Review

Cognitive theory and therapy of anxiety and depression: Convergence with neurobiological findings

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In this review paper a modified cognitive neurophysiological model of Aaron T. Beck's cognitive formulation of anxiety and depression is proposed that provides an elaborated account of the cognitive and neural mediational processes of cognitive therapy (CT). Empirical evidence consistent with this model is discussed that indicates the effectiveness of cognitive therapy could be associated with reduced activation of the amygdalohippocampal subcortical regions implicated in the generation of negative emotion and increased activation of higher-order frontal regions involved in cognitive control of negative emotion. Future cognitive neuroscience research is needed on the unique brain substrates affected by CT and their role in facilitating symptom change. This future research would have important implications for improving the efficiency and efficacy of this treatment approach.

A cognitive approach to emotional disturbance

Major depressive disorder (MDD) and anxiety disorders (i.e. emotional disorders) are the most prevalent of all psychiatric conditions, accounting for a substantial proportion of the mental health disease burden in Western countries. MDD has an estimated lifetime prevalence of 17%, whereas anxiety disorders have an even higher lifetime prevalence of between 25 and 30% [1,2]. Both types of disorders have an early onset in adolescence and young adulthood, take a recurring or chronic lifetime course, occur more often in women, and are associated with significant impairment in social and occupational functioning as well as reduced quality of life [3,4]. Although our knowledge of these disorders has grown exponentially, it is recognized that further advances will require more complex, multidimensional models that integrate and synthesize the multiple levels of human function affected by the emotional disorders.

In the past three decades psychological perspectives on anxiety and depression have placed a much greater emphasis on aberrant information processing in the etiology and maintenance of emotional disturbance. One of these cognitive perspectives, the schema-based theory proposed by Aaron T. Beck for MDD [5–7] and later for anxiety disorders [8], posits that prepotent maladaptive schematic representations of the self, world and future are activated by matching life experiences. This leads to a preferential processing bias for schema-congruent information and a consequent dominance of negative or threat-related thoughts, images and interpretations within the stream of consciousness [6,8]. Further explanation of the etiological (i.e. developmental) and descriptive (i.e. cross-sectional) aspects of the cognitive model is presented in Box 1. Hundreds of experimental, correlational and prospective studies have supported major tenets of the cross-sectional model, with moderate support also accruing for cognitive vulnerability [9,10].

Beck and colleagues also developed a psychotherapeutic approach derived from their schema-based theory [11].

Glossary

Attentional cueing task: The presentation of emotional versus neutral cue stimuli (i.e. facial expressions) followed by a varying target probe (i.e. one or two dots) in which reaction time to shift attention away from invalid emotion cues when identifying probe type is considered an indicator of cognitive control over emotional stimuli.
Bottom-up processing: (also known as data-driven or associative processing). A primitive automatic, effortless, implicit and preconscious processing of information dominated by the salient features of a relevant stimulus or situational cues and their schematic associations [27,28].
Cognitive behavior therapy: A therapeutic orientation that includes a variety of treatment approaches that target aberrant cognitive and behavioral elements of psychiatric disturbance to achieve symptom change.
Cognitive restructuring: The therapeutic strategy of identifying the core maladaptive thoughts and beliefs of emotional disturbance and then correcting them by evaluating their veracity and generating more adaptive, alternative modes of thinking that compete with the dysfunctional perspective.
Cognitive therapy: A structured, goal-directed and present-oriented psychotherapy that utilizes cognitive and behavioral strategies to achieve symptom reduction by specifically targeting the faulty cognitive structures and processes that maintain psychiatric disorders.
Emotional disorders: Psychological states that involve a maladaptive excess and/or deficiency in positive and/or negative emotion production and control. It is an umbrella term that includes states of anxiety and depression.
Emotional Stroop task: A color-naming task in which emotion and non-emotion words are printed in various colored ink. The task is to name the printed color while ignoring the meaning of the word. Increased delay in color-naming emotive vs. non-emotive words reflects greater interference of the emotion word's meaning, which is considered indicative of an automatic preferential processing bias for the emotional words.
Fronto-striato-thalamic circuits: Five parallel, partially segregated and reciprocal pathways that interconnect regions of the prefrontal cortex with subcortical structures in the striatum and thalamus. These pathways are involved in complex cognitive, attentional and higher-order executive functions that are implicated in self-referential information and emotional processing.
Top-down processing: (also known as reflective or effortful processing). A slow, deliberate, explicit and strategic form of rational processing that uses rule-based knowledge to guide the information processing system [27,28].

