

Cognitive Mechanisms of Treatment in Depression

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Cognitive abnormalities are a core feature of depression, and biases toward negatively toned emotional information are common, but are they a cause or a consequence of depressive symptoms? Here, we propose a ‘cognitive neuropsychological’ model of depression, suggesting that negative information processing biases have a central causal role in the development of symptoms of depression, and that treatments exert their beneficial effects by abolishing these biases. We review the evidence pertaining to this model: briefly with respect to currently depressed patients, and in more detail with respect to individuals at risk for depression and the effects of antidepressant treatments. As well as being present in currently depressed individuals, negative biases are detectable in those vulnerable for depression due to neuroticism, genetic risk, or previous depressive illness. Recent evidence provides strong support for the notion that both antidepressant drugs and psychological therapies modify negative biases, providing a common mechanism for understanding treatments for depression. Intriguingly, it may even be possible to predict which patients will benefit most from which treatments on the basis of neural responses to negative stimuli. However, further research is required to ascertain whether negative processing biases will be useful in predicting, detecting, and treating depression, and hence in preventing a chronic, relapsing course of illness. *Neuropsychopharmacology Reviews* (2012) **37**, 117–136; doi:10.1038/npp.2011.183; published online 5 October 2011

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INTRODUCTION

Neuropsychiatric disorders place a heavy burden on sufferers, their carers, and society. For example, depression is a common, debilitating, and life-threatening illness, projected to become the second leading cause of disability by 2020 by the World Health Organization. Therefore, the development of more efficacious treatment strategies remains a priority. Traditionally, treatment strategies for depression have been divided into ‘monoamine medication’ approaches, such as selective serotonin reuptake inhibitors (SSRIs) or selective noradrenaline reuptake inhibitors (SNRIs), and ‘psychological therapy’ approaches, such as cognitive behavioral therapy (CBT). The former approach is motivated by the monoamine hypothesis of depression (Asberg *et al*, 1976; Schildkraut, 1965), which holds that a neurochemical imbalance directly causes the core depressive symptoms of dysphoria (low mood) and anhedonia (loss of ability to experience interest or pleasure). The latter

approach conceptualizes depression as a state in which self-reinforcing dysfunctional negative schemata—fixed internal models of the self, the world, and the future that are instantiated by early adverse experiences—come to dominate every aspect of an individual’s information processing (Beck, 1967, 1976).

More recently, several reviews have converged on a cognitive neuropsychological model of depression, which attempts to reconcile these approaches (Clark *et al*, 2009; Harmer *et al*, 2009a; Robinson and Sahakian, 2008; Sahakian and Morein-Zamir, 2011). The central tenet of this model suggests a causal role for negative affective biases in the development, maintenance, and treatment of depression. Here, we extend this model, in particular emphasizing the potential importance of affective cognitive control in promoting resilience to depression (Figure 1), and review the evidence pertaining to it. As recent reviews have presented evidence supporting the presence of negative affective biases in depressed patients in some detail (Clark *et al*, 2009; Harmer *et al*, 2009a; Robinson and Sahakian, 2008; Sahakian and Morien-Zamir, 2011), we only provide a brief overview of these findings. We consider in greater depth the evidence that individuals at risk for

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depression exhibit negative affective biases, and that pharmacological treatments for depression affect such biases directly, predictions made explicitly by the cognitive neuropsychological model. At the end of this paper, we also consider the clinical implications of this model, specifically whether differential response to pharmacological *vs* psychological therapy on an individual level might be predicted by negative affective processing before treatment (Figure 2).

Treatments for Depression

Both the psychological and the monoamine models have yielded efficacious treatment strategies for depression, as supported by numerous systematic reviews (Fournier *et al*, 2010; Hollon *et al*, 2006), although it has been questioned whether the effects of some pharmacological treatments differ reliably from those of placebo, at least in mild-to-moderate cases of depression (Fournier *et al*, 2010). Indeed, available evidence suggests that a combination of the two approaches may provide the best long-term outcome (National Institute for Clinical Excellence, 2009; Simon *et al*, 2006). However, neither treatment approach works in every individual and a substantial minority of patients respond to neither, going on to experience chronic symptoms (Simon *et al*, 2006). It is also not possible to reliably predict on the basis of symptomatic profile whether an individual patient will respond better to one treatment approach or to the other. Unfortunately, in the past 20 years, no improved treatment options based on either these approaches (ie, medications targeting the monoamine systems or psychological therapies that work substantially better than those already available) have been developed for depression. The best monoamine medications remain ineffective in approximately 30–40% of patients in the short term (Trivedi *et al*, 2006), and despite the relatively superior long-term efficacy of psychological therapies, ~30% of patients will relapse within 12 months after treatment (Hollon *et al*, 2006).

Various approaches to psychological therapy exist, although it is beyond the scope of this review to examine them all here. However, it should be noted that the different therapies discussed in this review are based on quite different assumptions regarding the etiology of depressive symptoms. CBT (or simply cognitive therapy; CT) is focused on modifying negative cognitions (dysfunctional schemata) that are held to be the primary cause of depression (Beck, 1976). BA (behavioral activation) therapy, by contrast, adopts a more radical behaviorist approach, ignoring internal cognitions. It works on the assumption that avoidance (driven by negative reinforcement) is the central cause of depression, and seeks to re-engage patients in positively reinforcing activities (Dimidjian *et al*, 2011). Well-controlled trials have suggested equivalence between BA and CBT (Jacobson *et al*, 1996; Dimidjian *et al*, 2006). Cognitive bias modification (CBM) is a more experimental psychological treatment and most closely aligned with the model outlined in this review; whether this approach is as

efficacious as more traditional psychological treatments remains to be established (Hallion and Ruscio, *in press*). CBM assumes that negative affective biases are the central cause of depression, and attempts to train individuals to process positive information preferentially (MacLeod *et al*, 2002; Matthews and MacLeod, 2002).

The most recent innovative treatment options for depression have emerged from different models of the etiology of depressive illness. These are less well tested than monoamine medications and psychological therapies, and include fast-acting medications targeting the glutamate system, especially the NMDA receptor, directly (ketamine: Zarate *et al*, 2006) and indirectly through the cholinergic system (scopolamine: Furey and Drevets, 2006), repeated transcranial magnetic stimulation (rTMS) in the dorsal part of the prefrontal cortex (Fregni *et al*, 2006), and deep brain stimulation (DBS), particularly in the subgenual anterior cingulate cortex (ACC) region of the prefrontal cortex (Mayberg *et al*, 2005). In particular, the latter two methods have arisen from an appreciation of cognitive neuroscience findings in individuals with and without depression, ie, the neural circuits subserving mood and emotion processing in healthy volunteers (Phillips *et al*, 2003a), which seem to operate abnormally in depression (Mayberg *et al*, 1999; Phillips *et al*, 2003b).

The Cognitive Neuropsychological Model of Depression

At first glance, the ability of such a wide-ranging spectrum of options to treat depression, ranging from psychological therapies, through various pharmacological interventions, to invasive and non-invasive brain stimulation, is puzzling. What do these therapeutic approaches have in common? An increasingly influential explanatory framework suggests that distorted information processing, specifically relating to reward and emotional processing biases (which in this article we term 'affective processing'), may represent an important pathway through which these disparate treatments exert their beneficial effects (Clark *et al*, 2009; Harmer *et al*, 2009a; Robinson and Sahakian, 2008). Broadly, this cognitive neuropsychological approach conceptualizes core depressive symptoms, such as dysphoria and anhedonia, as learned states engendered by dysfunctional negative schemata, instantiated over long periods by affective information processing biases (Pringle *et al*, 2010).

