimaging investigations of the association between trait anxiety and brain function and structure have similarly evolved across this time period. In the remaining sections of this chapter, we examine what these studies can tell us about the brain basis of the association between trait anxiety and attentional capture by threat, the shared or distinct relationship with neuroticism, and the potential common underpinning of function across other domains of emotional processing.

Amygdala and Frontal Mechanisms underlying Attentional Capture by Threat: Hyper- and Hypo-Activity Linked to Trait Anxiety

Based on findings from the basic neuroscience literature, a relatively widely held view (which has recently come under renewed scrutiny; Pessoa and Adolphs, 2010; see also Chapter 15) is that a direct subcortico-thalamo-amygdala pathway facilitates the preattentive processing of threat-related stimuli (LeDoux, 2000; Tamietto & de Gelder, 2010). In line with this position, a number of neuroimaging studies conducted in the early 2000s reported that the amygdala response to threat-related stimuli such as fearful faces is not modulated by the focus of spatial attention (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Vuilleumier et al., 2001). These findings lent support to the proposition that the amygdala might provide the biological underpinning, or instantiation, of the preattentive threat detection mechanism described in cognitive models of anxiety. According to this proposal, amygdaloid activation might influence the competitive success of threat-related stimuli in winning attentional resources through a gain function analogous to that held to underlie the facilitation of the processing of targets by top-down attentional control (see Chapter 14).

Further support for this position appeared, initially, to be provided by findings that individuals with elevated anxiety levels show a stronger selective amyg-dala response to threat-related distracters (Bishop, Duncan, & Lawrence, 2004). However, in that study, it was state rather than trait anxiety that showed a relationship to the amygdala response to unattended threat stimuli. In addition, these results do not necessarily indicate that high anxious individuals show an increased *preattentive* amygdala response to threat-related distracters. An alternate possibility is that attentional resources may not have been fully occupied by the primary task, with attentional "spillover" facilitating the processing of threat-related distracters. Indeed, it has been demonstrated that when the perceptual demands or "load" of the main task is increased, a differential amygdala response to threat-related versus neutral distracters is no longer observed (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002); between-participant differences in the amygdala response to threat distracters as a function of anxiety also being eliminated (Bishop, Jenkins, & Lawrence, 2007).

An interesting model, of value in conceptualizing these findings, is the load theory put forward by Lavie (e.g., Lavie, 2005). Lavie argues that the debate between "early" and "late" accounts of selective visual attention (i.e., whether or not the processing of certain stimulus characteristics is obligatory and unconstrained by attentional resources) may be resolved by taking into account the perceptual load of the task at hand and allowing for two separate stages of attentional competition. According to this model, there is, first, a stage of early perceptual competition. The processing of distracters terminates at this stage when the perceptual load of the primary task is high. Second, under conditions of low perceptual load, competition is held to occur for further processing resources, including the initiation of behavioral responses, with active recruitment of control mechanisms being required to inhibit the processing of salient distracters and support task-related processing. Lavie's hybrid early/late model has primarily been used to account for findings showing that increasing perceptual load reduces or eliminates the processing

of affectively neutral salient distracters, such as moving dot patterns, lexical stimuli that promote competing responses to that required by the current target, and colorful or novel scenes (Lavie, 2005; Rees, Frith, & Lavie, 1997). It is, however, interesting to speculate whether the finding that the amygdala response to threat distracters is diminished under high load (Bishop et al., 2007; Pessoa et al., 2002) might be consistent with amygdaloid processing of threat-related stimuli being subject to similar perceptual processing limitations that have been found to affect the processing of other classes of salient visual stimuli.