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Box 1. A schema-based cognitive model of anxiety and depression

Beck's cognitive model of emotional disorders has been fully articulated in several publications [6–10]. The *descriptive* aspect of the model proposes three levels of cognition that are responsible for the persistence of anxiety and depression. At the deepest level are enduring structural representations of human experience, termed *schemas* that direct the identification, interpretation, categorization and evaluation of experience. Schemas are hypothetical constructs that are inferred from persistent, repetitive themes in thoughts and images as well as recurrent patterns of biased information processing (e.g. a tendency to selectively process negative self-referential information about social rejection). Schematic content (i.e. attitudes and beliefs) plays an important role in the cognitive model, with negative beliefs about the self, world and future (e.g. ''No one really likes me''; ''I will never be a success'') characterizing depression and beliefs about threat, danger and vulnerability indicative of anxiety states. These schemas are structurally rigid, impermeable and absolute, and their content a biased representation of experience. They are readily activated by a range of stimuli and once accessed dominate the information processing system. This results in *biased information* processing, which in depression involves preferential encoding and retrieval of negative self-referential information (i.e. schema congruent effect), whereas in anxiety a selective processing of threat, danger and helplessness is evident. The dominance of this negativity bias also interferes with the processing of more positive, schema-incongruent information. The culmination of biased information processing is the subjective experience of schema-congruent *negative 'automatic' thoughts*, images and memories that perpetuate a subjectively adverse emotional state. A central argument of the cognitive model is that the type of emotion experienced depends on the thought and belief content activated by life experiences.

The cognitive model also posits a *developmental level* of conceptualization that proposes a contributory role for cognition in the etiology of emotional disorders. The formation of dysfunctional schemas about the self are due to early adverse childhood events such as parental loss, rejection or neglect that sensitizes the individual to later losses in adolescence and adulthood [7]. These schemas become activated by later adverse events that impinge on these specific cognitive vulnerabilities and lead to systematic cognitive biases. Thus cognitive vulnerability to emotional disorders operates within a *diathesis-stress* framework, in which negative life stresses that match one's underlying negative schematic mode are more likely to precipitate a depressive or anxious episode than schema-incongruent life events. With repeated activation, the negative self-schemas acquire a more coherent and elaborated organization (i.e. morph into a *depressive or anxious mode*) that over time is more easily accessed by a wider range of milder stressful life events. The hypervalent depressive or anxious mode dominates the information processing apparatus, resulting in a concomitant weakening of cognitive control over emotion via the inability to access more adaptive, alternative modes of thinking. Numerous hypotheses derived from this model have been systematically evaluated in a voluminous research literature [9,10].

Cognitive therapy (CT) is a structured, collaborative and problem-oriented psychotherapy that seeks to reduce symptom expression by modifying maladaptive thoughts, attitudes and beliefs as well as the faulty information processing biases that characterize emotional disturbance [10,12]. De-activation of hypervalent dysfunctional schemas and improved access to more reflective, adaptive modes of thought and behavior are considered crucial to symptom amelioration (Box 2).

CT has been refined, elaborated and evaluated in hundreds of empirical studies. As a result of this rigorous testing, CT is now considered an empirically supported treatment for a variety of disorders including major depression, various anxiety disorders and bulimia nervosa [13,18][*]. It is also strongly recommended as a first-line treatment of choice for these disorders in national practice guidelines [19][†]. Moreover, CT is effective in moderate to severe major depression [15], has enduring treatment effects at termination [14], and is showing promise for other severe mental disorders such as schizophrenia and bipolar disorder [20,21].