In some ways, this notion is similar to longstanding psychological models of depressive symptoms that first stimulated the development of psychological therapies such as CBT (Beck, 1967, 1976). These earlier psychological models focused on the importance of early adverse life experiences, which were proposed to lead to cognitive distortions, errors such as overgeneralization and arbitrary inference, and ultimately negative schemata (Beck, 1976). In these models, the negative schemata ultimately cause biased information processing, and CBT highlights the importance of challenging internally generated negative automatic

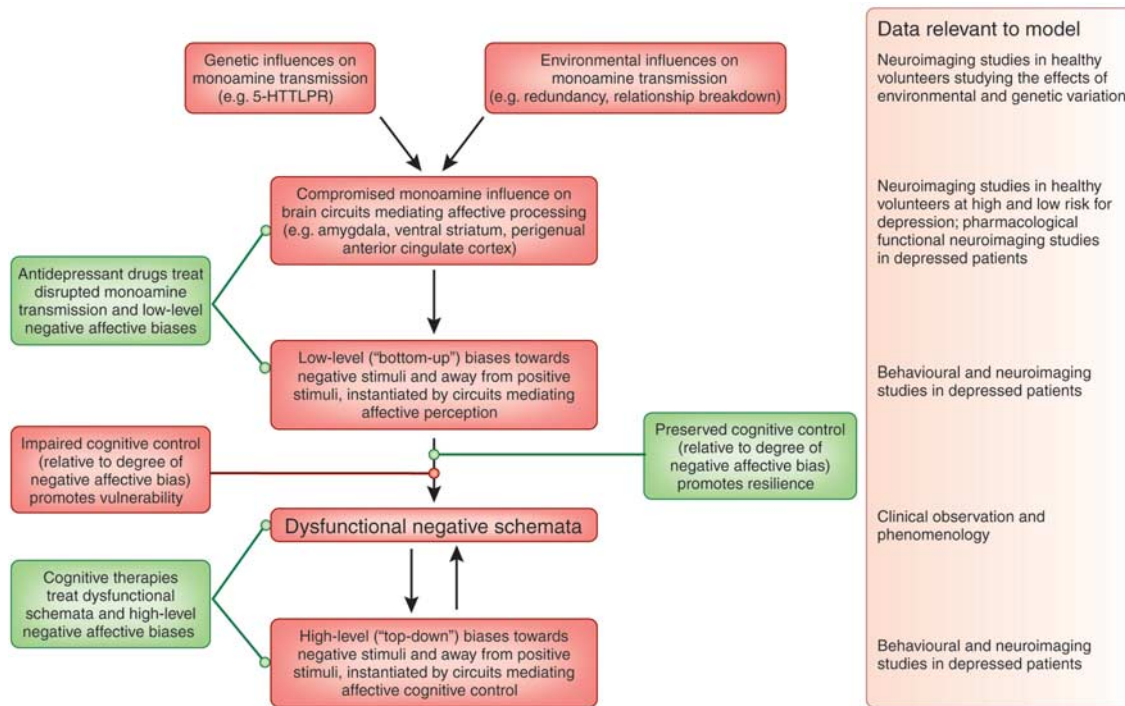


Figure 1. The extended cognitive neuropsychological model of depression. Red boxes indicate factors contributing to the development and maintenance of depressive symptoms. Green boxes indicate factors contributing to the treatment of and recovery from depression. 5-HTTLPR: serotonin transporter-linked polymorphic region.

thoughts, helping to break down schemata. In contrast to earlier psychological models, the cognitive neuropsychological approach suggests that the negative schemata are not the direct result of adverse early experiences, but instead are instantiated by negative affective processing biases. These biases are posited to be caused by alterations in monoamine transmission, which might themselves be related to either environmental or genetic factors, or more likely a combination of both (Figure 1). Although at first glance this distinction may appear subtle, its implications are substantial. In particular, the cognitive neuropsychological approach emphasizes a fundamental role for negative affective biases in the etiology and treatment of depression; moreover, it offers a framework in which the traditional ‘psychological’ and ‘neurochemical’ explanations of depression might be reconciled.

As reviewed briefly below and more extensively elsewhere (Clark *et al*, 2009; Gotlib and Joorman, 2010), negative affective biases have been reported to co-occur with depressive symptoms across a range of cognitive domains. Over time, such consistently biased input may shift the default automatic processing of affective information more negatively, creating stable dysfunctional self-reinforcing negative schemata, which ultimately themselves come to influence affective processing. These schemata are stable and self-reinforcing because, in addition to the ‘bottom-up’ negative biases that contributed to their formation (eg, perceptual biases), they may themselves instantiate ‘top-down’ negative biases that help to maintain the depressive state (eg, attentional biases) (see Figure 1). A broader

neuropsychological framework, although still perhaps oversimplistic, could incorporate not only just affective perception but also affective cognitive control (ie, the ability to regulate negative emotional experience, to challenge the negative automatic thoughts arising from the negative schemata, and to disregard external negative stimuli: Gotlib and Joorman, 2010), and also affective learning (ie, processes that create, maintain, or modify the negative schemata).

Contrary to traditional models of antidepressant drug action (Schildkraut, 1965), this framework suggests that pharmacological interventions do not affect mood directly. Instead, antidepressant drugs are proposed to alter the brain’s processing of affective stimuli (Clark *et al*, 2009; Harmer *et al*, 2009a; Robinson and Sahakian, 2008), allowing the learned states of dysphoria and anhedonia to remit gradually as the ‘bottom-up’ biases contributing to them are attenuated or abolished. Importantly, this model predicts that antidepressant drugs should positively bias emotional information in those without a history of affective disorders and in currently depressed individuals (Harmer *et al*, 2009a). This idea echoes a prominent and complementary model of psychosis, the ‘aberrant salience’ hypothesis, in which antipsychotic drugs are proposed to exert their beneficial effects by dampening down the brain’s processing of stimuli that are inappropriately assigned importance or relevance, allowing delusions to remit gradually (Kapur, 2003). Such a gradual change is consistent with findings that, although monoamine medications typically exert their effects at the synapse within hours, recovery from depression typically takes at least several weeks.

In the cognitive neuropsychological model, the effects of psychological therapies such as CBT are quite different to those of antidepressant medications. Instead of acting on information processing biases directly, CBT is proposed to contribute to the gradual breakdown of the dysfunctional schemata that maintain the learned states of dysphoria and anhedonia in a 'top-down' manner, by training affective cognitive control (in other words, teaching patients to disengage from negative external stimuli and internal representations) and stimulating re-learning. As these schemata may themselves also contribute to affective information processing biases, psychological therapies may resolve high-level (eg, attentional) negative biases, although their effect on low-level (eg, perceptual) negative biases would be predicted to be relatively minor.

Finally, and more speculatively, in this framework, novel treatment approaches for depression could be conceptualized as making the negative schemata more plastic and temporarily amenable to change (drugs altering NMDA receptor function directly such as ketamine or indirectly such as scopolamine), increasing affective cognitive control (rTMS in the dorsal prefrontal cortex), or directly modulating neural circuits participating in affective perception and regulation (DBS in the subgenual ACC).

Predictions of the Cognitive Neuropsychological Model

This model of the etiology and treatment of depressive symptoms, inspired by cognitive neuroscience and focusing on distorted affective processing, has a number of attractive features. It is consistent with some of the core diagnostic criteria for depression that are most obviously cognitive in nature, such as anhedonia and difficulty in decision making. It provides a single framework for the mechanisms of a disparate spectrum of efficacious interventions, and helps to explain the different timescales over which they work. It helps to understand why some comorbidities among psychiatric disorders are so common: eg, the co-occurrence of depressive symptoms with psychotic symptoms that occurs in both schizoaffective disorder and affective psychosis; both of these could potentially be explained in terms of compromised affective cognitive control. The framework is also consistent with findings of pleiotropy, one genetic variant conferring risk for a number of different disorders, a pattern increasingly emerging from genome-wide association studies (Huang *et al*, 2010; Purcell *et al*, 2009). Finally, although broad in scope, this framework makes some clear testable predictions, which form the focus for the rest of this review:

- (1) Dysfunctional affective cognitive processes should be detectable reliably in currently depressed patients, in various different cognitive domains (such as perception, attention, learning and memory, and cognitive control);
- (2) As dysfunctional affective cognitive processes are proposed to drive the development of the negative schemata that cause core depressive symptoms, they

should be detectable in individuals at risk for depression before the onset of frank illness, although they may not completely disappear after remission;

- (3) Treatments for depression should modify affective perception, affective cognitive control, or affective learning, although different modalities of treatments may operate on different processes: eg, antidepressant drugs may positively bias affective perception, whereas psychological therapies may alter negative affective cognitive control. Antidepressant drugs should positively bias affective information processing in both healthy volunteers and in depressed individuals;
- (4) Changes in negative affective biases in those who are ultimately going to benefit from treatment should be detectable early in the course of treatment. However, as the cognitive processes altered by psychological therapies and antidepressant drug treatments may be different, cognitive predictors of response to these two treatment modalities may also be different;
- (5) Early intervention in at-risk individuals (eg, cognitive training, medication) should prevent the incidence of illness by inhibiting the development of dysfunctional schemata.