An alternate theoretical stance to that put forward by Mathews and Mackintosh (1998) is that elevated trait anxiety is associated with impoverished recruitment of the frontal mechanisms required for task-focused attentional control. If high trait anxious participants show impaired recruitment of attentional control mechanisms, this could result in increased "capture" of attentional resources by threat-related distracters. As just outlined, Lavie argues that the active recruitment of attentional control mechanisms to support the processing of targets and inhibit the processing of distracters is particularly required under conditions of low perceptual load to prevent salient distracters from receiving further processing. In support of this claim, Lavie cites findings that groups characterized by weakened attentional control – specifically the elderly and children – show particularly large response competition effects under low perceptual load conditions (Huang-Pollock, Carr, & Nigg, 2002; Maylor & Lavie, 1998). In an interesting parallel, elevated trait anxiety was found to be associated with diminished activation of the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and anterior cingulate cortex (ACC) in response to threat distracters under conditions of low but not high perceptual load (Bishop et al., 2007). This finding suggests that trait anxiety might be linked to impoverished recruitment of frontal regions required for

attentional control under task conditions where these mechanisms are needed to regulate trial-by-trial fluctuations in processing competition from emotionally salient distracters.

This raises two further questions. First, can we say anything about the relative attentional control functions of the lateral prefrontal and anterior cingulate cortical regions shown to be under-recruited by high trait anxious individuals? Second, if trait anxiety is linked to difficulties in the use of these frontal regions to regulate attention, will they also be apparent when distracter salience is unrelated to threat value? In regard to the former question, it has been suggested that specific subregions of the prefrontal cortex may play differing roles in top-down attentional control, with the ACC involved in detecting the presence of competition for processing resources and the lateral prefrontal cortex (LPFC) responding to increased expectation of processing competition by augmenting top-down control to support the processing of task-relevant stimuli (Botnivick, Cohen, & Carter, 2004; see Figure 24.4 for illustration of the regions concerned). Evidence for this account has primarily come from studies using response-competition tasks with affectively neutral stimuli (e.g., Carter et al., 2000; Macdonald, Cohen, Stenger, & Carter, 2000), including ones that manipulate the frequency, and hence the expectancy, of high competition trials (Carter et al., 2000). Through application of an equivalent frequency manipulation to a task requiring attentional control over threat distracters, it is possible to investigate whether ACC and LPFC regions show parallel differential responses to unexpected (infrequent) and expected (frequent) threat-related distracters, respectively. This was indeed found to be the case (Bishop, Duncan, Brett, & Lawrence, 2004). Further, the results of this study indicated that individuals with high levels of anxiety showed impoverished recruitment of both these mechanisms (state anxiety analyses were reported, similar results were observed with trait anxiety, unpublished data).
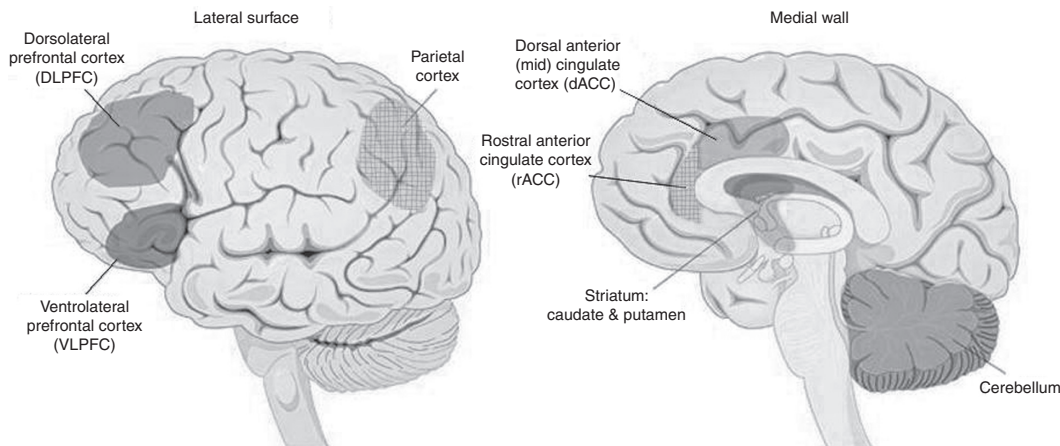
Figure 24.4. Frontal brain regions implicated in attentional regulation of emotionally and non-emotionally salient stimuli include the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex, (VLPFC), rostral anterior cingulate cortex (rACC), and dorsal anterior (mid) cingulate cortex (dACC). Subgenual anterior cingulate cortex is not shown here. Adapted with permission from Bush, 2010.

