

Neural mechanisms of the cognitive model of depression

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Abstract | In the 40 years since Aaron Beck first proposed his cognitive model of depression, the elements of this model — biased attention, biased processing, biased thoughts and rumination, biased memory, and dysfunctional attitudes and schemas — have been consistently linked with the onset and maintenance of depression. Although numerous studies have examined the neural mechanisms that underlie the cognitive aspects of depression, their findings have not been integrated with Beck's cognitive model. In this Review, we identify the functional and structural neurobiological architecture of Beck's cognitive model of depression. Although the mechanisms underlying each element of the model differ, in general the negative cognitive biases in depression are facilitated by increased influence from subcortical emotion processing regions combined with attenuated top-down cognitive control.

Schemas

Internal beliefs or representations of stimuli, ideas or experiences that — if negative — can simultaneously contribute to and be exacerbated by depressive symptoms.

Beck's introduction of the cognitive model of depression over 40 years ago¹ advanced our understanding of the monolithic concept of depression that afflicts millions of people (BOX 1). The cognitive model is an empirically based framework for identifying and understanding factors that maintain an episode of depression. The cognitive model also served as the foundation for the development of cognitive therapy, a highly effective and durable treatment for a wide variety of disorders, including depression². Recent developments in neuroimaging and cellular biology have enabled researchers to examine components of the cognitive model and isolate their underlying biological mechanisms.

In this Review, we synthesize research findings from neuroimaging studies and provide a neurobiological formulation of the cognitive model of depression³. Other neurobiological models^{4–8} have also provided compelling and parsimonious accounts of depression but have focused primarily on the affective disruption associated with the disease. With this Review we aim to link neurobiological and cognitive perspectives of depression, providing an integrated account of the neurobiological substrates that perpetuate the maladaptive behaviours that comprise the cognitive model of depression. Furthermore, developing an integrative model is in line with a central tenet of the US National Institute of Mental Health's strategic plan to strengthen the public health impact of translational research⁹ and, perhaps more importantly, will yield a fuller, more nuanced understanding of this complex and debilitating disorder.

The cognitive model of depression

According to Beck's cognitive model of depression (FIG. 1), biased acquisition and processing of information has a primary role in the development and maintenance of depression^{1,3,10}. In this model, latent schemas — internally stored representations of stimuli, ideas or experiences — are activated by internal or external environmental events and then influence how incoming information is processed¹. Schemas influence information processing by guiding how stimuli are encoded, organized and retrieved. In this sense, they determine how an individual interprets their experiences in a given context. Adverse events that occur early in life might lead to the development of depressive schemas, which are generally characterized by negative self-referential beliefs. Such latent depressive self-referential schemas can be activated by subsequent stressors, which are often salient events that reflect the underlying schema content (for example, a job loss may be devastating for someone who equates full time employment with self worth)³. Once activated, depressive schemas confer vulnerability for depression onto the individual by altering information processing with negative self-referential thoughts about the self, the personal world and the future — also known as the negative cognitive triad¹¹.

Activation of depressive self-referential schemas leads to specific impairments in attention, interpretation and memory¹¹. Negative and pessimistic processing of one's self and context become pervasive, including interpretations, evaluations and appraisals¹¹. As a result, the individual with depression develops schema-based

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Box 1 | Description and epidemiology of major depressive disorder.

The Diagnostic and Statistical Manual of Mental Disorders (4th edition) defines major depressive disorder (MDD) as the presence of five (or more) depressive symptoms (for example, sad mood, anhedonia, fatigue, impaired concentration, worthlessness and suicidal ideation). Symptoms must be present for most of the day, nearly every day, and should represent a substantial change from previous functioning. One of the symptoms must be either depressed mood or anhedonia. Symptoms must also cause considerable distress or impairment in social, occupational or other important areas of functioning. These symptoms should not be attributable to substances, medical conditions or the death of a loved one. Each component of the cognitive model (for example, biased attention, processing and memory) is proposed to maintain a depressive episode, although we speculate that some elements of the model may be more closely linked to particular symptoms than others. For example, anhedonia is probably associated with altered processing of positive stimuli, whereas feelings of worthlessness may be more closely tied with biased thoughts and rumination. A persistent sad mood is probably maintained in part by an attentional bias towards negative information in the environment. Future research that links symptom profiles to specific elements of the cognitive model would help to further refine the cognitive model of depression.

Recent epidemiological research indicates that among adults residing in the United States, the 12-month prevalence rate for MDD was 6.6% (95% confidence interval; 5.9%–7.3%) and lifetime prevalence for MDD was 16.2% (95% confidence interval; 15.1%–17.3%). According to the World Health Organization, MDD is a leading cause of disability worldwide among people of 5 years of age and older. The annual economic cost of MDD in the United States alone is a staggering US\$70 billion in medical expenditure, lost productivity and other costs^{127,128}. Approximately 51% of individuals who experienced MDD in the past year received healthcare treatment for MDD, although treatment was considered adequate in only 21% of the cases¹²⁹. Thus, MDD is a prevalent and pervasive mental health disorder that, unfortunately, is often not optimally treated.

dysfunctional attitudes whereby he or she views themselves as defective and day-to-day life as rife with struggle, and assumes that their current difficulties or suffering will continue indefinitely¹. The activation of these dysfunctional attitudes increases the likelihood that the depressed person will selectively attend to mood-congruent stimuli, thereby encoding negative affective information and filtering out positive information¹². This process increases awareness for depressive elements in the environment and can decrease positive emotion experienced during a pleasing event, a phenomenon often referred to as a positive blockade¹³. Similarly, there is strong evidence for memory biases in depression. In particular, individuals with depression tend to exhibit preferential recall of negative over positive material¹⁴.

Recent research has suggested that specific impairments in memory and attention are related to inhibitory deficits or, in other words, the inability to disengage from negative stimuli. Several theorists have suggested that inhibitory deficits are manifested clinically as a ruminative response style^{3,15,16}. Depressive rumination — the tendency to think repetitively about the causes and consequences of negative affect — has been associated with the onset¹⁷, deteriorating course¹⁸, chronicity¹⁹ and duration of depression^{17,20}.