Below we review the evidence pertaining to these predictions.

DYSFUNCTIONAL AFFECTIVE COGNITIVE PROCESSING IN DEPRESSED PATIENTS

Emotional Perception

Emotional disturbance is at the core of depressive symptomatology, and cognitive disturbances interact with the affective tone of stimulus material. Affective processing biases are apparent behaviorally in several domains of cognitive processing, including perception, attention, memory, and reward/feedback processing. Deficits in the perception or identification of facial emotions have been reported consistently in depression (Persad and Polivy, 1993; Rubinow and Post, 1992), although the exact nature of the abnormality varies. Some have argued for a general decrease in sensitivity to emotional faces (Leppanen, 2006; Mikhailova *et al*, 1996; Rubinow and Post, 1992) whereas others have argued for an overall negative bias compared with controls (Gur *et al*, 1992; Surguladze *et al*, 2004). For example, Gilboa-Schechtman *et al* (2002) reported both greater sensitivity to sad faces and greater response bias toward labeling faces as sad. Conversely, other studies have suggested that depressed patients show reduced sensitivity toward happy faces (Joormann and Gotlib, 2006; Murphy *et al*, 2009; Yoon *et al*, 2009).

Some of these discrepancies may reflect differences in the precise requirements of different emotion perception tasks. Similar discrepancies exist in the neuroimaging literature, which broadly focuses on aberrant amygdala responses to facial emotion or emotionally valent pictures (eg, from the

International Affective Picture System: IAPS) in depression. Some fMRI studies have reported enhanced amygdala response to negative faces (Fu *et al*, 2004, 2008; Sheline *et al*, 2001; Surguladze *et al*, 2005) even in the absence of awareness (Suslow *et al*, 2010; Victor *et al*, 2010), but this pattern has not always been replicated (Dannowski *et al*, 2008; Gotlib *et al*, 2005; Keedwell *et al*, 2005; Lawrence *et al*, 2004). Biased responses in other brain regions have also been reported, but again these vary between studies. Crucial factors underpinning these discrepancies include task characteristics (eg, overt vs incidental vs covert processing of emotion) and patient characteristics (notably medication status). Overall, the balance of evidence suggests a relative bias away from positive and toward negative emotional perception in depression, mediated by abnormal responses within the extended limbic system, in particular the amygdala.

Emotional Attention

Negative biases have also been observed on attentional tasks (see Gotlib *et al*, 2004a, b; Gotlib and Joormann (2010) for a review). In emotional Stroop tasks, depressed patients tend to take longer to name the color of negative emotional words (Broomfield *et al*, 2007; Gotlib and Cane, 1987; Gotlib and McCann, 1984; Segal *et al*, 1995; see Williams *et al* (1996) for a review), whereas in an affective go/no-go task, depressed patients, including first episode-depressed adolescents, were slower to respond to happy targets (Erickson *et al*, 2005; Kaplan *et al*, 2006; Kyte *et al*, 2005; Murphy *et al*, 1999). Some studies have suggested that depressed patients fail to display a bias toward positive emotional material, whereas such a bias is detectable reliably in healthy volunteers (McCabe and Gotlib, 1995). Visual search (Rinck and Becker, 2005) and dot-probe tasks with either words (Mathews *et al*, 1996) or faces (Gotlib *et al*, 2004b; Joormann and Gotlib, 2007) have also revealed negative attentional biases in depressed patients. However, an important caveat to these findings is that negative biases have typically not been detected when stimulus presentations are very brief (Mogg *et al*, 1993, 1995). Hence, some investigators suggest that the negative attentional biases identified at longer stimulus durations are driven by a difficulty in disengaging from negative stimuli, as opposed to a tendency to allocate greater attentional resources to them initially (Gotlib and Joormann, 2010). Consistent with the notion of impaired attentional disengagement from negative stimuli, neuroimaging studies primarily emphasize a role for the prefrontal cortex, especially perigenual ACC, including Brodmann areas 24, 25, and 32, in mediating negative attentional biases in depression. Mitterschiffthaler *et al* (2003) reported enhanced perigenual ACC response to negative words in an emotional Stroop task, and similar findings have been reported for the affective go/no-go (Elliott *et al*, 2002). Several fMRI studies also suggest that in attentional contexts, enhanced lateral inferior frontal cortex response is associated with the impaired ability to divert attention from task-irrelevant

negatively toned information (Dichter *et al*, 2009a; Elliott *et al*, 2002; Wang *et al*, 2008).

Emotional Memory

Depression is also associated with negative biases in memory tasks (Gur *et al*, 1992; Matt *et al*, 1992; Mogg *et al*, 1995). Again, this bias can be manifest either as a bias toward negative material or as a bias away from positive material. Thus, some studies find that depressed patients tend to preferentially remember negative stimuli (Bradley *et al*, 1995, 1996; Dorenfeld and Roberts, 2006; Dunbar and Lishman, 1984; Rinck and Becker, 2005) whereas others find that patients do not show the normal bias toward remembering positive material exhibited by non-depressed individuals (Ellwart *et al*, 2003; Gilboa-Schechtman *et al*, 2002; Gotlib *et al*, in press; Harmer *et al*, 2009b). Again, specific task characteristics may be an important contributory factor in these different results. For example, Barry *et al* (2006) suggested that higher-level conceptual memory tasks are more likely to elicit biases than purely perceptual tasks. Neuroimaging studies suggest that these biases are mediated by limbic regions, including the amygdala; depressed patients showed greater right amygdala response and enhanced amygdala-hippocampal connectivity to subsequently remembered negative pictures (Hamilton and Gotlib, 2008).

Reward and Punishment Processing

Another area in which affective biases contribute to cognitive function in depression is in response to performance feedback, reward, and punishment (see Eshel and Roiser (2010) for a review). It has been proposed that depressed patients may show exaggerated responses to negative performance feedback (Elliott *et al*, 1997; Murphy *et al*, 2003). Neuroimaging studies suggest this effect may be mediated by relatively enhanced amygdala response (Taylor Tavares *et al*, 2008) and attenuated dorsal ACC response (Steele *et al*, 2007) to feedback. However, somewhat paradoxically, a recent study found that depressed individuals reported less intense feelings of regret than did healthy volunteers after negative feedback, a tendency that was particularly pronounced in individuals with high levels of anhedonia (Chase *et al*, 2010a). Studies have also assessed responses to rewards and reward-related learning. Reward processing in depression has not been widely studied using neuropsychological tasks, although reduced reward responsiveness has been observed behaviorally in some studies (Henriques and Davidson, 2000; Robinson *et al*, in press; Pizzagalli *et al*, 2008). In this latter study, reduced responsiveness was related to the specific symptom of anhedonia, a relationship also observed by Chase *et al* (2010b) in depressed patients.

The functional neuroimaging literature on reinforcement processing in depression is considerably more extensive with reports of reduced response to reward in the amygdala

and striatal regions (Pizzagalli *et al*, 2009; Wacker *et al*, 2009), which may reflect attenuated reward prediction error signaling (Gradin *et al*, 2011), although this finding has not always been replicated (Knutson *et al*, 2008). Forbes *et al* (2009) reported that the degree of striatal response to reward predicted real-life measures of positive affect in depressed patients. Reduced amygdala/striatal response and enhanced perigenual ACC response to rewards is the opposite pattern to that described for negative feedback above, suggesting a valence-specific imbalance in the response of these regions. However, it should be noted that many of the above studies used experimental paradigms in which the presence of negative feedback was confounded with the absence of positive feedback, making it difficult to draw firm conclusions from this literature. In those studies that did examine reward and punishment processing independently, abnormal reward processing has been reported more commonly (Knutson *et al*, 2008; Pizzagalli *et al*, 2009; Wacker *et al*, 2009).

The Influence of Cognitive Control

Negative affective processing biases may depend on both enhanced 'bottom-up' responses to emotionally salient stimuli and poorer 'top-down' cognitive control mechanisms, required to suppress responses to emotionally valenced but task-irrelevant information (Clark *et al*, 2009; Phillips *et al*, 2003b). Such cognitive control mechanisms include being able to attend selectively, ignoring distracting information, being able to disengage attention from stimuli quickly when they cease to be relevant, and being able to store and manipulate stimulus representations online when they have disappeared. Numerous studies have reported deficits on tests involving cognitive control in depressed patients (see Castaneda *et al* (2008) for a review; Channon *et al*, 1993; Elliott *et al*, 1996; Taylor Tavares *et al*, 2007), and neuroimaging studies support these behavioral findings (Desseilles *et al*, 2009; Siegle *et al*, 2007).