Intriguingly, a more recent study has produced findings that are discrepant from both those of Bishop and colleagues (2004) and those from the earlier response-competition literature. Using a "face/word" version of the Stroop task, Etkin, Peraza, Kandel, and Hirsch (2006) asked volunteers to indicate whether faces showed fearful or happy expressions while ignoring the word "happy" or "fearful" superimposed on each face. They reported that activation of the ACC, rather than the LPFC, increased when processing competition was expected (frequent face/word incongruent trials) and that LPFC activity increased when processing competition was infrequent or unexpected. One interesting difference from the study by Bishop, Duncan, Brett, and Lawrence (2004) is that in Etkin"s task, both the distracters and targets were emotionally valenced, with the valence of targets and distracters being balanced across "high-conflict" and "low-conflict" trials; those conditions differed instead in face/word congruence. It is difficult to disentangle effects of emotional congruency from response congruency in this design. However, this still does not easily explain why the conditions under which the LPFC and ACC were activated differed from those previously observed in both emo-

tional distracter and response-competition paradigms. One hopes that these discrepant findings will spark further research that may help resolve and unite these results and advance our theoretical understanding of the role of the ACC and LPFC in the detection and resolution of different types of processing competition.

A further point worth considering here concerns the role of rostral versus dorsal subdivisions of the ACC (see Figure 24.4). Early studies reported dorsal ACC activity when processing competition arose from response competition, and rostral ACC activity when processing competition was caused by the presence of emotionally salient but task-irrelevant distracters (Bishop, Duncan, Brett, & Lawrence, 2004; Bush, Luu, & Posner, 2000). This distinction is also apparent within the psychiatric imaging literature (Bush et al., 1999; Shin et al., 2001). However, more recently this distinction has been challenged by a range of studies suggesting a role for the dorsal ACC in emotional processing – not only in emotional distracter tasks but also in studies investigating the anticipation and experience of pain and the expression of conditioned fear (Bishop et al., 2007; Milad, Quirk, et al., 2007; see Shackman et al., 2011,

for a comprehensive review). This also calls for further investigation of the precise function of this region. The difference in nomenclature conventions used across groups and the changes in those terms across time complicate this investigation. In this chapter we follow the nomenclature convention introduced by Mayberg and colleagues (1999) and adopted in our earlier work (Bishop, Duncan, Brett, & Lawrence, 2004 , 2007) whereby rostral ACC excludes subgenual ACC (the region ventral to the corpus callosum). The subdivision referred to here as the dorsal ACC or dACC (see Figure 24.4) has elsewhere been renamed the dorsal anterior mid-cingulate gyrus since this term arguably reflects more accurately the region under consideration (Bush, 2010).

The second question raised above concerns the nature of the association between trait anxiety and the deficient recruitment of frontal attentional control mechanisms. Is this association specific to attentional control over threat, perhaps being secondary to hyper-responsivity of the amygdala to threat-related stimuli? Or does it reflect a more general dysregulation of frontal attentional function that is independent of amygdala responsivity to threat? The cognitive literature provides some suggestion that the latter might be the case, with findings linking trait anxiety to impoverished or inefficient attentional control (Derryberry & Reed, 2002; Eysenck, Derakshan, Santos, & Calvo, 2007). In a test of the hypothesis that trait anxiety is associated with reduced recruitment of frontal attentional control mechanisms even in the absence of threat-related stimuli, Bishop (2009) examined DLPFC recruitment while volunteers performed a response-competition task under conditions of low versus high perceptual load. High trait anxious volunteers showed reduced DLPFC recruitment to high response-competition trials under conditions of low but not high perceptual load, in line with the Lavie model and consistent with trait-anxiety-related dysregulation of frontal attentional mechanisms extending beyond the specific case of attentional control over threat. Further support for a threat-