Thus, in Beck's cognitive model of depression, early adverse events (in combination with genetic and personality factors) contribute to the establishment of depressive self-referential schemas (also known as latent dysfunctional attitudes). Negative schemas, once they have been activated by stressors, influence information processing in the brain, resulting in negatively

biased attention, processing and memory. Specific biases in attention and memory result from inhibitory deficits, which also contribute to a ruminative response style that perpetuates negative thoughts about the self, the world and the future. This process instigates a feedback loop within the cognitive system that serves to initiate and maintain an episode of depression (FIG. 1).

Correlates of the cognitive model

In the following sections, we review recent discoveries regarding the functional and structural neurobiological architecture associated with depression, and then present these findings in the context of the cognitive model. Integrating neurobiological data within a cognitive framework will allow for a holistic, theory driven examination of the model, which is crucial for advancing our understanding of the aetiology and treatment of depression. In parallel with existing neurobiological models of depression that focus on affective symptomatology^{4–8}, our Review suggests that cognitive biases in depression are due to maladaptive bottom-up processes (that is, patterns of activation starting in subcortical brain regions that are lower along the cognitive hierarchy, which proceed sequentially to connected cortical areas higher up) that are generally perpetuated by attenuated cognitive control (that is, failure of regions higher up the cognitive hierarchy to effectively regulate activity in those lower regions).

Biased attention for emotional stimuli. The inability to allocate attention to appropriate emotional cues is central to the cognitive model²¹. For individuals without mood disturbance, attention is generally biased towards positive stimuli²². However, individuals with clinical depression have no such selective attention towards angry, happy or neutral stimuli, and instead show an attentional bias for sad stimuli²². The inability to disengage from negative stimuli is thought to exacerbate symptoms of dysphoria and perpetuate the positive feedback loop of depressive symptoms²³. Below, we discuss the neural mechanisms that may underlie biased attention in individuals with depression.

Cortical areas that are associated with attention in healthy individuals, including areas that control shifts in gaze, include the intraparietal sulcus, precentral sulcus, superior temporal sulcus and prefrontal cortex (PFC)²⁴. These areas help to select competing visual stimuli, which are represented in the visual cortex as mutually suppressive signals. The directing of attention to one stimulus simultaneously suppresses the processing of other, competing stimuli²⁵. The act of switching attention requires attentional disengagement, which necessitates top-down intervention from high-order cortical structures such as the ventrolateral prefrontal cortex (VLPFC; associated with control over stimulus selection), dorsolateral prefrontal cortex (DLPFC; associated with executive functioning) and superior parietal cortex (associated with shifts in gaze)^{26–29} (FIG. 2).

It is possible that in depression, attentional focus on a negatively valenced stimulus effectively blocks out the processing of other, potentially more positive

Cognitive hierarchy

An ordering of brain regions based on the relative complexity and abstraction of their cognitive functions.

Dysphoria

A negative mood state characterized by feelings of discontent, anguish, distress and depression.

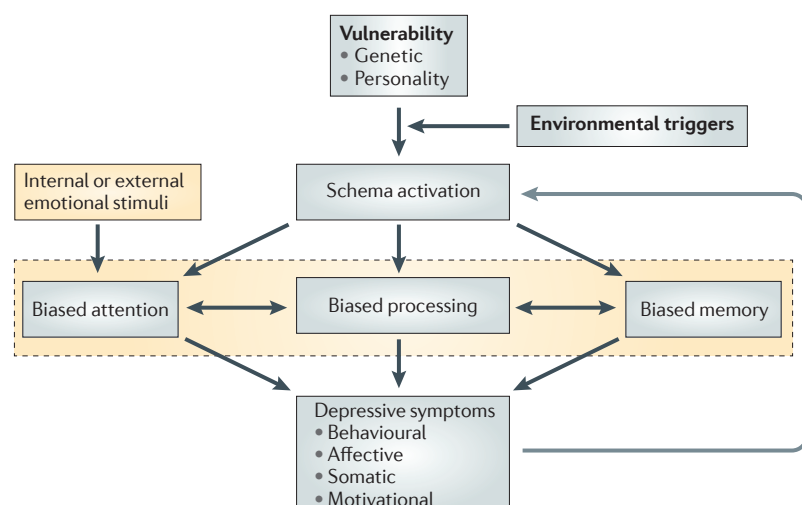


Figure 1 | Information processing in the cognitive model of depression. Activation of depressive self-referential schemas by environmental triggers in a vulnerable individual is both the initial and penultimate element of the cognitive model. The initial activation of a schema triggers biased attention, biased processing and biased memory for emotional internal or external stimuli. As a result, incoming information is filtered so that schema-consistent elements in the environment are over-represented. The resulting presence of depressive symptoms then reinforces the self-referential schema (shown by a grey arrow), which further strengthens the individual's belief in its depressive elements. This sequence triggers the onset and then maintenance of depressive symptoms.

information. Indeed, there is evidence that people with depression show increased attention for negative stimuli and decreased attention for positive stimuli compared with non-depressed individuals¹². This effect may stem from inefficient attentional disengagement from negative stimuli, which in individuals with depression is associated with decreased activity in the right VLPFC, right DLPFC and right superior parietal cortex compared with healthy controls^{26,27}. We propose that reduced activity in these regions contributes to difficulty with disengagement from negative stimuli in individuals with depression, thereby lengthening the duration of exposure to depressive items^{26,27,30,31}.

One putative mechanism that contributes to impaired disengagement is deficient inhibition (that is, the inability to disengage can be viewed as an impaired ability to inhibit attention for negative stimuli). Normal inhibitory processing has been associated with activity in the rostral anterior cingulate cortex (ACC)^{32,33}, but the pattern of ACC activity is substantively different in individuals with depression. Healthy individuals show greater rostral ACC activity when successfully inhibiting attention to positive stimuli, whereas individuals with depression show greater activation when successfully inhibiting attention to negative stimuli^{34–36}. This suggests that healthy individuals require greater cognitive effort to divert attention away from positive stimuli, but individuals with depression require greater cognitive effort to divert attention away from negative stimuli. In the context of the cognitive model, altered rostral ACC function probably contributes to biased attention for negative information in depression by disrupting efficient inhibition of negative stimuli.