Do cognitive control deficits in depression contribute to negative affective biases? Several studies have reported that negative emotional stimuli interfere with cognitive control in behavioral tasks (Joormann *et al*, 2010a, b; Joormann and Gotlib, 2008, 2010). Two studies have tested this hypothesis explicitly using fMRI. Fales *et al* (2008) used an attentional interference task with emotional distracters. Amygdala responses to unattended negative stimuli were increased in depressed patients relative to controls, but actively ignoring negative stimuli failed to engage prefrontal regions, consistent with a deficit in cognitive control. Dichter *et al* (2009b) used an emotional oddball task, finding that depressed patients exhibited greater PFC responses when required to disengage from processing negative stimuli. These studies suggest that abnormal PFC function may mediate poor cognitive control in depression, which contributes to negative affective biases. However, more work is required in this field, in particular to

determine whether low- and high-level negative affective biases are related to each other.

In summary, the emotional biasing of cognition in depression occurs at various levels of processing. Biases both toward negative information and away from positive information may be important. At the neural level, enhanced responses to negative information are observed in regions of an extended limbic system (including the amygdala, hippocampus, and perigenual ACC). There is also reduced response of lateral prefrontal regions and dorsal ACC in situations in which responses to task-irrelevant emotional information must be suppressed, potentially suggesting a failure of cognitive control mechanisms.

DYSFUNCTIONAL COGNITIVE PROCESSING IN INDIVIDUALS AT RISK FOR DEPRESSION

Although numerous studies have detected negative affective biases in currently depressed patients, there is less evidence for such biases before development of depression, or indeed that negative affective biases predict subsequent mood disturbance. In particular, we are aware of only one published study that has attempted to predict the subsequent development of depression in high-risk individuals on the basis of negative affective processing biases (decreased sensitivity to reward predicted future depressive episodes: Forbes *et al*, 2007). This may be due to the challenging longitudinal experimental designs required, as never-depressed at-risk individuals, who in all other respects would be considered healthy volunteers, cannot be recruited and followed up through clinical services in the same manner as depressed patients. Nonetheless, several studies examining negative affective biases in individuals at risk for depression have been performed. These are of critical importance, as they speak to a question about which the cognitive neuropsychological model of depression makes a clear prediction: are negative affective biases in depressed patients a cause or a consequence of symptoms?

Neuroticism and Affective Biases

Together with stressful life events and genetic liability, one of the most well-established risk factors for depression in individuals who have never suffered from a depressive episode is neuroticism, a personality trait closely related to anxiety (Kendler *et al*, 1993, 2002). In addition, longitudinal studies have demonstrated that neuroticism seems to increase after recovery from a depressive episode relative to before the episode (the 'scar' effect: Kendler *et al*, 1993). Neuroticism is reliably elevated in first-degree relatives of depressed patients (Hecht *et al*, 2005; Ouimette *et al*, 1996; Rothen *et al*, 2009). Consistent with the cognitive neuropsychological model of depression, neuroticism is also inversely associated with central serotonin function (Flory *et al*, 2004).

There exist numerous demonstrations that highly neurotic never-depressed individuals exhibit negative affective

processing biases. Negative biases have been reported in the cognitive domains of perception (Chan *et al*, 2007; Fruhholz *et al*, 2010), learning/memory (Bradley and Mogg, 1994; Martin *et al*, 1983; Rijdsdijk *et al*, 2009; Ruiz-Caballero and Bermudez, 1995), and reward/feedback processing (Forbes *et al*, 2007; Robinson *et al*, 2010), although not attention (Chan *et al*, 2007; Rijdsdijk *et al*, 2009). This lack of negative attentional biases in individuals at high risk of developing depression speaks to a subtle but important difference between the cognitive neuropsychological model and traditional psychological models of depression. Traditional psychological models propose that all negative affective biases are driven by the negative schemata (Beck, 1976). In the cognitive neuropsychological model, the causal process is the other way around: lower-level 'bottom-up' negative affective biases (eg, perceptual) drive the development of the negative schemata, which themselves may subsequently engender 'top-down' biases (eg, attentional). Hence, the presence of negative perceptual (ie, 'bottom-up') biases coincident with an absence of negative attentional (ie, 'top-down') biases in individuals at high risk for depression is more consistent with the cognitive neuropsychological model than traditional psychological models of depression.

Brain imaging studies have reported that more neurotic individuals display heightened responses to negative emotional stimuli in limbic regions such as the amygdala (Canli *et al*, 2001; Chan *et al*, 2009; Haas *et al*, 2007, 2008; Hooker *et al*, 2008; Stein *et al*, 2007), along with impaired connectivity between limbic regions and ventral aspects of the prefrontal cortex (eg, the subgenual ACC) (Cremers *et al*, 2010; Pezawas *et al*, 2005).

Affective Biases in Individuals at Genetic Risk for Depression

Although fewer investigations of negative affective processing in first-degree relatives of patients with depression have been performed, convergent results with the literature on neuroticism have emerged. This pattern might not be surprising, as relatives of depressed patients also tend to score higher on measures of neuroticism (Kendler *et al*, 1993, 2002). A few studies have identified negative affective biases in first-degree relatives of depressed patients (Joormann *et al*, 2010a; Joormann *et al*, 2007; Le Masurier *et al*, 2007; Mannie *et al*, 2007). Again, these findings are complemented by neuroimaging investigations that identified increased responsiveness to negative emotional stimuli in the amygdala (Monk *et al*, 2008; van der Veen *et al*, 2007; although see Mannie *et al*, 2011) and reduced ventral striatal responsiveness to reward (Foti and Hajcak, 2011; Gotlib *et al*, 2010). In addition, close relatives of depressed patients have less efficient activation of parietal and temporal networks during working memory performance (Mannie *et al*, 2010), consistent with impaired cognitive control representing a vulnerability factor for developing depression.

A small number of studies have examined the effects of genetic polymorphisms believed to confer risk for

depression on negative affective biases in never-depressed individuals. The polymorphism most often examined is the serotonin transporter-linked polymorphic region (5-HTTLPR), which alters *in vitro* (Hu *et al*, 2006), although possibly not *in vivo* (Murthy *et al*, 2010) expression of the serotonin transporter, the target of SSRIs. Carriers of the 5-HTTLPR *s* allele, which is associated with increased vulnerability to depression (Clarke *et al*, 2010), especially in the context of stressful life events (Caspi *et al*, 2003; Gibb *et al*, 2009; although see Risch *et al* (2009)), have been reported to exhibit negative affective biases (Beevers *et al*, 2011; Fox *et al*, 2009; Hayden *et al*, 2008; Kwang *et al*, 2010; Perez-Edgar *et al*, 2010). However, findings are inconsistent, as other studies have reported no negative affective biases in *s*-allele carriers (Roiser *et al*, 2005, 2007) or only demonstrated biases under conditions of induced stress (Markus and De Raedt, 2011) or tryptophan depletion (Roiser *et al*, 2006). Like highly neurotic individuals and relatives of depressed patients, carriers of the *s* allele also exhibit hyperactivation of the amygdala (Hariri *et al*, 2002; see Munafò *et al* (2008) for meta-analysis).