independent relationship between trait anxiety and impoverished recruitment of frontal attentional control mechanisms comes from the ERP literature. Using an antisaccade task (where volunteers must saccade away from the position in which a cue is presented), Ansari and Derakshan (2011) found that high trait anxious individuals showed longer antisaccade latencies together with reduced frontocentral activity during antisaccade preparation.

The studies discussed here provide some initial evidence that trait anxiety is linked to impoverished recruitment of frontal regions important for attentional control both when processing competition is caused by threat-related distracters and when it is caused by response conflict. This raises the question of whether this deficient recruitment can be remediated by cognitive interventions such as attentional training. A number of early trials provide some initial hope that this might indeed be the case (Amir, Weber, Beard, Bomyea, & Taylor, 2008; Hakamata et al., 2010).

Although work reviewed here suggests a relationship between trait anxiety and frontal dysfunction in the absence of task-related differences in amygdala activity (Bishop, 2009), this leaves open the question as to whether trait anxiety is also linked to amygdala hyper-responsivity to threat in the absence of differential activation of frontal mechanisms. To address this question, we need to turn to tasks that require the relatively passive processing of threat-related stimuli in the absence of demands on attention or other executive processes. Surprisingly few such studies exist that meet the constraints of having examined amygdala function and also having measured individual differences in trait anxiety. In one early study, Etkin et al. (2004) reported that trait anxiety was associated with elevated amygdala responsivity to masked threat-related faces, but not to unmasked threat-related faces. In a second study, Stein, Simmons, Feinstein, and Paulus (2007) reported that elevated STAI trait scores were linked to greater amygdala activity during conditions requiring matching of facial emotions

than during conditions requiring matching of basic shapes.

One intriguing possibility is that an association between trait anxiety and amygdala responsivity to threat-related stimuli might primarily be seen when the stimuli are ambiguous or require some form of resolution of their threat value (Whalen, 2007). This is arguably more the case for masked than for unmasked threat-related faces and also potentially the case when different faces with varying emotional expressions need to be judged for their equivalence in expression. This is clearly a tentative hypothesis, and it remains to be more firmly established under precisely which conditions trait anxiety is linked to amygdala hyper-responsivity to threat. Furthermore, given the possibility that frontal mechanisms may be important for certain forms of ambiguity resolution (Kim et al., 2003; Nomura et al., 2003), it will also be important to confirm that trait-anxiety-related differences in amygdala responsivity to weak or ambiguous threat stimuli are not secondary to the differential recruitment of frontal mechanisms.

Neuroticism and the Brain Mechanisms Influencing Attentional Capture by Threat

As reviewed in previous sections of this chapter, in recent years an increasing number of studies have examined the relationship between trait anxiety and recruitment of the frontal and amygdaloid mechanisms implicated in attentional control over threat distracters. This makes it possible to start to ask relatively specific questions about which parts of the neural circuitry influencing attentional capture by threat show altered function in high trait anxious individuals. Although the corresponding literature on neuroticism is more limited, we can look at the initial studies available to begin to assess whether neuroticism and trait anxiety show similar relationships with regional brain function – as might be expected if they both represent the same single underlying construct – or whether neuroticism and

trait anxiety only partially covary in their relationship with the function of discrete brain mechanisms as might, for example, be predicted by Clark and Watson's tripartite model (see Figure 24.1).

At the time of writing, three studies have examined the correlates of neuroticism while participants perform fMRI tasks involving manipulation of selective attention and emotional stimuli. Two of the three – one using the Emotional Stroop task and the other the probe detection task – reported no significant association between neuroticism scores and regional brain activity during conditions of attentional competition from emotional stimuli (Amin, Constable, & Canli, 2004; Canli, Amin, Haas, Omura, & Constable, 2004). However, given that the sample size in each case was fairly small for a correlational study (12 or fewer subjects), it is difficult to draw strong conclusions from these null results.