Anterior cingulate cortex (ACC). The frontal part of the cingulate cortex. As with many brain areas, subdivisions within the ACC, such as the dorsal, rostral and ventral ACC, are determined by functional differences rather than anatomical landmarks. As such, 'boundaries' for these regions may vary slightly across studies.

In summary, the observed differences in cortical activity between healthy individuals and individuals with depression can be individually associated with elements of biased attention. Within the cognitive model framework, individuals with depression are less efficient at selecting stimuli (related to decreased VLPFC function), coordinating disengagement from negative stimuli (related to decreased DLPFC and ACC function), and shifting gaze onto other, potentially adaptive stimuli (related to decreased superior parietal cortex function) (FIG. 2).

Biased processing of emotional stimuli. Once stimuli have been perceived from the environment, the cognitive model predicts that individuals with depression will show particular awareness for negative aspects of the stimuli¹⁴. Below, we discuss the neural mechanisms that might underlie this bias (FIG. 3).

Emotional stimuli are relayed to the thalamus, which projects directly to the amygdala³⁷. The amygdala, a brain structure that is involved in detecting emotion (possibly linked to its proposed role in salience detection^{38,39}), interprets and perpetuates the emotional quality of the stimulus and seems to be regulated in part by indirect inhibitory input from the left DLPFC^{40,41}. Amygdala activity increases in healthy individuals during processing of emotional information⁴² but has an inverse relationship with left DLPFC activation, which is suggested to represent a system of higher-order cognitive intervention^{26,40,42,43}.

When individuals with depression process negative stimuli, they show amygdala reactivity that is more intense (by up to 70%) and longer lasting (up to three times as long) than in healthy controls, even when an emotional task is immediately followed by a non-emotional task^{41,43}. The association seems to be linear in individuals with depression, such that processing of increasingly sad faces is accompanied by increasing activation in the left amygdala and putamen⁴⁴. Recent studies indicate that this pattern of amygdala response, indicative of biased stimulus processing, is automatic and exists even if the emotional valence of the stimulus is masked to the conscious mind through subliminal presentation^{45–47}. An increased amygdala response is associated with faster processing of negative stimuli and with decreased levels of psychological well-being⁴⁸. Furthermore, excessive amygdala reactivity in individuals with depression persists even after the aversive stimulus is no longer present⁴⁹, although antidepressant medication has been shown to diminish the extent of amygdala reactivity to negative stimuli^{50,51}. Thus, it seems that individuals with untreated depression are not only more likely to attend to negative stimuli than healthy controls (see above) but experience a stronger and longer lasting neural response to these stimuli (for an in-depth review of functional changes following depression treatment, see REF. 52).

In individuals with depression, increased amygdala reactivity creates a bottom-up signal that biases emotional stimulus processing in higher cortical areas and can maladaptively alter perceptions of the environment

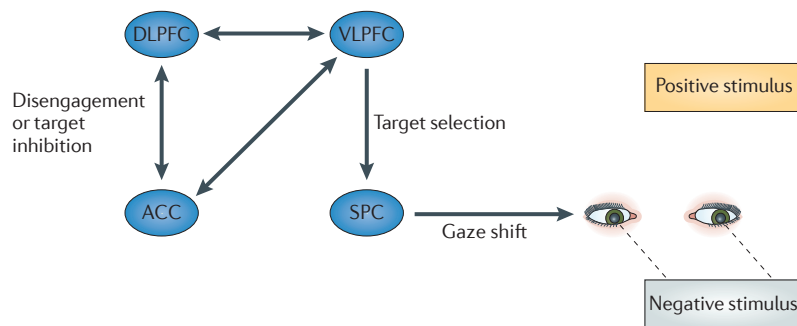


Figure 2 | Putative cognitive neurobiological model of biased attention for negative stimuli in individuals with depression. The areas that are associated with biased attention for negative stimuli include the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and superior parietal cortex (SPC). Although it is unclear which process instigates the bias, research indicates that the VLPFC is involved in selecting gaze targets, the DLPFC and ACC inhibit the VLPFC to promote disengagement, and the SPC is involved in coordinating shifts in gaze. All four regions show decreased functional activity (shown in blue) in individuals with depression compared with healthy controls, suggesting that all three of the above steps are attenuated to some degree. Arrows are intended to represent functional connections, not necessarily anatomical connections.

and of social interactions⁴⁶. The perception of negative information may persist as a result of reduced cognitive control over the amygdala associated with aberrant activation in the bilateral DLPFC^{26,31,41}. Anatomical and functional abnormalities in the DLPFC differentiate individuals with depression from healthy individuals — for example, decreased grey matter volume⁵³, lower resting-state activity and decreased reactivity to both positive and negative stimuli³¹. These abnormalities may contribute to a decoupling of left DLPFC and amygdala activation, particularly when cognitive resources are being otherwise used, although individuals with depression may not show both effects simultaneously⁵⁴. Additionally, hyperactivity in the right DLPFC, commonly observed alongside left DLPFC hypoactivity^{55,56}, is associated with anticipation of negative stimuli⁵⁷ and may bias attentional resources towards emotional stimuli⁵⁸. Altered function bilaterally in the DLPFC has been associated with decreased cognitive control, thereby facilitating heightened amygdala reactivity and ultimately contributing to dysfunctional emotional processing^{31,43,59,60}.

A discrete, though not mutually exclusive, explanation for the sustained processing of negative emotional information in individuals with depression involves differences in the thalamocortical pathway — a pathway responsible for organizing and processing environmental stimuli⁶¹. Pertinent elements of this pathway include the thalamus, responsible for the distribution of afferent signals^{62,63}, the dorsal ACC, a region that relays top-down cognitive control from the DLPFC⁶⁴, and the subgenual cingulate cortex, a region that integrates emotional feedback from the limbic system and projects to higher-order cognitive structures⁶¹ (FIG. 3).

Dysphoric individuals show increases in thalamic activity during depressive episodes^{61,65,66}. It has been posited that the increase in activity in individuals with

depression may be a compensatory mechanism, attempting to make up for lost signal resulting from reduced functional connectivity between the medial thalamus and the dorsal ACC^{61,67}. The dorsal ACC exerts less inhibitory influence over the limbic system in individuals with depression, meaning that ‘more depressive’ limbic feedback is able to proceed via bottom-up pathways through the subgenual cingulate cortex upstream to the higher-order regions⁶¹. Therefore, in the context of the cognitive model, impaired connectivity between the thalamus and the ‘cognitive’ dorsal ACC may increase routing of information through the ‘emotional’ subgenual cingulate cortex, which increases the perceived emotionality of incoming stimuli for individuals with depression.