Affective Biases in Recovered Depression

Individuals who have previously suffered from a major depressive episode but subsequently recovered are at considerably increased risk for developing further episodes (Kendler *et al*, 1993). As such, studying recovered depressed individuals, particularly in the unmedicated state, might provide important insights into the cognitive mechanisms underpinning depression (Bhagwagar and Cowen, 2008). The literature investigating negative affective biases in recovered depressed patients is rather mixed (Leppanen, 2006). For example, behavioral biases toward negative stimuli or away from positive stimuli persisting into remission have been reported for emotion face perception (Anderson *et al*, in press; Bhagwagar *et al*, 2004; Fritzsche *et al*, 2010; LeMoult *et al*, 2009; Leppanen *et al*, 2004) and for attentional processing in a dot-probe task (Joormann and Gotlib, 2007). However, some have reported qualitatively distinct emotional face perception in recovered patients compared with currently depressed individuals (Anderson *et al*, in press). Other studies have reported persistent negative biases only if a transient negative mood is induced in remitted patients (Ramel *et al*, 2007; Timbremont and Braet, 2004). Negative mood induction is also associated with altered neural responses in remitted depressed patients during emotional faces processing (Gemar *et al*, 2007; Liotti *et al*, 2000) or words (Ramel *et al*, 2007). In the absence of mood induction, some brain imaging studies reported persistent abnormalities of amygdala response to negative faces in recovered patients (Kaplan *et al*, 2006; Victor *et al*, 2010), although others have not shown this effect (Thomas *et al*, 2011). This discrepancy might reflect differences in patient characteristics. Thomas *et al* (2011) reported that neural responses to negative faces in remitted patients were associated with trait rumination,

such that those with lower levels of rumination (and therefore potentially less likely to relapse) showed reduced responses to sad faces compared with patients with higher levels of rumination. The low ruminators also tended to be less responsive to sad faces than healthy volunteers, consistent with the observation that remitted patients who were able to remain well off medication for an extended period may demonstrate a positive bias in emotional processing (Gotlib and Cane, 1987; Roiser *et al*, 2009). Finally, impaired cognitive control also seems to persist in remitted depressed patients (Paelecke-Habermann *et al*, 2005; Preiss *et al*, 2009; Smith *et al*, 2006), suggesting that 'top-down' processes might mediate biases in recovered as well as in currently depressed patients.

In summary, studies have reported that individuals at risk for depression, whether by virtue of high neuroticism, genetic risk or previously having suffered from a depressive episode, exhibit low-level negative affective biases that are qualitatively similar to those present in the depressed state. However, it is not yet clear whether high-level biases (eg, negative cognitive control) exist in high-risk individuals before the onset of depression: the model outlined in this paper predicts that they should not. Finally, the evidence pertaining to negative biases in individuals in remission from depression is more mixed, with some studies reporting negative biases and others positive biases. These discrepant results may reflect differences in patient characteristics.

EFFECTS OF TREATMENTS FOR DEPRESSION ON AFFECTIVE PROCESSING

If negative affective biases are the source of the cognitive schemata that stimulate and maintain depressive symptoms, then successful treatments should alter such biases, and changes should be evident even before patients' symptoms begin to improve (Clark *et al*, 2009; Harmer *et al*, 2009a). In addition, the effects of treatments for depression on affective biases may also be observable in healthy volunteers (Harmer, 2008). Experimental research is now beginning to address these questions.

Antidepressant Medication Effects on Affective Processing in Healthy Volunteers

Perturbations of monoamine systems have long been known to alter behavior on tests of affective processing in healthy volunteers. For example, tryptophan depletion, which is believed to reduce central serotonin synthesis, impairs reward processing (Rogers *et al*, 2003) and abolishes positive attentional biases in healthy volunteers (Murphy *et al*, 2002). Conversely, administration of antidepressant drugs targeting the serotonin (eg, citalopram) or noradrenaline (eg, venlafaxine) systems enhances positive biases in healthy volunteers when administered subchronically (eg, for 7–14 days; Harmer *et al*, 2004). However, single-dose studies have yielded less clear results, with some reporting

enhanced fear processing and others reporting more positive biases after SSRI administration (Grillon *et al*, 2007; Harmer *et al*, 2003a,b; see Pringle *et al* (2010) for a review). The explanation for this inconsistency is not yet clear, but may be related to early anxiogenic effects sometimes observed during treatment in depressed patients; possibly a specific subgroup of individuals is particularly vulnerable to these effects (Harmer *et al*, in press).

The ability of monoamine medications to positively bias affective processing is broadly supported by brain imaging findings (Harmer *et al*, 2009a), although with one discrepancy. Several pharmacological fMRI studies have reported that even single-dose antidepressant administration in healthy volunteers reduces amygdala (Anderson *et al*, 2007; Harmer *et al*, 2006; Murphy *et al*, 2009; Norbury *et al*, 2007) and prefrontal (Miskowiak *et al*, 2007; Norbury *et al*, 2008) responses to negative stimuli (including fearful faces), and increases responses to positive stimuli (Anderson *et al*, 2011; Norbury *et al*, 2009). This pattern is in line with the prediction that these drugs positively bias affective processing (Harmer *et al*, 2009a), although it raises the question of why some single-dose behavioral studies reported greater sensitivity to negative stimuli (Pringle *et al*, 2010). Possibly this pattern of results might reflect sample selection, as individuals who are highly anxious may be less likely to participate in fMRI experiments (Harmer *et al*, in press); however, this hypothesis has yet to be tested explicitly. The few subchronic studies (ie, using dosing regimes of up to 2 weeks) that have been performed with fMRI yielded comparable results to single-dose studies (Arce *et al*, 2008; van Marle *et al*, 2011).

Few fMRI studies investigating the effects of monoamine manipulations on reward processing have been performed. Interestingly, one found different effects of subchronic serotonin and noradrenaline manipulation on reward-related responses in the ventral striatum and orbitofrontal cortex (McCabe *et al*, 2010). Although 7 days of citalopram reduced responses to both appetitive and aversive stimuli (sweet and rotten flavors), 7 days of reboxetine only reduced responses to aversive stimuli. This pattern is consistent with reports that SSRIs can cause emotional blunting in some patients, whereas this side effect is less common with SNRI treatment (Price *et al*, 2009). Supporting this notion, another study reported reduced striatal reward prediction error signals in healthy volunteers administered SSRIs (Kumar *et al*, 2008).

Antidepressant Medication Effects on Affective Processing in Depressed Patients

According to the cognitive neuropsychological model of depression, the main beneficial effect of antidepressant drug action is to eliminate or reverse negative affective biases in depressed patients. Therefore, a strong prediction of this model is that negative affective processing biases should be altered in depressed patients with successful treatment (Clark *et al*, 2009; Harmer *et al*, 2009a). Moreover, such

changes should be observable early in the course of treatment in patients who will subsequently remit. However, remarkably few studies have addressed this question, and to our knowledge none have examined behavioral measures of affective biases before and after treatment in a longitudinal design. With respect to early effects of treatment, Tranter *et al* (2009) reported that reboxetine and citalopram increased recognition not only of happy faces but also disgust and surprise, 2 weeks after treatment commencement; the authors note that these improvements might simply be due to practice. However, the degree of improvement in the recognition of happy faces did correlate with subsequent response to treatment, consistent with the cognitive neuropsychological model. Using a single-dose design, Harmer *et al* (2009b) reported that reboxetine ameliorated negative perception and memory biases in unmedicated depressed patients. The available brain imaging data are consistent with this behavioral effect: Keedwell *et al* (2010) found that deactivation to negative faces in the subgenual ACC after 2 weeks of treatment was predictive of poorer mood response at 8–16 weeks.

A greater number of studies have investigated the effects of antidepressant medication on affective processing biases in depression before and after treatment using fMRI. These studies have reported remarkably reliable results since Sheline *et al* (2001) first identified reduced amygdala responses to negative faces in depressed patients after SSRI treatment relative to before treatment, even when stimuli were presented outside visual awareness (using a masking procedure). This initial finding, which was not observed in untreated healthy volunteers scanned twice over the same time period, has been replicated in studies using similar designs (Anand *et al*, 2007; Fu *et al*, 2004), including in one study that featured a placebo arm in depressed patients (Victor *et al*, 2010). Effects on responses in brain regions other than the amygdala have also been reported, eg, in the subgenual cingulate (Keedwell *et al*, 2009). Fu *et al* (2007) also reported increased visual cortex responses to happy faces after antidepressant treatment, which correlated with the degree of mood improvement. Studies treating with SNRIs have reported similar effects for both negative and positive stimuli, especially in the perigenual ACC, a region with extensive reciprocal connections with the amygdala and other prefrontal regions (Davidson *et al*, 2003; Kalin *et al*, 1997; Schaefer *et al*, 2006).