Progress on the cognitive basis of anxiety and depression has been made independently of any consideration of its biological correlates even though genetic predisposition and neurophysiological processes were always thought to be important [7]. However, recent advances in behavioral genetics and functional neuroimaging research now enable us to begin mapping the neural mechanisms of emotional disorders and their treatment [22–24]. Concurrently, cognitive neuroscience has recognized that the neural architecture of emotion generation and regulation involves interplay between two modes of information processing: automatic, reflexive, bottom-up and effortful, symbolic, top-down processes [7,25–27]

The objective of the current paper is to propose a more integrated perspective on the change mechanisms in CT of anxiety and depression that takes into account recent findings on the neurophysiology of anxiety, depression, and their treatment. We begin by reviewing evidence that CT produces symptom relief in anxiety and depression by correcting biased information processing and dysfunctional schema activation. An elaborated refinement of the cognitive model is presented in Figure 1 that includes the neurophysiological aspects of schema activation and cognitive control of emotion. Evidence from neuroimaging research consistent with this elaborated model indicates that CT is associated with decreased activity in the amygdalohippocampal subcortical region (i.e. bottom-up processing) and increased activation in the frontal cortical regions (i.e. top-down processing). Research on specific therapeutic elements of CT, such as cognitive restructuring and reappraisal, is discussed within the context of the cognitive control of negative emotion and associated activation of prefrontal regions. In our conclusion we propose that a greater emphasis on laboratory-based cognitive neuroscience research that elucidates the impact of specific CT intervention strategies on particular cognitive processes and their neurophysiological concommitments will enhance our knowledge of treatment mediators and thereby improve the effectiveness of CT for anxiety and depression.

Cognitive mediation in treatment of anxiety and depression

CT is a complex therapeutic intervention that involves many components targeting various cognitive, behavioral,

[*] Society of Clinical Psychology, American Psychological Association, Division 12 (2006). Information retrieved from website on research-supported psychological treatments (http://www.PsychologicalTreatments.org).

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Box 2. Efficacy of CT for emotional disorders

CT is a structured, skills-based psychotherapy that focuses on modifying the faulty thoughts, evaluations, attributions, beliefs and processing biases that characterize anxiety and depression [10,12]. It is assumed that CT results in significant reduction of symptoms by weakening or deactivating disorder-related maladaptive schemas and strengthening alternative, more positive modes of thinking. Patients are taught to identify their maladaptive thinking, evaluate its accuracy, generate more adaptive and realistic perspectives, and 'test-out' the utility of their new perspective through structured behavioral homework assignments. CT is a problem-oriented psychotherapy that helps patients to learn more adoptive cognitive and behavioral approaches to life difficulties that contribute to the persistence of emotional disturbance. Both cognitive and behavioral intervention strategies play an integral role in the therapy. It is recognized that correction of biased information processing in anxiety and depression most often occurs when the patient is confronted repeatedly with incongruent experiences, such as mastery tasks, that cannot be accommodated by the depressive or anxious mode. Furthermore, repeated evaluation of one's reaction to events will lead to a diminished concern over the troubling events, a heightened sense of control and self-efficacy, and the adoption of more effective problem-solving skills [12].

The efficacy of CT for anxiety and depression has been rigorously evaluated. Butler and colleagues [13] reviewed 16 meta-analyses of CT (or CBT) and concluded that CT for depression is a highly effective treatment. However, it might be only slightly more effective than other *bona fide* psychotherapies, and is equivalent to antidepressant medication at the acute treatment phase [12]. CT for depression does seem to have more enduring treatment effects than medication, for example Hollon et al. reported that CT reduced 13–24 month risk of depressive relapse by 70% compared with a medication continuation reduction of 30% [14]. CT has also been found to be effective for moderate to severe MDD [15] and could remain potent even with patients having a prior history of poor response to antidepressant medication [16]. Thase and colleagues [17] found that CT either alone or in combination with citalopram was as effective as switching to an alternative medication in MDD patients with an initial poor response to citalopram. Generally CT or CBT has shown similar levels of efficacy in the treatment of anxiety disorders, with between 60 and 80% exhibiting clinically significant improvement especially at 6 and 12-month follow-up [10,13]. Once again CT produces more enduring effects in anxiety disorders than medication discontinuation [14].

interpersonal and affective responses. Its primary mechanism of action is assumed to involve change in biased information processing (i.e. cognitive mediation). In fact there is now considerable evidence that CT produces change in negative cognition that precedes and predicts reductions in depressive and anxious symptoms [28–31]. Most studies report that CT produces significant reductions in negative thinking as well as increased endorsement of positive cognitions [32,33]. CT also produces a reduction in threat-related thinking in anxiety disorders [34–36]. Overall, there is strong evidence to support the conclusion that CT has an impact on the negative thinking styles associated with symptom expression.