The research discussed above indicates that negative stimuli have a higher salience in individuals with depression compared with healthy people. In addition, they generally experience a positive blockade, in the sense that they have decreased capacity to process positive emotion and that positive stimuli seem to have decreased salience^{13,68}. For example, processing of happy faces involves activation of the right fusiform gyrus in healthy individuals, but activity in this area decreases as depressive symptoms increase⁴⁴. Unlike the experience of negative emotion, which is common to mood and anxiety disorders, decreased positive emotion is thought to be a distinctive feature of depression⁶⁹.

In healthy individuals, the ability to experience and maintain positive affect is closely associated with brain systems that mediate reward and motivation, which include the nucleus accumbens^{70,71}. Top-down activity from the PFC has been shown to trigger dopamine release, which incites nucleus accumbens and amygdala activity in response to rewards^{72,73}. In effect, specific patterns of activity in the PFC have been shown to predict the extent and duration of affective responses to reward⁷⁴.

Decreased positive affect in response to reward in individuals with depression¹³ is consistent with functional MRI results indicating that nucleus accumbens and PFC activity decreased more dramatically in individuals with depression than in healthy controls during the period following positive stimulus presentation^{75,76}. The decrease in nucleus accumbens and PFC activity was especially prominent when subjects were asked to consciously upregulate or sustain positive mood⁷⁵, suggesting an impaired capacity to maintain positive affect through top-down control. Indeed, when individuals with depression were asked to maintain positive mood following a reward, those who showed sustained nucleus accumbens and PFC activity reported more positive affect several days later than those with substantial decreases in nucleus accumbens and PFC activity⁷⁵.

Additionally, decreased reward responses can perpetuate depressed mood by failing to trigger adaptive behaviours. In healthy individuals, the nucleus accumbens is associated with the hedonic coding of incoming stimuli for rewarding properties, which can then be interpreted by the caudate nucleus to prompt appropriate reinforcement mechanisms^{77–79}. As was previously

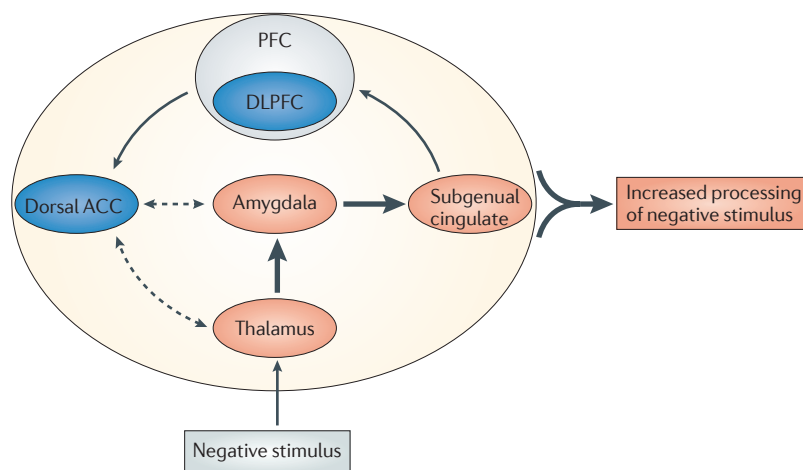


Figure 3 | Putative cognitive neurobiological model of biased processing of negative stimuli in individuals with depression. Negative signals from incoming stimuli induce hyperactivity (shown in red) in the thalamus, from the thalamus to the amygdala and on to the subgenual cingulate cortex, which relays limbic activity to higher cortical regions such as the prefrontal cortex (PFC). Concurrently, hypoactivity (shown in blue) in the dorsolateral prefrontal cortex (DLPFC) is associated with attenuated cognitive control, which impairs the ability of the dorsal anterior cingulate cortex (dorsal ACC) to adaptively regulate the lower regions. The net result of this process is increased awareness and conscious processing of negative stimuli in the environment. Solid arrows (which show intact associations) and dashed arrows (which show attenuated associations) are intended to represent functional connections, not necessarily anatomical connections. Thicker arrows show increased signal.

discussed, nucleus accumbens activity is influenced by PFC activity in healthy individuals⁷⁴. In individuals with depression, reduced nucleus accumbens responses to rewards are associated with diminished volume and activity in the caudate nucleus^{76,77}, and this suggests that rewarding properties associated with a stimulus may not be accurately labelled⁷⁷. As a result, rewarding stimuli may fail to trigger reinforcement mechanisms, which could impair the ability of individuals with depression to pursue rewarding behaviours⁷⁹. Based on this evidence, we propose that decreased PFC activity reduces reward sensitivity of the nucleus accumbens, which, in turn, contributes to the inability of individuals with depression to adaptively alter reward-seeking behaviour.

In summary, several lines of research point to separate mechanisms (for example, amygdala hyperactivity, hypoactivity in the DLPFC and blunted nucleus accumbens response), in individuals with depression, that increase the salience of negative stimuli and decrease the salience of positive or rewarding stimuli (FIG. 3). As a result, a person with depression displays a cognitive bias towards negative information and away from positive information, thus contributing to the maintenance of a depressed mood state.

Biased thoughts and rumination. According to the cognitive model, internalizing negative emotional stimuli (that is, letting negative life events influence self esteem and self image) leads to the experience of depression symptoms¹, and the relationship between risk factors and onset of depression symptoms has been shown to

be mediated in part by ruminative patterns of thought⁸⁰. In addition, depressive symptoms are often reinforced by ruminative thoughts, particularly those that constantly remind the individual of his or her perceived flaws¹⁹. We propose that rumination is associated with three elements: altered emotion and memory processing, increased self-referential processing and decreased top-down inhibition of these processes.

Ruminative thoughts are associated with activity in regions involved in emotional recall, such as the amygdala and hippocampus^{81,82}. In individuals with depression, rumination has been correlated with sustained amygdala activation paired with increased reactivity in the subgenual cingulate cortex⁸². Interestingly, amygdala activation was weakly associated with the severity of depression but strongly associated with that of rumination, indicating the central role of emotional processing in ruminative thought⁸².