In a subsequent larger study (n = 36), Haas, Omura, Constable, and Canli (2007) administered a Stroop-like task, similar to that of Etkin et al. (2006), in which trials differed in the emotional congruence of target words and the expressions of background faces. In this study, the words did not map directly onto the names of the facial expressions, thereby reducing the association between emotional incongruency and response conflict. Individuals with high neuroticism levels were found to show increased amygdala and subgenual anterior cingulate activity to trials with emotionally incongruent face/word pairs (collapsing positive-face/negative-word and negative-face/positive-word trials). This result is intriguing, but difficult to relate to findings from imaging studies examining the influence of trait anxiety on the neural mechanisms regulating selective attention to threat, because the task manipulation used by Haas and colleagues (emotional congruency) is not one of distracter threat-relatedness, being orthogonal to distracter valence. One possibility is that the heightened amygdala responsivity to emotionally incongruent stimuli in high-N individuals reported here might primarily reflect

sensitivity to stimuli that are ambiguous in their emotional significance, in line with the proposals put forward by Whalen and colleagues (Whalen, 2007).

To explore the "ambiguity sensitivity" hypothesis further, we review studies that have examined the influence of neuroticism on regional brain activity to emotional stimuli using passive viewing or cognitively undemanding tasks. Here, the question of interest is whether neuroticism is particularly linked to heightened amygdala responsivity to emotional stimuli when these stimuli are in some form ambiguous in their valence or threat-relatedness. Canli and colleagues reported that although the amygdala response to happy faces and positive images was predicted by extraversion, there was no relationship between neuroticism and amygdala responsivity to either negative emotional faces or negative emotional images (Canli et al. 2001, 2002). Similarly, Britton, Ho, Taylor, and Liberzon (2007) found no relationship between neuroticism and amygdala responsivity during the passive viewing of emotional images, facial expressions, and emotional films. Cremers et al. (2010) also found no relationship between neuroticism and the amygdala response to negative emotional faces during a gender discrimination task. The one exception is a study by Chan, Norbury, Goodwin, and Harmer (2009) that examined amygdala responsivity to fearful, happy, neutral, and morphed facial expressions during a gender discrimination task in individuals high and low in neuroticism. Here high N scores were associated with stronger amygdala activity to faces with expressions "morphed" partway between neutral and fear. It could be argued that these morphed facial stimuli are milder or more ambiguous in their threat value than the "fully" negative stimuli used in the other studies. However, this one finding does not permit any definitive conclusions to be drawn in favor of the "ambiguity" account without further empirical investigation.

It also remains to be established whether neuroticism is associated with impoverished recruitment of the frontal mechanisms supporting attentional control, during nonemotional task performance, in a similar manner to that observed for trait anxiety. There is little existing work that pertains to this issue. Using an oddball detection task, Eisenberger, Lieberman, and Satpute (2005) found that neuroticism was associated with reduced lateral prefrontal cortical and rostral ACC recruitment but increased dorsal ACC activity. Further detailed investigation of the relationship between neuroticism and recruitment of lateral frontal and anterior cingulate subregions is required to form a clearer picture of the commonalities and differences in the relationship between neuroticism and trait anxiety with regional brain function. In particular, as noted earlier, the precise role of the dorsal ACC in cognitive and emotional processing remains an issue under active debate.

It is hoped that this chapter has provided a flavor of how, in line with the case made by Kosslyn and colleagues, it is possible to conduct neuroimaging studies that may advance both our understanding of the brain mechanisms supporting attentional capture by threat and the relationship between trait anxiety and variation in the function of these mechanisms. Although there are fewer studies pertaining to neuroticism, the available studies serve to generate hypotheses that could form the basis of future research. The work reviewed here also raises questions as to the extent to which the association among trait predisposition to anxiety, amygdala hyperactivity, and frontal hypoactivity is dependent on task domain. Specifically, will the associations reported here also be observed in the context of performance of other tasks? Or even in the absence of any task? Studies pertaining to these questions are reviewed in the next two sections.