There is empirical evidence that CT produces changes in information processing bias, especially for anxiety disorders. CT, or cognitive behavior therapy (CBT), leads to significant reductions in attentional bias for threat as indicated by improvements on the emotional Stroop task [37–39]. Furthermore, training in attentional disengagement from threat information can reverse the threat bias and produce significant reduction of anxious symptoms [40,41]. This form of training is considered a method of redirecting attention and thereby correcting attentional threat bias rather than as a strategy that promotes the avoidance of threat [42]. Nevertheless, improvements in emotional processing cannot be attributed solely to the effects of CT but instead reflect the process of symptom remission more generally because other treatment modalities, such as pharmacotherapy, also produce change in information processing [43].

CT might have more specific effects in promoting change in the deeper, more enduring cognitive structures or schemas that characterize depression vulnerability [44]. For example in a study of CT and medication, MDD patients randomly assigned to CT plus pharmacotherapy showed greater organization and interconnectedness of positive schematic content at post-treatment than the group receiving pharmacotherapy alone [33]. This enhanced consolidation of positive schemas should result in a more positive self-referential processing style and maintenance of an asymptomatic state. Additionally, CT produces significantly less cognitive reactivity (i.e. lower endorsement of negative schema content) after a sad mood provocation at post-treatment than pharmacotherapy; increased cognitive reactivity is associated with higher depressive relapse [45,46]. In these studies cognitive reactivity refers to the differences in thought and belief content as well as information processing styles that emerge after induction of a negative mood state. Most of this research has focused on depression and shown that formerly depressed individuals who are vulnerable to depression endorse more negative beliefs and exhibit an enhanced negative information processing bias after a sad mood provocation relative to a nonclinical comparison sample [47].

Overall there is considerable empirical support that cognitive mediation is a key mechanism of change in CT. CT is an effective treatment for anxiety and depression (Box 2), and it improves emotional processing as indicated by reductions in negative thinking, alteration of the information processing bias, and a shift from negative schema activation to endorsement of more positive attitudes and beliefs. Other studies show that training in cognitive bias and improvement in cognitive control reduces symptoms of emotional disturbance [48] that is consistent with the cognitive mediation view that improved emotional processing is integral to treatment effectiveness. However, more refined, experimental treatment process research is needed to address the thorny issues of causality and the importance of emotional processing changes in CT relative to other mechanisms of change such as behavioral activation. Moreover a more elaborated perspective on cognitive mediation in terms of the treatment's selective effect on top-down or bottom-up processes would greatly enrich cognitive explanations for symptom change. Although various researchers have speculated that cognitive interventions such as cognitive restructuring (see Glossary) primarily alter the control of negative emotion via top-down processes [25,49,50], more sensitive experimental neuroimaging research is needed that maps out the neural