Some studies have suggested that prefrontal-limbic connectivity increases after antidepressant administration (Anand *et al*, 2005, 2007; Chen *et al*, 2008). Although these results would be consistent with increased top-down control of emotional processing after treatment, it should be noted that the methods used to assess functional connectivity in these studies cannot determine the direction of connectivity; additionally, most examined connectivity over the entire fMRI time series, precluding consideration of valence-specific changes. Only one study (Anand *et al*, 2005) examined whether antidepressant administration alters valence-specific changes in connectivity. They found that

ACC–amygdala connectivity remained abnormally low in depressed patients during the processing of negative stimuli even after sertraline treatment, although connectivity during the resting state increased (Anand *et al*, 2007). Inefficient recruitment of prefrontal and parietal regions during working memory performance also seems to persist after successful SSRI treatment (Schoning *et al*, 2009; Walsh *et al*, 2007), consistent with the notion that impaired cognitive control may be an enduring feature of depressive illness, and is not remediated by antidepressants.

Predicting Response to Antidepressant Treatment using Affective Processing

The results discussed above raise the question of whether it might be possible to predict response to antidepressants based on affective processing biases before commencement of treatment. Unfortunately, most of the studies discussed above did not report the results of such an analysis. Nonetheless, a number of studies have implicated the perigenual ACC (including subgenual, pregenual, and dorsal ACC: Brodmann areas 24, 25, and 32) in response to antidepressant treatment. Two groups, using drugs targeting different monoamine systems, reported that perigenual ACC deactivation to negative stimuli at baseline was predictive of subsequent poorer antidepressant treatment response (Chen *et al*, 2007; Davidson *et al*, 2003); reduced connectivity between the adjacent orbitofrontal cortex and caudate during emotional processing has also been linked to poor venlafaxine response (Lisiecka *et al*, 2011). Interestingly, a recent study reported that increased perigenual ACC response while viewing sad film clips in medicated remitted depressed patients was associated with relapse 18 months later (Farb *et al*, 2011). Consistent with a role for perigenual ACC in recovery from depression, several PET studies reported that increased resting-state glucose metabolism in this region at baseline was predictive of poor outcome after antidepressant drug treatment (Kegeles *et al*, 2003; Konarski *et al*, 2009; Mayberg *et al*, 1997).

To our knowledge, only two studies have used behavioral measures of affective processing to predict which patients will respond to antidepressant drug treatment, although their results are difficult to interpret as some patients were taking antidepressant medication at baseline (Rottenberg *et al*, 2005; Johnson *et al*, 2007; see later discussion). In keeping with a possible role for cognitive control in recovery from depression (Gotlib and Joormann, 2010), several studies reported that poor performance on tests of cognitive control was associated with poor response to antidepressant drug treatment (Baldwin *et al*, 2004; Gudayol-Ferre *et al*, 2010; Kalayam and Alexopoulos, 1999; Kampf-Sherf *et al*, 2004; Potter *et al*, 2004). This finding is consistent with a report that lower dorsal ACC responses during working memory performance (interpreted as indicating more efficient processing) predicted better response to antidepressant treatment (Walsh *et al*, 2007).

Effects of Psychological Therapies on Affective Processing

Although there has been less research on the effects of psychological therapies on affective processing in depression, the results of those studies that have been conducted provide an interesting complement to the psychopharmacological data discussed above. Although no studies have yet reported behavioral measures of affective biases before and after psychological treatment to our knowledge, some fMRI studies have been conducted. One advantage of studying individuals undergoing psychological therapy is that the participants are usually unmedicated, avoiding potential for the effects of medication on neurovascular coupling to confound results (Schleim and Roiser, 2009). Only two studies have investigated the effects of psychological therapy on emotional processing in depression using fMRI in a longitudinal design. Fu *et al* (2008) reported that CBT attenuated amygdala responses and enhanced perigenual ACC responses to negative faces, such that post-treatment patients and controls no longer differed in these regions. Ritchey *et al* (2011) reported a strikingly similar pattern of results, using IAPS pictures instead of faces.

Two studies have investigated reward processing before and after psychological therapies. Dichter *et al* (2009a) found increased striatal responses during a gambling game after BA, a psychological therapy specifically targeted at decreasing engagement with punishing stimuli and increasing engagement with rewarding ones. However, whether this finding might be related to the reward-processing aspects of BA *per se* is unclear, as another study reported that increased striatal responsiveness during reward processing predicted future improvement after CBT (Forbes *et al*, 2010). However, although the changes observed in the studies discussed above were not observed in healthy volunteers over the same time period, none included a control condition in depressed patients, raising the possibility that non-specific temporal effects might have influenced the results in the depressed patient group.

Predicting Response to Psychological Therapy using Affective Processing

Some of the studies discussed above also addressed the question of predicting response to psychological therapy. In one study, the greater the response to negative stimuli in the left ventrolateral and right dorsolateral PFC, the greater the subsequent improvement in symptoms (Ritchey *et al*, 2011). Another study also showed this effect in the right dorsolateral PFC, but in the left dorsolateral and left ventrolateral PFC and dorsal perigenual ACC, the opposite relationship applied (ie, greater deactivation to negative stimuli predicted better response: Fu *et al*, 2008). Using a multivariate pattern analysis approach, the same authors found that responses to negative faces in similar regions predicted subsequent recovery from depression (Costafreda *et al*, 2009).

Other investigators reported a similar relationship between pre-treatment response to negative stimuli in the

perigenual ACC and subsequent benefit from psychological therapies (Dichter *et al*, 2010; Siegle *et al*, 2006). Siegle *et al* (2006) reported that response to CBT was associated with greater amygdala response and greater perigenual ACC deactivation before treatment. Similarly, Dichter *et al* (2010) reported that greater dorsal perigenual ACC responses during an attentional task featuring negative distractors predicted better subsequent response to BA (see Figure 2). Interestingly, a recent study found that lower pupil dilation to negative stimuli was strongly predictive of response to psychological therapy, as were reduced prefrontal responses (Siegle *et al*, 2011). As with response to antidepressant medications, a role for perigenual ACC in mediating response to psychological therapies is supported by longitudinal PET studies (Kennedy *et al*, 2007; Konarski *et al*, 2009).

Effects of Less Common Treatments on Affective Processing

Finally, some studies have begun to investigate the cognitive effects of more experimental antidepressant approaches. Mood response to sleep deprivation (a highly effective intervention that unfortunately lasts only until patients fall back to sleep) was consistently predicted by pre-treatment resting-state hypermetabolism in the perigenual ACC measured using PET (see Gillin *et al* (2001) for a review), and a similar finding was reported in the amygdala (Clark *et al*, 2006). So far as we are aware, behavioral and neural responses to negative stimuli have so far not been investigated in such studies in depressed patients after sleep deprivation. However, a recent study in healthy volunteers reported that sleep deprivation increased positive ratings of pictures, and increased response to positive stimuli in the amygdala, putamen, and dopaminergic midbrain (Gujar *et al*, 2011). Salvatore *et al* reported that greater perigenual ACC responses to negative faces (2009) and ACC-amygdala connectivity during a working memory task (Salvatore *et al*, 2010) both predicted greater improvement after ketamine administration. Although DBS in the subgenual ACC was reported to improve cognitive performance on some measures in a case series (McNeely *et al*, 2008), and to reduce perigenual ACC metabolism (Mayberg *et al*, 2005), effects on measures of affective processing have not yet been reported.

Consistent with the notion that cognitive control may have a key role in recovery from depression, modafinil, which improves working memory in healthy volunteers (Turner *et al*, 2003), has been reported to boost the antidepressant effect of fluoxetine (Abolfazli *et al*, 2011; DeBattista *et al*, 2004; Fava *et al*, 2005; Rasmussen *et al*, 2005). However, the cognitive mechanisms underpinning this effect have yet to be clarified. Possibilities include improved cognitive control, as demonstrated in chronic schizophrenia and attention deficit hyperactivity disorder patients after single-dose modafinil administration (Turner *et al*, 2004a,b) or even a direct effect on emotional processing, as recently demonstrated in first-episode psychosis patients (Scoriels *et al*, 2011).