Trait Anxiety and Hyper-Amygdala and Hypo-Frontal Function: The Case of Fear Conditioning

The rodent fear conditioning literature provides strong evidence for the role of frontal

inhibitory influences on the amygdala in the attenuation of physiological and behavioral fear responses. Findings indicate that the amygdala is involved in the acquisition and expression of cued fear, with medial prefrontal cortical inputs inhibiting amygdala responsivity to conditioned fear stimuli (CSs) following extinction training (Maren & Quirk, 2004; Sotres-Bayon, Bush, & LeDoux, 2004). Human studies of conditioned fear have implicated similar circuitry with ventral medial regions of prefrontal cortex (vmPFC) facilitating context-specific recall of "CS – unconditioned stimulus (UCS) absent" associations formed during extinction training (Milad, Wright, et al., 2007; Phelps et al., 2004). Disruption to this circuitry has been documented in adults with posttraumatic stress disorder (Milad et al., 2009) and has been proposed to be of potential relevance to other anxiety disorders.

Recently, a handful of studies have begun to address whether trait vulnerability to anxiety is linked to altered functioning of this circuitry. Two initial studies reported that high trait anxious individuals showed elevated amygdala activity during extinction (Barrett & Armony, 2009; Sehlmeyer et al., 2011). Associations of extinction-related ACC activity with trait anxiety were also reported, but the directionality and specific locus of these effects did not replicate across the two studies. In recent work from our own lab, we found that elevated amygdala activity to a CS that predicted an aversive stimulus (the UCS) mediated the relationship between trait anxiety and the strength of initial acquisition of skin conductance responses to the predictive CS (Indovina et al., 2011). We also found that trait anxiety was negatively related to recruitment of ventral frontal regions linked to context-appropriate down-regulation of both cued and contextual fear *prior* to omission of the UCS. Hierarchical regression revealed that the relationship between trait anxiety and amygdala responsivity to the predictive CS was independent of that between trait anxiety and context-appropriate ventral PFC recruitment. It is interesting

to note that the medial and lateral regions of ventral prefrontal cortex reported in this study, the activation of which was associated with lower cued and contextual fear responses, overlap with those reported elsewhere to be activated during deliberate emotion regulation and affective stimulus reappraisal (see Chapter 16). Delgado and colleagues have further reported that activation of similar ventral PFC regions accompanies a reduction in conditioned fear, regardless of whether it occurs due to extinction or emotion regulation (Delgado, Nearing, LeDoux, & Phelps, 2008).

Together with the work reviewed earlier, these findings raise the possibility that individual variation in the recruitment of different subregions of frontal cortex may influence volunteers' ability to regulate their emotional responses to the anticipation of aversive stimuli, as well as their locus of attention when threat-related visual stimuli are presented. It is important to note that characteristics such as trait anxiety may map onto individual differences not only in the ability to regulate responses to aversive stimuli but also in the nature of the regulation strategy selected. Initial studies have begun to examine the brain regions activated by different emotion regulation strategies (e.g., Vrtička, Sander, & Vuilleumier, 2011), but as yet this work has not been integrated with investigation of individual differences in strategy selection or success in implementation.

Trait Vulnerability to Affective Disorder: What Might We Learn from Resting State Studies?