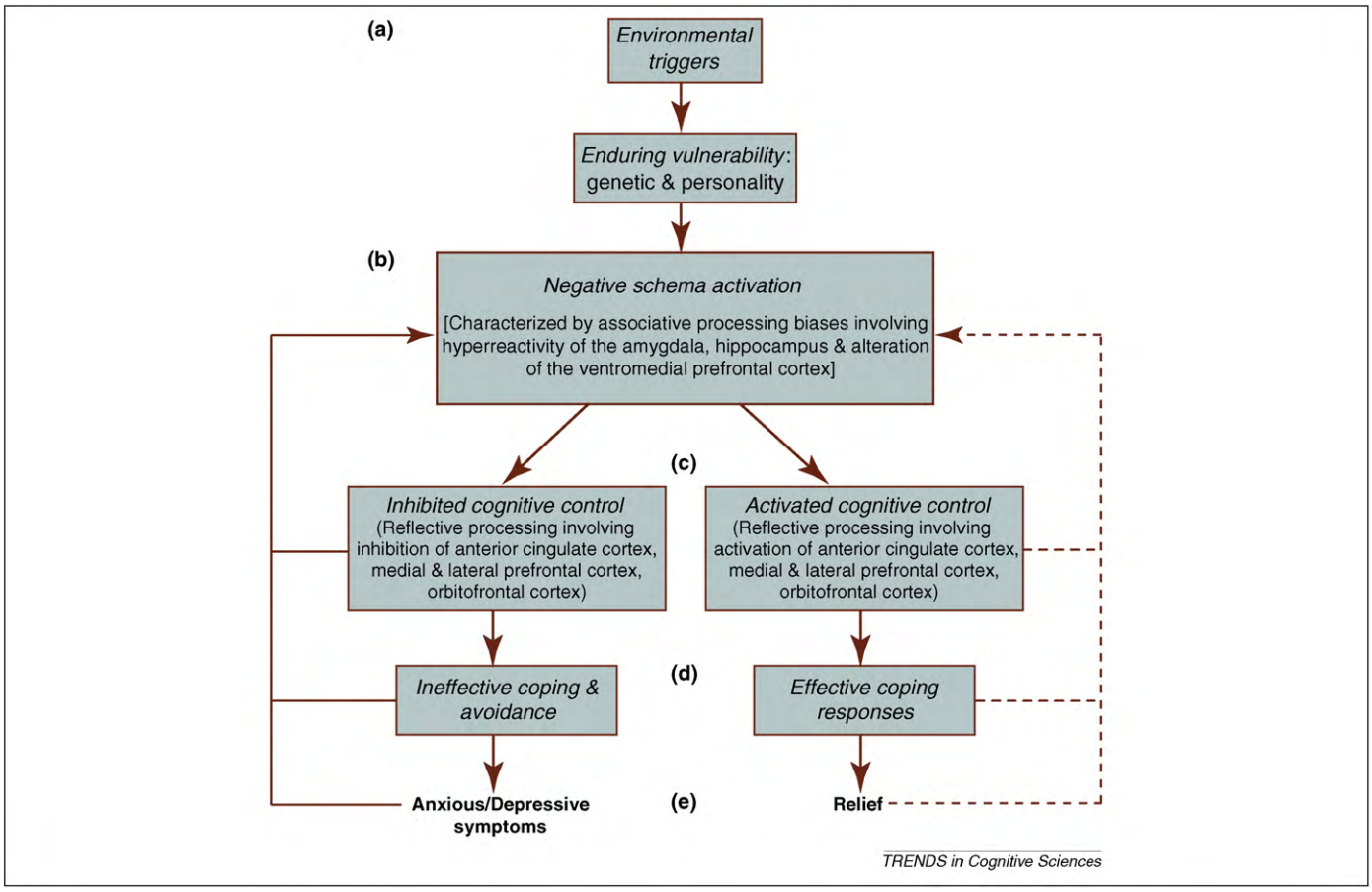

Figure 1. Neurophysiological aspects of Beck's cognitive model of anxiety and depression **(a)** The upper two boxes refer to proposed etiological factors in anxiety and depression. **(b)** The center box represents automatic, cognitive processing that is key to emotion generation. **(c)** A more reflective, rule-based cognitive control system based in higher-order cortical structures is activated in response to negative schema activation and automatic biased information processing. **(d)** Inhibition of the cognitive control system results in poor coping, avoidance and the occurrence of a depressive or anxious symptom state, whereas activation of cognitive control contributes to relief and the deactivation of negative schema activation. **(e)** A positive feedback loop is created in which presence of anxious/depressive symptoms, ineffective coping and inhibited cognitive control contribute to continued activation or diminution of negative schemas and automatic biased processing.

pathways of cognitive change affected by specific cognitive interventions.

Figure 1 illustrates a cognitive model of anxiety and depression that takes into account neurophysiological aspects of emotional disturbance. It is increasingly recognized that anxiety and depression, in particular, involve selective activation of automatic (i.e. bottom-up) cognitive processes possibly emanating from sustained activation of negative representational structures (i.e. schemas) and selective impairment in elaborated cognitive control responsible for the inhibition of negative material [48]. Based on this model, CT could achieve symptom reduction by directly inhibiting bottom-up processes (B), and/or it could dampen down negative schema activation by strengthening the more reflective, top-down cognitive control or inhibition system (C).