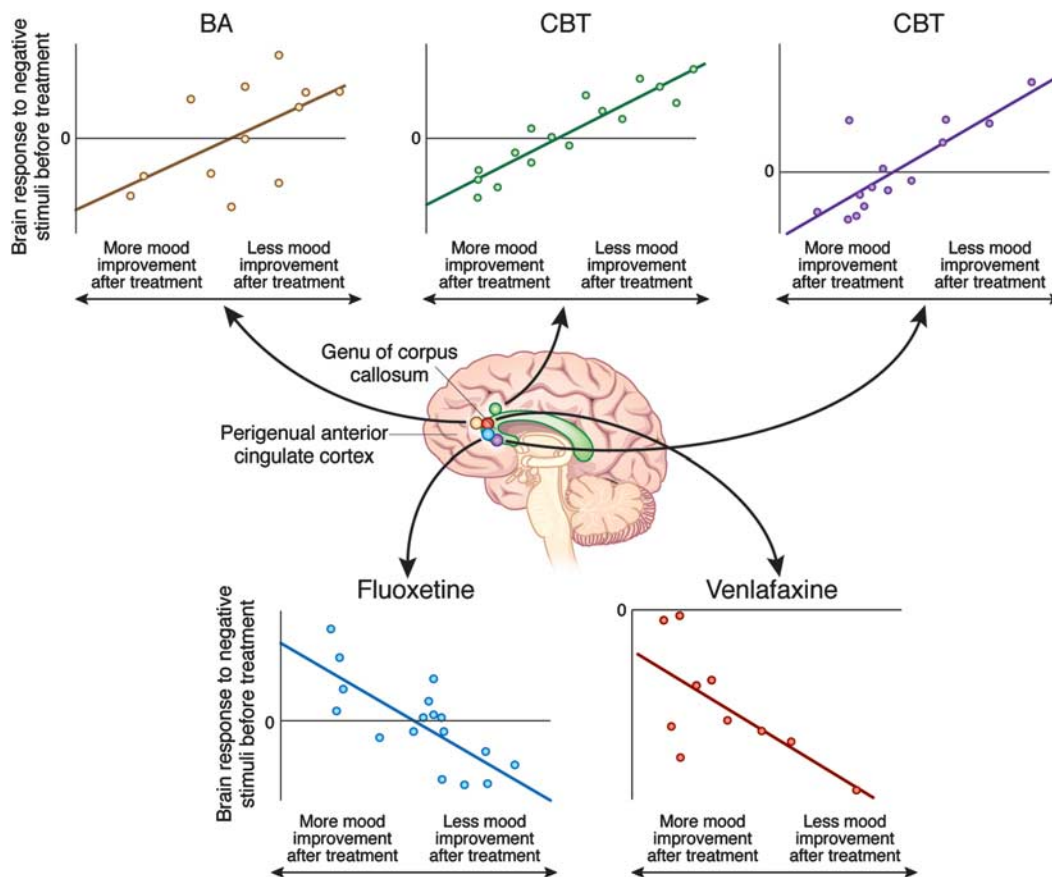


Figure 2. Hemodynamic responses to negative stimuli in the perigenual anterior cingulate cortex (ACC) predict subsequent response to treatment in depression, but in different directions for pharmacological and psychological treatments. Individuals with greater perigenual ACC responses to negative stimuli have greater mood improvement after treatment with fluoxetine or venlafaxine, whereas the converse is true for responders to cognitive behavioral therapy (CBT) and behavioral activation therapy (BA) (see also DeRubeis *et al* (2008)). Data redrawn from Chen *et al* (2007—blue), Davidson *et al* (2003—red), Dichter *et al* (2010—yellow), Fu *et al* (2008—green) and Siegle *et al* (2006—purple). It must be noted that all studies other than one (Davidson *et al*, 2003) measured change from baseline in symptoms. Davidson *et al* (2003) included only symptoms after treatment, but reported that there was no correlation between baseline severity and perigenual ACC response to negative stimuli.

In summary, antidepressant drugs bias affective processing positively in patients with depression, and effects seem to be detectable early in the course of treatment. Similar results have been reported in healthy volunteers, although there have been some conflicting reports regarding the effects of acute dosing. Psychological therapies have also been reported to bias affective processing positively, but only a handful of relevant reports exist and more research is required in this area. Finally, initial results tentatively suggest that it might be possible to predict whether a depressed patient is more likely to respond to antidepressant drug treatment or to psychological therapy depending on their perigenual ACC response to negative stimuli (see DeRubeis *et al* (2008) and Figure 2).

FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

The past decade has seen an explosion of research into cognitive abnormalities in depression, much of which has focused on understanding the negative affective biases that

are hypothesized to have a central causal role in the generation of dysphoria and anhedonia (Clark *et al*, 2009; Harmer *et al*, 2009a; Robinson and Sahakian, 2008; Sahakian and Morein-Zamir, 2011). However, many questions remain unanswered, in particular relating to the possible clinical benefits that understanding the role of negative affective biases in depression might bring. Although there are hints in the literature that understanding cognitive abnormalities in depression might be useful in tailoring treatments on an individual patient basis, improving existing psychological therapies, helping to identify individuals at high risk for depression, and possibly even preventing the incidence of depression through early intervention, these predictions remain almost entirely untested. In this final section, we discuss some preliminary data pertaining to these questions, and make some recommendations for future research.

Predicting Differential Response to Treatment

When a depressed patient first contacts his or her doctor, a number of first-line treatment options are available, broadly

falling into the monoamine medication or psychological therapy approaches, or some combination of the two. Some patients benefit greatly from medications, whereas psychological therapies have little impact; in others, the converse is true. Certain clinical characteristics such as severity, younger age of onset and chronicity (Hamilton and Dobson, 2002), as well as poor cognitive control (Gotlib and Joormann, 2010), are predictive of poor response to treatment generally. However, such variables have not generally been found to predict which treatment strategy is likely to be more beneficial for a given patient (Frank *et al*, 2011). Although it has been proposed that stratification by genotype may aid in the tailoring of treatment strategy on an individual basis (Serretti *et al*, 2007), the available data suggest that the discriminating power of individual genetic variants is likely to be too low to be of use clinically (Ising *et al*, 2009; Uher *et al*, 2010).

On the basis of findings that changes in negative affective biases in depressed individuals may occur very early during successful treatment (Harmer *et al*, 2009b; Tranter *et al*, 2009), it may be possible to use sub-chronic pharmacological challenges to predict which individuals are more likely to benefit from treatment with antidepressant medications. The cognitive neuropsychological model would predict that those individuals showing the greatest positive change in low-level affective processing after a short period of treatment (up to 1 week) should ultimately experience the greatest benefit after 6 weeks of treatment. Conversely, a lack of effect on affective processing after 1 week may indicate that other treatment approaches would likely be more successful. However, to our knowledge, no studies have yet investigated this question.

Could affective cognition be used to predict differential response to treatment with medication or psychological therapy even before treatment? On the basis of the model outlined above, it would be predicted that depressed individuals with more pronounced low-level (eg, perceptual) biases at baseline but with less pronounced high-level (eg, attentional) biases might respond best to antidepressant medication; the opposite pattern would be predicted for those who respond well to psychological therapies. Depressed individuals with both low- and high-level negative affective biases might experience the greatest benefit from a combination of medication and psychological therapy.

No study has yet addressed these predictions directly, but two reported that negative memory biases at baseline were associated with outcome after treatment with a mixture of antidepressant drug treatments and psychological therapy (Johnson *et al*, 2007; Rottenberg *et al*, 2005). However, the direction of the effect was inconsistent between these studies. Consistent with the central tenet of the cognitive neuropsychological model that monoamine medications exert their effects by attenuating or reversing low-level negative affective biases, Rottenberg *et al* (2005) reported that depressed individuals with a greater intensity of negative autobiographical memories at baseline showed the best response to antidepressant drug treatment; subgroup analysis including only individuals who were

unmedicated at baseline confirmed this effect. By contrast, Johnson *et al* (2007) found that better memory for positive words predicted better subsequent treatment response 9 months later. As over one-third of the participants in the latter study were medicated at baseline, and no subgroup analyses were reported, it is possible that the negative biases had already been reversed in some medicated patients, who were still nonetheless depressed, explaining this apparent discrepancy with the cognitive neuropsychological model (also see Tranter *et al* (2009)). Further work is required using longitudinal designs in which depressed patients are unmedicated during baseline assessment to clarify the interpretation of these findings.