In addition, rumination seems to be facilitated by a broader version of the neural network that is associated with self-referential processing (FIG. 4). The medial prefrontal cortex (MPFC)⁸³ — a key region associated with rumination⁸³ — projects directly to the amygdala⁸⁴, is considered the home of the internal representation of self⁸⁵ and is associated with both self-referential attribution as well as self-referential appraisal^{61,81,86}. Attempting to decrease rumination through cognitive reappraisal correlates with decreased MPFC activity, suggesting that ruminators who decrease negative cognition also decrease self-reference^{86,87}. Therefore, increased MPFC activation in response to negative rumination (that is, prior to reappraisal) may underlie the tendency of individuals with depression to interpret stimuli as self-referential^{81,86}.

Prolonged processing of emotional experiences in people with depression — a result of ruminative thought — is probably maintained by impaired top-down cognitive control over limbic areas, which is generally associated with hypoactivation in the left DLPFC and VLPFC concurrent with rumination^{31,86,88}. Decreased activity in these regions might impair the ability of individuals with depression to block out negative, repetitive thoughts¹⁶. More specifically, DLPFC and VLPFC hypoactivity are correlated with altered patterns of rostral ACC activity (that is, decreased activation while inhibiting positive stimuli and increased activation while inhibiting negative stimuli, as discussed above), which is thought to contribute to rumination by facilitating the inhibition of positive information and impeding the inhibition of negative information^{34–36}. The presence of either decreased inhibition for negative affect or increased inhibition for positive affect predicts greater depression severity³⁴.

Thus, ruminative thought patterns in depression are facilitated by sustained amygdala, hippocampal and subgenual cingulate cortex activation (which prolongs the emotional experience), increased MPFC activity (which promotes self-referent cognition) and altered rostral ACC function (which modulates inhibition of emotional stimuli) (FIG. 4). These effects, in turn, lead to greater rumination and often a more severe episode of depression¹⁹.

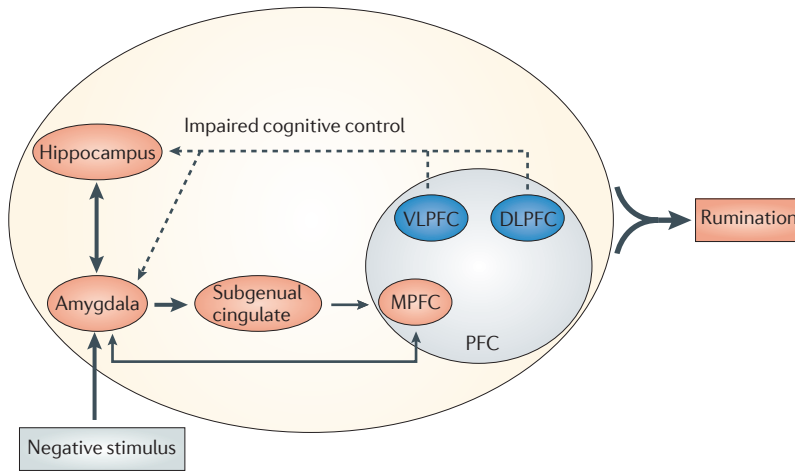


Figure 4 | Putative cognitive neurobiological model of ruminative thought in individuals with depression. Regions that are proposed to be involved in rumination include the amygdala and the hippocampus, two proximal structures that exhibit mutual facilitation during processing of emotional stimuli. Among people with depression, hyperactivation (shown in red) in the amygdala and hippocampus correlates with increased activity in the subgenual cingulate cortex, a region that integrates limbic feedback and relays it to the prefrontal cortex (PFC). Activity in the subgenual cingulate seems to correspond with increased activity in the medial prefrontal cortex (MPFC), a region that shows default-mode activity and is associated with internal representations of self. Concurrently, in individuals with depression, activation seems to be decreased (shown in blue) in neighbouring PFC regions that are associated with cognitive control, specifically the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC). Consequently, these regions are thought to have less regulatory influence on subcortical regions that are involved in memory, and this facilitates the undesired recall of mood-congruent (generally negative) events. The net result of this process is an increase in ruminative thought. Solid arrows (which show intact associations) and dashed arrows (which show attenuated associations) are intended to represent functional connections, not necessarily anatomical connections. Thicker arrows show increased signal.

Biased memory for negative stimuli. The extent to which negative stimuli are disproportionately encoded and recalled as part of short- and long-term memory is an important element of the cognitive model of depression¹⁴. Biased memory is closely related to biased attention and processing, in that increased awareness for negative stimuli influences the probability that negative information will be encoded and later recalled^{89,90}. As such, the neurological correlates of biased memory not only include regions associated with memory but also share characteristics with the pathways of biased attention and processing.

As with biased processing, amygdala reactivity plays a key part in biased memory through bottom-up influence of other areas⁹¹. Activity in the amygdala facilitates the encoding and retrieval of emotional stimuli in healthy individuals^{92,93} by modulating activity in the hippocampus, a region central to episodic memory^{94,95}, and in the caudate and putamen, regions that are associated with skill learning⁹⁴. In individuals with depression, hyperactivity in the right amygdala was associated with better encoding of negative stimuli, but not positive or neutral stimuli⁹¹. Furthermore, in individuals with depression, amygdala activity during encoding was correlated with increased hippocampus, caudate and putamen activity,

which in turn facilitated recall of negative, but not positive, information⁹¹. This finding suggests that memory biases in depression may be due to both increased amygdala function during encoding and enhanced hippocampal, caudate and putamen activity during recall of negative information compared with that of healthy individuals (FIG. 5).

Attempting to recall emotionally charged autobiographical memories yields divergent neural responses in individuals with depression and healthy individuals. The ventral MPFC, a region that is associated with abstract representations of reward value (amongst other functions)^{96,97}, is hyperactive during recall of self-relevant happy events and hypoactive during recall of self-relevant sad events in individuals with depression compared with healthy controls⁹⁸. One interpretation is that individuals with depression require greater cognitive effort (for example, by the MPFC) to recall happy personal memories, whereas recall of negative memories requires less top-down influence (partly owing to increased automatic bottom-up processing of sad stimuli)⁹⁸.