As indicated in the following discussion, recent studies in neuroimaging provide new findings that indicates CT could lead to symptom reduction by change in both bottom-up (i.e. automatic schema deactivation) and top-down (i.e. strengthen reflective cognitive control) systems.

The neural basis of CT

Neuroimaging studies of CT provide new insights into its cognitive and neurophysiological mediators of change. In his review Linden [24] concluded that CT (or CBT) can lead to reduction in fronto-striato-thalamic activity for anxiety disorder but the findings are less consistent for depression. Across studies successful treatment with CT has been associated with both increases and decreases in prefrontal metabolism, although Linden suggested that CT for depression probably operates via change in top-down processes whereas pharmacotherapy leads to symptom reduction via bottom-up processes. In their more recent neuroimaging review, Frewen and colleagues [23] concluded that CT of major depression alters functioning in the dorsolateral, ventrolateral and medial regions of the prefrontal cortex and in the anterior and posterior regions of the cingulate cortex. For anxiety disorders, there is evidence that CBT increases activity in the ventral and dorsal anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), and the right ventrolateral cortex, and decreases activity in the amygdala, hippocampus, periaqueductal gray, and the anterior and medial temporal cortex. The ACC and mPFC have been implicated in higher-order executive cognitive functions such as working memory, reasoning, problem solving, self-referential processing and cognitive control of emotions; cognitive processes also targeted by CT [27,51–53]. These findings are consistent with the view that CT produces symptom

reduction primarily through its impact on higher-order executive functions such as problem solving, cognitive reappraisal and self-referential thinking.

One of the most significant neuroimaging studies on the effects of CT on depression was conducted by Goldapple and colleagues. [49]. Positron emission tomography (PET) measurements were taken on 17 outpatients with MDD before and after CBT. Analysis revealed the CBT group had significant increases in hippocampal and dorsal mid-cingulate metabolic activity coupled with widespread decreases in the medial and ventrolateral PFC and orbital frontal regions. The authors concluded that CBT produces depressive symptom reduction via modulation of top-down cognitive processes involved in the encoding and retrieval of negative associative memories, production of rumination, and the overprocessing of irrelevant information. In another study in which fMRI measurement was taken while depressed patients completed self-ratings of emotionally valenced words at pretreatment, stronger recovery after 16 sessions of CT was achieved by individuals who exhibited decreased pretreatment reactivity to emotional words in the subgenual cingulate cortex and increased reactivity in the amygdala [54]. These results indicate that CT could be most beneficial for depressed individuals who have heightened emotional reactivity and deficient regulatory control.

A few studies have investigated the neural basis of CBT for anxiety disorders. For example, a study in which fMRI scans were performed on eight patients with post-traumatic stress disorder (PTSD) after a trial of exposure and cognitive restructuring found significantly increased bilateral rostral ACC and reduced amygdala activation while the patients processed fearful faces [55]. A PET scan study of group CBT versus citalopram for social anxiety found that both treatments led to significant symptom improvement and decreased regional cerebral blood flow in the amygdalohippocampal region [56]. Patients with obsessive–compulsive disorder exhibit hyperactivation of the orbitofrontal cortex (OFC), caudate nucleus, thalamus and ACC during provocation of symptoms, but with symptom improvement either from pharmacotherapy or behavior therapy decreases have been reported in the OFC, dorsolateral PFC and ACC along with increases in posterior brain activity related to action-monitoring [57,58]. Together these studies indicate that symptom improvement with CT and CBT for anxiety or depression is associated with decreased activity in the amygdalohippocampal subcortical regions that involve bottom-up emotion processing and improved activity of top-down processes in the mPFC, OFC and ACC involved with cognitive control of emotion [27,59,60].

Neurophysiological correlates of cognitive control

As discussed previously, treatment process research has shown that CT produces symptom change by correcting the maladaptive information processing biases that characterize anxiety and depression. Neuroimaging studies investigating the neural substrates of cognitive control of emotion shed light on the neurophysiological effects of specific therapeutic ingredients of CT such as cognitive restructuring that involves the reappraisal of emotional stimuli.