Recently, there has been increasing interest in whether the functional and structural connectivity between different brain regions may be informative even in the absence of task performance. One high-profile example is the recently launched Human Connectome Project, which aims to "comprehensively map human brain circuitry . . . using cutting-edge methods of noninvasive neuroimaging . . . yield[ing] invaluable

information about brain connectivity, its relationship to behavior, and the contributions of genetic and environmental factors to individual differences in brain circuitry" (http://humanconnectome.org/). This interest has been accompanied by a renewed emphasis on examining the function of brain regions in the context of the networks in which they are embedded as "nodes." It has also brought increased recognition of the need to study individual differences in order to understand normative brain function. It is beyond the scope of the current chapter to provide a comprehensive review of this literature (see Deco et al., 2011). We limit this section to a consideration of a few findings to date that may inform our understanding of the brain basis of trait vulnerability to affective disorder.

Roy et al. (2009) provided a detailed report of connectivity between the amygdala and other brain regions at rest. Positive correlations were found between resting state blood-oxygen-level-dependent (BOLD) activity in the amygdala and a number of brain regions, including the medial frontal gyrus, rostral ACC, dorsal ACC, insula, thalamus, and striatum. Negative correlations were also observed between the amygdala and areas, including the superior frontal gyrus, bilateral middle frontal gyrus, posterior cingulate cortex, precuneus, and parietal and occipital lobes. Further analyses were conducted to profile the connections of different amygdala subnuclei. These provided some suggestion of negative connectivity between the basolateral nucleus and central nucleus of the amygdala, as well as opposing patterns of connectivity between these subnuclei with the medial frontal gyrus and anterior cingulate cortex.

These findings are intriguing, but have several limitations. First, as noted by the authors, it is extremely difficult to specify amygdala subnuclei on echoplanar images. Although the probabilistic approach adopted by Roy and colleagues can provide an estimate, it is not clear if the level of accuracy achieved is sufficient for analyses

of this nature. Second, an issue that pertains to all resting state studies is that it is not clear how to interpret negative versus positive patterns of BOLD connectivity at rest. Are inhibitory connections at the neuronal level likely to be reflected as negative BOLD connectivity patterns? This is often assumed but far from established. A third problem is that it is unclear as to what criteria should be used for including or excluding regions in different "resting state" networks, raising spectra of the criticisms applied to the circuits of Papez (1937) and MacLean (1949). Specifically, with both seed-based and component-based approaches, the same question occurs as to what threshold to use – whether in terms of significance levels for whole-brain seed-driven analyses or the number of components for independent or principal-components-based analyses. As the field develops, the challenge will be to find ways to address these issues.

Building on the work by Roy and colleagues, Kim et al. (2011) examined the influence of individual differences in self-reported pre-scan anxiety on resting state functional connectivity. They reported that anxiety levels significantly modulated connectivity between the amygdala and only two regions. High state anxious individuals showed negative amygdala-vmPFC connectivity contrasting with positive functional connectivity between these regions in low state anxious individuals. In addition, they also showed an absence of the negative connectivity between the amygdala and dorsal medial PFC observed in low state anxious volunteers. The effects of anxiety in this study are particularly of interest because of their selectivity. In advancing our understanding of trait vulnerability to affective disorder, a limitation is that the primary analyses presented used state anxiety measures, with analyses using trait anxiety measures being described as showing similar but weaker trends. One hopes that future studies will further explore the extent to which anxiety-related variability in amygdala-frontal functional connectivity at rest reflects stable

individual differences versus effects of a temporary mood state.

Trait Vulnerability to Affective Disorder: From Correlation to Causation?

If, based on the studies reviewed in this chapter, we come to the conclusion that there are stable trait-related differences in the function of amygdala-frontal circuitry, what might cause these differences? There are a number of possibilities, which are by no means mutually exclusive. These include structural or functional differences in one or both regions reflecting either genetic or environmental influences, differences in the integrity of tracts connecting these regions, and differences in neurochemical modulation of one or both regions, again potentially reflecting either genetic or environmental influences uniquely or in combination.