In summary, it seems that biased memory for negative stimuli in depression may be associated with hyperactivity in the amygdala, triggering bottom-up regulation of the hippocampus, caudate and putamen, which may allow for depressive recall without the need to recruit top-down prefrontal regions, although further research will be needed to support this perspective (FIG. 5).

Dysfunctional attitudes and negative schemas. Dysfunctional attitudes, specifically negative self-referential schemas, play a central part in the cognitive model of depression. Here, the individual forms firm beliefs or representations about themselves, their environment or their future that directly relate to their own self worth. Although relatively few studies have examined the networks involved with dysfunctional attitudes, existing research has identified several areas that are associated with these maladaptive beliefs. During negative self-referential tasks, individuals with depression show activation in the MPFC, ACC and amygdala that is correlated with depression symptom severity^{85,99–102}. These regions, which represent the higher, intermediate and lower levels of the cognitive hierarchy, respectively, comprise a network of self-referential thought, in which maladaptive patterns of activation lay the groundwork for biased schemas (FIG. 6).

The roles of these regions may be inferred from what is known about their involvement in other processes. The amygdala, which is located near the bottom of the cognitive hierarchy, is closely implicated in emotionality and emotional processing^{103,104}. The MPFC, which is located near the top of the cognitive hierarchy, is thought to be the key region for internal representation of self⁸⁵. In fMRI studies, this area shows the highest baseline activation when the subject is not actively involved in a task, suggesting that the MPFC may respond to self-focused stimuli⁸⁵. The ACC serves three key intermediary functions; the dorsal ACC relays top-down cognitive signals⁶⁴, the ventral ACC influences the extent to which incoming sensory information is labelled with emotional

valence¹⁰⁵ and the rostral ACC influences the extent to which incoming sensory information is labelled as self-referential¹⁰⁶. Individuals with depression have been shown to exhibit decreased resting-state connectivity between the dorsal ACC and limbic areas⁶⁷, which is associated with increased amygdala responses to negative stimuli⁶⁷ (which is probably related to decreased cognitive intervention). Hyperactivation in the amygdala, MPFC and ACC together predict a greater propensity towards self-attribution of external stimuli^{102,106}, which — owing to biased attention and processing in individuals with depression — is more likely to be negative. Thus, consistent with the cognitive theory of depression, the amygdala, ACC and MPFC form a circuit that, if hyperactive, may facilitate and maintain the negative, self-referential beliefs of a person with depression (FIG. 6).

Extensive research has also focused on the role of serotonin transporter (5-HTT) binding as a key moderator of pessimism, a specific self-referential schema^{107,108}. In the synapse, elevated levels of 5-HTT binding facilitate serotonin reuptake, which, by decreasing the amount of available extracellular serotonin, is thought to contribute to a heightened risk of depression¹⁰⁹. In patients with depression who show marked pessimism — a form of dysfunctional attitude as measured by the Beck Hopelessness Scale¹¹⁰ — 5-HTT binding was elevated in the PFC, ACC, putamen and thalamus compared with those who do not show marked pessimism¹⁰⁷. Similar serotonin binding results were found in adults with a history of recurrent depression, which suggests that vulnerability to dysfunctional attitudes is biologically present even when depressive symptoms are not¹¹¹ (for reviews on the role of serotonin and other neuropeptides in depression, see REFS 112,113).

Self-referential schemas therefore probably result from a sequence of processes, starting with altered resting-state functional connections and proceeding to include aberrant activity in lower emotion detection regions (the amygdala), intermediate regions mediating stimulus encoding (the rostral and ventral ACC) and higher-order, self-referential brain regions (the MPFC). In the context of the cognitive model of depression¹, these regions form a pathway that emphasizes the emotionality and self-referential nature of incoming stimuli. In addition, decreased serotonin expression, facilitated by increased 5-HTT binding, seems to have a prominent role in the development of dysfunctional attitudes (FIG. 6).

An integrated cognitive–biological model

As reviewed above, the neurobiological mechanisms that putatively underlie cognitive biases in depression seem to be influenced by two key processes: neurobiological processes that initiate the cognitive bias and attenuated cognitive control, which allows the bias to persist (FIG. 7). Based on the presented findings, we propose that the former process is best attributed to a bottom-up pathway that begins with hyperactivity of the limbic system (most notably the amygdala) and proceeds through the subgenual cingulate cortex, ACC, caudate, putamen, nucleus accumbens and hippocampus, to the PFC and

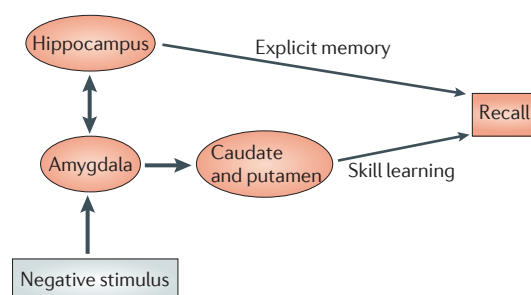


Figure 5 | Putative cognitive neurobiological model of biased memory for negative stimuli in individuals with depression. Biased memory in individuals with depression is another process that is consistently correlated with amygdala hyperactivity (shown in red). As negative stimuli are processed, amygdala activity is heightened and sustained. This leads to reciprocal activation in the hippocampus, a region that is critical to episodic memory formation, as well as the caudate and putamen, two regions that are closely involved with implicit memory and skill learning. In individuals with depression, this circuit is hyperactive during the processing of negative, but not positive, stimuli, and has been shown to increase the rate of recall of negative, but not positive, stimuli. Arrows are intended to represent functional connections, not necessarily anatomical connections. Thicker arrows show increased signal.

frontal cortex. Limbic hyperactivity is associated with a redistribution of cerebral blood flow, which modulates the distribution of oxygen and incites reciprocal suppression in regions that are ‘higher up’ along the cognitive hierarchy¹¹⁴. In this way, heightened functional responses to emotion stimuli directly influence the individual’s capacity to accurately interpret information in their environment.