To our knowledge, no behavioral studies have yet investigated whether measures of affective bias can predict response to psychological therapies *vs* pharmacological therapies. However, fMRI studies using pre-treatment affective bias challenges have been undertaken, allowing a comparison of predictors of response to psychological *vs* pharmacological therapies at a neural level. Several studies have assessed whether pre-treatment neural responses to affective stimuli in the perigenual ACC can predict responses to treatment (Figure 2; see also DeRubeis *et al* (2008)). Two studies, using fluoxetine and venlafaxine, respectively, reported that greater perigenual ACC responses to negative stimuli pre-treatment, contrasting negative faces with 'baseline' fixation cross (Chen *et al*, 2007) or negative IAPS pictures with matched neutral stimuli (Davidson *et al*, 2003), predicted better subsequent mood response. By contrast, Siegle *et al* (2006) and Fu *et al* (2008) reported that lower pre-treatment responses (in fact deactivations relative to baseline) to negative words relative to neutral words in perigenual ACC predicted better response to CBT. A similar relationship was identified in a more dorsal perigenual ACC region by Dichter *et al* (2010), in a study using response to negative pictures to predict response to BA.

The contrast between higher perigenual ACC response to negative stimuli predicting a greater benefit from antidepressant medication, but lower perigenual ACC response predicting greater benefit from psychological therapy is striking (DeRubeis *et al*, 2008). This pattern is consistent with our proposal that psychological therapies exert their beneficial effects through enhancing affective cognitive control, as this subregion of the ACC is believed to be critically implicated in the implicit regulation of negative emotion, by its interaction with the amygdala (Etkin and Schatzberg, 2011). These data indicate that pre-treatment baseline response in the perigenual ACC may predict likely response to a given treatment, or even which treatment is more likely to be effective. However, it should be noted that these studies used different types of emotional stimuli (faces, pictures, and words), and had different task demands inside the scanner (gender classification, passive viewing, self-referential rating, and target detection), which complicates the interpretation of this apparent dissociation. Furthermore, the foci within the perigenual ACC that predicted response varied between the studies; even adjacent perigenual ACC regions are associated

with distinct patterns of connectivity (Beckmann *et al*, 2009). There is a clear need for further studies examining and directly comparing predictors of both types of treatment response to test the hypothesis that neural responses to affective stimuli may represent biomarkers for differential treatment response.

New Approaches to Treatment Based on the Cognitive Neuropsychological Model: A Role for Cognitive Enhancement?

This review has focused on the important role for types of 'hot' (ie, emotionally laden) cognition in mediating the development and treatment of depressive symptoms. However, as the model we outline also suggests a key role for cognitive control in recovery from depression, especially with respect to the mechanism of action of psychological therapies, it is possible that 'cold' cognition (information processing without an affective component) might be a useful novel therapeutic target. Indeed, some clinicians have developed effective psychological therapies on this very basis: mindfulness-based CT (Teasdale *et al*, 1995, 2000) does not promote the challenging of negative automatic thoughts *per se*, but instead prevents them from escalating by encouraging patients to disengage from them to minimize their emotional impact, which could be conceptualized as a form of cognitive control. This is important because antidepressant drugs, whether targeting the serotonin or noradrenaline systems, generally have not been found to improve cognitive control (Chamberlain *et al*, 2006; Riedel *et al*, 2005).

The reliable finding that impaired cognitive control predicts poor response to treatment has already been used to motivate novel pharmacological approaches to treatment in depression. Modafinil, a cognitive enhancer (Turner *et al*, 2003), has been found to improve response to antidepressant treatment response in a number of studies (Abolfazli *et al*, 2011; DeBattista *et al*, 2004; Fava *et al*, 2005; Rasmussen *et al*, 2005). Whether this effect is mediated through improved cognitive control specifically has yet to be determined; it would also be of great interest to investigate whether the same benefit would be observed if modafinil was used as an adjunct to psychological therapy. However, some tangential evidence supporting the notion that improving cognitive control might improve depression has emerged from trials of cognitive training in patients with dementia. In several well-controlled trials, cognitive training targeting at relieving symptoms of dementia had the unexpected simultaneous effect of improving depressive symptoms (Davis *et al*, 2001; Loewenstein *et al*, 2004; see Sitzler *et al* (2006) for a review). However, further work is required to ascertain whether similar cognitive training in non-demented depressed individuals might improve symptoms.

It has also not yet been investigated whether circuitry-based interventions, including DBS in the subgenual cingulate cortex and TMS in the dorsolateral prefrontal

cortex, might potentiate the effects of psychological therapies. Such an effect would be predicted from the cognitive neuropsychological model, as there is evidence that both of these interventions enhance activity in neural circuits subserving cognitive control (Lozano *et al*, 2008; Speer *et al*, 2000).

Tailoring Psychological Therapies to Individual Patients

Another question arising from our review is whether specific types of negative bias might be better treated by specific psychological therapies. We would predict that depressed patients exhibiting profound reward-processing deficits, which correlate with anhedonia (Chase *et al*, 2010b), would benefit more from psychological therapies focused on re-engaging in positively reinforcing activities, such as BA, than those focused on challenging negative schemata, such as CBT. Another important development in the field of psychological treatment is CBM, a therapy initially developed for anxiety (MacLeod *et al*, 2002; Matthews and MacLeod, 2002). Although research into CBM is still in its infancy, and different investigators have attempted to modify different cognitive processes (eg, attention *vs* appraisal), several studies have reported beneficial results in dysphoric participants (see Hallion and Ruscio, in press for a review). A few studies have reported the effects of this technique on symptoms in depressed individuals, although with mixed results (Baert *et al*, 2010). We suggest that the scope of CBM might usefully be broadened to other domains of cognition, eg, reinforcement processing. In particular, it would be of great interest to examine whether reward reactivity and/or reward learning could be enhanced through CBM techniques, and whether manipulating reward processing might be beneficial in the treatment of anhedonia. Whether CBM and circuit-based interventions, such as rTMS, might work more efficaciously when used in combination is not yet known, but this is a result that would be predicted on the basis of the model outlined in this paper.

Identifying and Treating Individuals at Risk for Depression

A final important question is whether individuals who are at risk for developing depression might be identified on the basis of negative affective biases, and whether preventative measures (such as CBT or CBM) could be administered proactively, reducing the incidence of depression through resilience mechanisms (Elliott *et al*, 2010). Although such a strategy would require intensive resources, there are some preliminary data suggesting that this approach might be worthwhile (Koster *et al*, 2009). One large trial reported a substantial reduction in the incidence of depression using a CBT intervention in adolescent offspring of depressed parents (Garber *et al*, 2009). However, not all individuals who develop depression can be identified on the basis of genetic risk. Hence, negative affective biases may have an important role in future studies.

In support of this notion, it has been reported that negative attentional biases in non-depressed individuals are strongly predictive of subsequent responses to stress (Fox *et al*, 2010). Moreover, interventions other than CBT may also be efficacious. For example, CBM has been reported to alter the processing of negative stimuli in healthy volunteers (Tran *et al*, 2011), an effect that appeared to be mediated by the lateral PFC in one study (Browning *et al*, 2010). The converse effect has also been demonstrated: MacLeod *et al* (2002) randomized individuals to receive training to attend preferentially to positive or negative stimuli using a dot-probe task. Those trained to attend to negative stimuli were subsequently more vulnerable to low mood after experimentally induced stress.

These findings raise the possibility that training individuals at risk for depression to process positive information preferentially using CBM could potentially help to prevent them from becoming ill (Matthews and MacLeod, 2002). Watkins *et al* (2009) reported that training dysphoric individuals to become more concrete and specific in their thinking reduced depressive symptoms, although follow-up was not conducted to determine whether the incidence of depression was decreased. Another study successfully trained depressed individuals to forget negative material using a 'think/no-think' procedure (Joormann *et al*, 2009), although again the long-term effects on symptoms was not assessed.

CONCLUSIONS

Depression is characterized by negative affective biases that may have a central role in the development of illness and response to treatment. These biases are also present in individuals at risk of illness, including those who are highly neurotic, have a close relative with depression, or have suffered from depression in the past. Preliminary data supporting the cognitive neuropsychological model of depression have demonstrated that antidepressant drugs can alleviate or even reverse negative affective biases, although further research is required using longitudinal designs in currently depressed patients. Future studies should address whether negative affective biases are able to predict which patients will respond well to specific treatment approaches (eg, pharmacological vs psychological treatment), and whether the incidence of depression might be reduced by programs aimed at modifying cognitive biases in individuals at high risk of illness. Preventing the development of depression and treating it early and effectively before it becomes a chronic, debilitating disorder must be a priority target for society and governments (Beddington *et al*, 2008; Collins *et al*, 2011; Sahakian *et al*, 2010).

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