Neurophysiological research has shown that individuals with a depressive or anxious disorder exhibit increased activation in the amygdala and subgenual cingulate cortex, and decreased dorsolateral and ventrolateral PFC activity when processing emotional stimuli [59,61,62]. In their review paper, Ochsner and Gross [27] concluded that higher-order cortical regions such as the OFC, ACC and medial and lateral PFC are involved in the cognitive control of emotion. Healthy individuals instructed to suppress unwanted thoughts exhibit increased activation in the ACC and dorsolateral PFC [63,64]. Experimental studies of cognitive reappraisal indicate it is effective in reducing negative emotion to provocation tasks and is associated with increased activation of the dorsolateral and ventrolateral PFC and ACC, as well as decreased activity in the amygdala [65,66]. Depressed individuals exhibited greater activation of the right PFC and reduced activation in the left PFC when reappraising negative images that indicates an inefficient engagement of top-down PFC regulation of emotion [67]. Based on an attentional cueing task involving happy, sad and neutral faces, Beevers and colleagues found that dysphoric compared to nondysphoric individuals showed impaired engagement of the lateral PFC and parietal regions on trials that required cognitive control over emotion stimuli [68]. Finally, cognitive training to attend to or avoid threat stimuli altered lateral PFC activity to emotional stimuli [69]. Together these findings indicate that various cognitive strategies representing the regulation of negative emotion through top-down processes activate PFC and ACC regions in a manner consistent with the neural mechanisms of CT depicted in Figure 1. However the ACC, in particular, is a complex structure, engaged in both top-down and bottom-up attention and response selection processes. It functions as an amplifier and filter of emotional and self-referential information via neuroanatomical connections upward into the PFC and downward to subcortical structures such as the thalamus [70,71].

Conclusion and future directions

In recent years considerable progress has been achieved in the development, evaluation and understanding of the change processes involved in the psychological treatment of clinical depression and the anxiety disorders. CT is a theory-derived, evidence-based psychotherapy for anxiety and depression that has been rigorously evaluated in numerous clinical trials. However, treatment process research that elucidates the mechanisms of therapeutic change in CT has lagged behind the advances attained in the outcome research. The emergence of a new generation of research utilizing laboratory-based information processing tasks and neuroimaging measurement pre- and post-treatment are providing new insights into the mediators of change in CT.

In this paper we presented a refined and elaborated cognitive theory of anxiety and depression that integrates Beck's previous cognitive formulation with more recent findings on the neurophysiology of cognition and emotion (Figure 1). In this model the production of anxious or depressive symptoms is a culmination of heightened

Box 3. Questions for future cognitive neuroscience research on CT

- Does symptom reduction occur primarily by improving activation of the cortical regions involved in cognitive control of negative emotion, or is de-activation of the subcortical regions implicated in negative emotion generation the primary mechanism of change in CT [10]?
- Based on symptom provocation experiments such as the mood induction task, what are the specific cognitive and neural processes involved in the generation and regulation of fear and sadness and how do they interact with specific therapeutic elements of CT to effect symptom change?
- Is symptom remission in CT of anxiety and depression a result of improved emotional processing or do other mediators of change contribute to treatment effectiveness such as behavioral activation?
- What are the common and specific brain pathways involved in symptom change in CT relative to other types of interventions such as pharmacotherapy?

activation of bottom-up processes (i.e. negative schemas) involving the amygdalohippocampal subcortical region and inhibited access to the reflective processes of cognitive control (i.e. top-down processing) involving the ACC, medial and lateral PFC, and orbitofrontal cortex. Findings from treatment dismantling studies, neuroimaging of CT, and information-processing provocation research indicates that symptom reduction in CT is associated with alterations in the brain regions implicated in the production and control of negative emotion [48].

Many key questions remain about the mechanisms of change in CT for anxiety and depression (Box 3). To improve our understanding of the therapeutic process, comparative experimental studies are needed that isolate specific elements of CT, measure their effects on particular cognitive and neural processes involved in negative emotion, and compare the findings across depressed, anxious and healthy samples. Ultimately a greater understanding of the mechanisms of change in evidence-based treatments such as CT will lead to improvements in the effectiveness of our interventions for emotional disorders.

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