The second component takes the form of attenuated cognitive control — a diminishing of the top-down system that prevents unrestrained activation in emotional regions of the brain. This attenuation in cognitive control seems to be region specific (for example, the MPFC for self-referential schemas, the DLPFC for rumination and biased processing and the VLPFC for biased attention) and curbs the top-down relationship (through the ACC and thalamus) with pertinent subcortical regions. With limited top-down cognitive control from the PFC, the consequences of maladaptive bottom-up activity persevere, including enhanced amygdala reactivity (which contributes to biased attention and processing), blunted nucleus accumbens response (which contributes to positive blockade) and aberrant functioning of the caudate and putamen (which contributes to dysfunctional attitudes and biased memory). In the context of the cognitive model of depression, subcortical regions, unchecked by cognitive control, reinforce the cognitive biases, leading to the ultimate outcome of increased awareness for schema-consistent stimuli, which in turn perpetuates depression.

The cognitive–neurobiological model that we propose (FIG. 7), which implicates bottom-up activation that is unchecked by top-down cognitive control, is

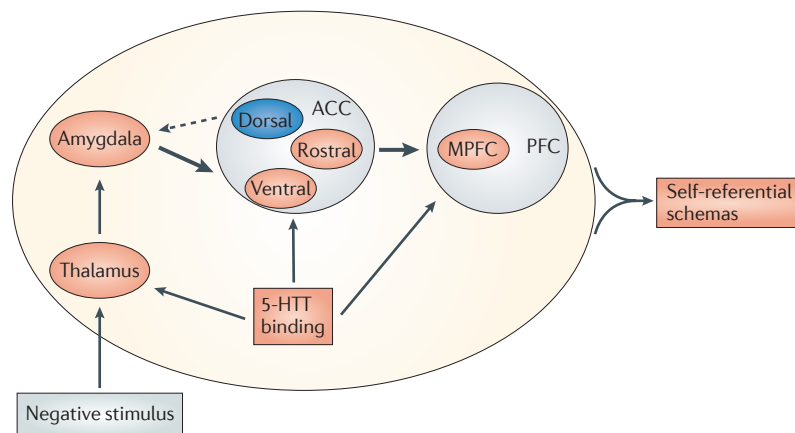


Figure 6 | Putative cognitive neurobiological model of self-referential schemas in individuals with depression. The development and reinforcement of self-referential schemas in depression are perpetuated by consistent patterns of hyperactivation (shown in red) along a pathway that increases the salience and self-referential elements of negative stimuli or events. Signals that represent negative stimuli or events are routed by the thalamus along the cognitive hierarchy, starting with the amygdala. Increased amygdala activity induces increased activity in its projection regions, specifically the anterior cingulate cortex (ACC). Different subregions of the ACC have different cognitive roles, with the ventral ACC being involved in labelling stimuli with emotional valence and the rostral ACC being involved in labelling stimuli with self-reference values. However, the dorsal ACC, which is involved in relaying top-down cognitive inputs, shows reduced functional connectivity with limbic regions, which contributes to attenuated cognitive control. Activity in the ACC is correlated with hyperactivity in the medial prefrontal cortex (MPFC), a higher-order region that is associated with internal representations of the self. Finally, increased serotonin transporter (5-HTT) binding in the PFC, ACC, putamen and thalamus has been associated with increased dysfunctional attitudes among individuals with depression. Solid arrows (which indicate intact associations) and the dashed arrow (which indicates an attenuated association) are intended to represent functional connections, not necessarily anatomical connections. Thicker arrows show increased signal.

consistent with current models of depressive phenomenology, most notably those of Phillips^{7,8} and Mayberg⁴⁻⁶. Phillips and colleagues describe the neural substrates of depression that are associated with altered emotion processing, which they break down into three functions: identifying the emotional significance of incoming stimuli, producing an affective state in response to these stimuli and regulating the parameters of the affective state⁸. The first two functions are associated with a ventral system (including, for example, the amygdala, striatum and subgenual cingulate), whereas the third — regulatory — function is associated with a dorsal system (including, for example, the PFC and dorsal ACC)⁸. Similarly, Mayberg conceptualizes depression as a multidimensional, systems-level disorder that stems from limbic-cortical dysregulation^{5,6}. Mayberg's model is characterized by decreased activity in dorsal neocortical regions paired with increased activity in ventral paralimbic regions, a relationship that is mediated by aberrant rostral ACC activity^{5,6}. Our formulation integrates the hierarchical structure of these systems-level models for emotion regulation with the dominant cognitive model of depression.

Fortunately, the cognitive-neurobiological model proposed in this Review points to potential techniques to interrupt the cycle of altered cognitive processing in

depression. From a global perspective, increasing the amount of serotonin that is available in the PFC may ameliorate excessive 5-HTT binding and bolster cognitive control, which could decrease the propensity to attend to schema-consistent (that is, negative) stimuli. Such a mechanism could explain the success of serotonin-based pharmaceutical interventions, such as selective serotonin reuptake inhibitors^{109,115}. Using deep brain stimulation to reduce hyperactivity in the subgenual cingulate cortex, thereby reducing bottom-up influence to some extent, seems to be a promising treatment for depression¹¹⁶. Less invasively, specific cognitive biases (and presumably the neural circuits that support these biases) can be targeted with cognitive interventions such as attention training, in which patients learn to automatically shift attention away from negative material¹¹⁷, or interpretation training, in which individuals with depression repeatedly learn to develop less negative and more benign interpretations of ambiguous situations¹¹⁸. These approaches have a lot of potential, but they are in the very early stages of development and their effectiveness in individuals with clinical depression has not yet been established¹¹⁹. In addition, traditional cognitive behavioural therapy (CBT) is used to target the elements of Beck's model, particularly dysfunctional attitudes, using direct cognitive interventions such as thought records and guided discovery¹²⁰. Using CBT and other techniques to ameliorate cognitive biases aims to undermine patients' perceived accuracy of the schema¹²¹. As a result, fewer negative stimuli elicit bottom-up reactivity and the burden on cognitive control systems to regulate subcortical regions would also be mitigated¹²². This hypothesis is supported by research showing that CBT normalizes amygdala and DLPFC activity in individuals with depression⁵².