The evidence pertaining to these alternatives is relatively limited. Diffusion tensor imaging findings suggest that reduced integrity of white matter tracts (as indexed by fractional anisotrophy) that link the amygdala to vmPFC in humans may indeed be associated with trait vulnerability to anxiety (Kim & Whalen, 2009). Positron emission topography studies meanwhile point to a relationship between neuroticism and resting state frontal hypo-perfusion (Deckersbach et al., 2006). Arguably the most intriguing findings are those emerging from the rodent and human literature on the effects of stress and gene-environment interactions on amygdala-frontal circuitry (see Arnsten, 2009, and Chapters 22 and 25). Periods of acute stress are associated with neurochemical changes, including elevated levels of noradrenaline and dopamine release (Goldstein, Rasmusson, Bunney, & Roth, 1996). High levels of these catecholamines enhance amygdala function (Debiec & LeDoux, 2006), but undermine prefrontal cortical function (Arnsten, Mathew, Ubriani, Taylor, & Li, 1999). Chronic stress leads to long-term alterations in the frontal-

amygdala network, with contrasting patterns of dendritic change being reported in the frontal cortex and amygdala. Whereas amygdaloid dendrites increase (Vyas, Mitra, Shankaranarayano Rao, & Chattarji, 2002), neurons in the PFC show a reduction in dendritic branches, which appears linked to deficient performance on measures of executive control (see Holmes & Wellman, 2009, for a review). Genetic differences, including common genetic polymorphisms influencing catecholamine metabolism in the frontal cortex (e.g., the COMT val 158 met polymorphism), as well as ones affecting serotonergic modulation of amygdala activity (e.g., polymorphisms in the serotonin transporter gene), may well interact with such environmental influences (Hyde, Bogdan, & Hariri, 2011) and also with the effects of early life stress on gene expression (Francis, Champagne, Liu, & Meaney, 1999). Hence, a combination of genetic and environmental influences potentially leads to changes in both frontal and amygdala integrity and function. Increased integration of the stress, epigenetics, and functional genomics literatures with that reviewed in the earlier sections of this chapter may/might enable us to move beyond description of the cognitive and neural correlates of trait vulnerability to affective disorders to begin to outline causal trajectories underlying observed individual differences in affective style, disorder-related symptomatology, processing of emotionally salient stimuli, and associated brain function.

Conclusions

Studying trait vulnerability to affective disorder may both inform our understanding of healthy brain function and provide an important bridge to studies of psychiatric disorder. It may also enable us to establish markers of elevated risk for psychiatric illness that could be used to identify individuals who might benefit from preventive interventions (e.g., cognitive training) before a deepening spiral into clinically significant illness occurs. To date,

cross-group studies of normative brain function and between-group studies of specific affective disorders far outnumber studies using continuous trait measures to study the brain basis of vulnerability to affective disorder. These latter studies face a number of challenges. In addition to the need for well-validated trait measures of affective style and vulnerability, rigor in neuroimaging design and analysis is likely to be an important determinant of progress in this field. Exciting advances are being made in the methods and techniques available, both within neuroimaging and converging approaches. By incorporating these advances and by drawing on models derived from both the human cognitive and basic neuroscience literatures, it will be possible to test increasingly sophisticated hypotheses regarding the brain basis of vulnerability to affective disorder.

Outstanding Questions and Future Directions

- How do different dimensions of personality relate to vulnerability to affective disorder?
- Are there multiple "pathways" by which dysregulation of amygdala/frontal circuitry confers vulnerability to affective disorder?
- To what extent does this dysregulation reflect genetic influences, the effects of early life stress on gene expression, or the direct effect of chronic or acute stress on this circuitry?
- On a methodological front, how can we best balance hypothesis-driven research with exploratory investigations? Within the area of neuroimaging, what are the respective limitations of different methods of data acquisition and styles of analysis (e.g. region-of-interest approaches versus whole-brain analyses)?
- If we seek to understand genetic influences on brain mechanisms implicated in vulnerability to affective disorder, how can we deal with the multiple comparisons problem due to both brain voxel and genetic polymorphism array size?

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