Future research should seek to identify which neurobiological mechanisms contribute to the selective processing towards negative, and away from positive, environmental stimuli. Maladaptive activity in the amygdala and PFC seems to be frequently associated with biased information processing, but few research studies have addressed why negative stimuli are favoured over equally salient positive or fearful stimuli in individuals with depression. Cognitive theory¹ suggests that negative mood states favour processing of mood congruent stimuli. There is evidence to support this idea¹²³ but additional imaging work is needed to confirm this initial finding. In addition, researchers should endeavour to address the dearth of longitudinal studies in this area. Cognitive biases could theoretically serve as a predictor of the length and severity of depressive episodes, as some studies suggest^{124,125}. Similarly, CBT can modulate cognitive and behavioural factors that maintain biases in attention, information processing and memory¹²², but few such studies have investigated these effects over time. Furthermore, the processes that contribute to the development of these cognitive and neural anomalies remain largely unknown, although a growing field of research implicates childhood abuse with the onset of cognitive biases later in life¹²⁶. Once biases have been formed, the extent

Thought record

A tool used in cognitive therapy to help to identify erroneous thought patterns and assist in the formulation of more balanced thoughts.

Guided discovery

The process of asking questions in order to uncover and evaluate the validity and functionality of beliefs about oneself, the world and other people.

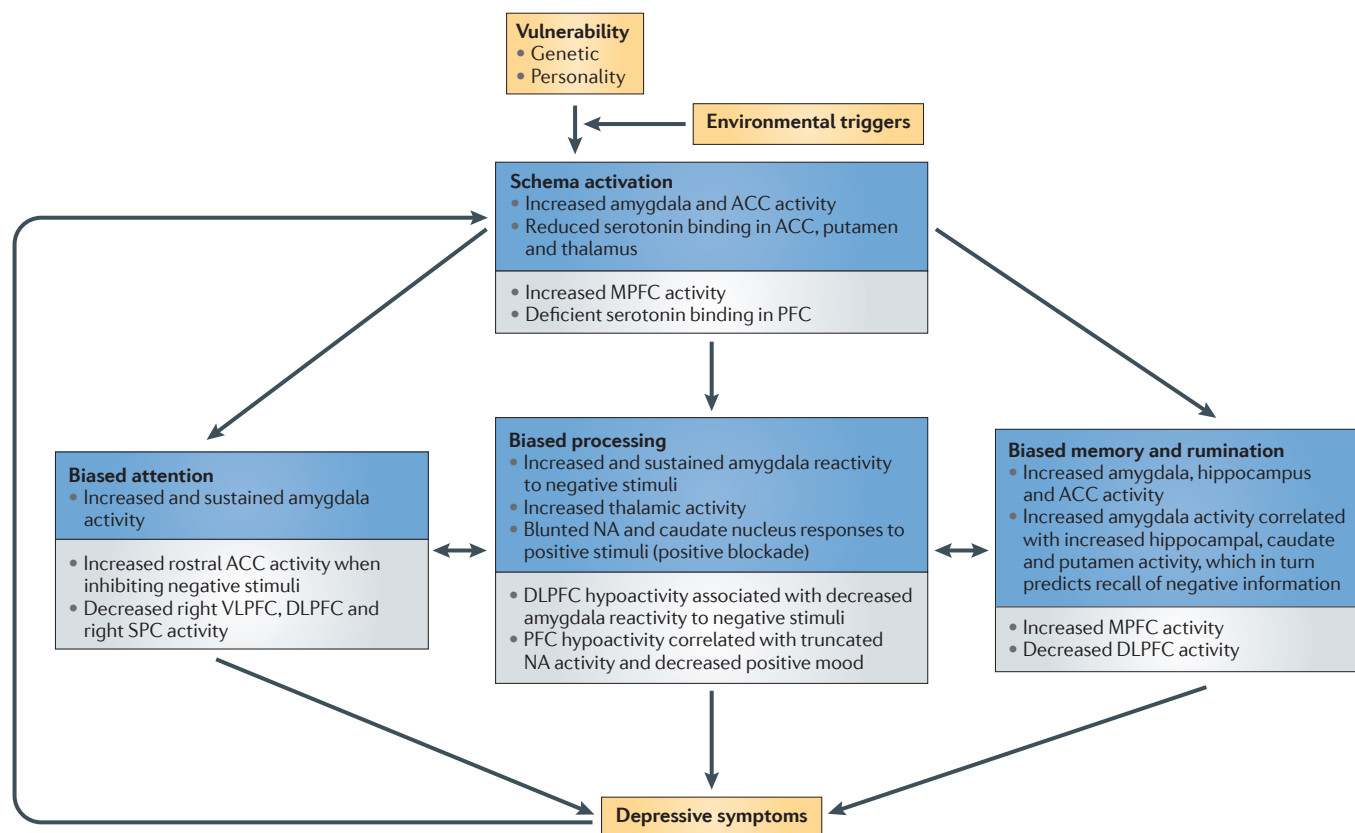


Figure 7 | Summary of an integrated cognitive neurobiological model of depression. This flowchart shows the sequence of events that is proposed to be involved in the development of depression, beginning with depression vulnerability factors and environmental stressors, and resulting in depressive symptoms. The figure outlines the neurobiological events that are associated with each step of the cognitive model: schema activation, biased attention, biased processing, and biased memory and rumination. The brain regions in this flowchart are divided into two groups: regions associated with bottom-up, limbic system influences (shown by the blue boxes), and regions that maintain bottom-up influences through altered top-down, cognitive control (shown by the grey boxes). Note that all elements contribute directly to depressive symptoms, and that depressive symptoms also feed back into the system, thus exacerbating schema activation. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; NA, nucleus accumbens; PFC, prefrontal cortex; SPC, superior parietal cortex.

to which their neurobiological underpinnings are necessary or sufficient for the maintenance of depression is another important direction for future research.

With this Review, we hope to have provided a preliminary framework that identifies the neurobiological underpinnings of Beck's cognitive model of depression. In so doing, we provide a psychobiological formulation that synthesizes cognitive and neurobiological areas of

research. From our perspective, research that integrates work across levels of analysis is crucial to the development of a more thorough understanding of major depressive disorder. Doing so would not only improve aetiological models of depression but could also facilitate the development of more effective somatic and psychological treatments, and reduce the suffering associated with this debilitating disorder.

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