



Depression: from psychopathology to pathophysiology

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Major depression is a psychiatric disorder with high prevalence. Both specialists in cognitive psychopathology and neurobiologists have proposed explanations of the process/systems that exhibit altered functioning during this disorder. Psychological processes that are dysfunctional in depressed patients include alterations in self-referential schemas, cognitive biases, ruminations and processing mode (over-general versus concrete). These cognitive processes are associated with altered function of specific brain systems, including prefrontal areas and cingulate cortex (both involved in self-referential processes and rumination), amygdala (cognitive bias), lateral habenula (cognitive bias) and hippocampus (cognitive bias and overgeneral processing). This review aims to present a coherent view integrating these two approaches in a unique model.

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Introduction

According to the World Health Organization, major depression has become the second most prevalent cause of illness-induced disability worldwide [1•]. Depressed mood, lack of interest with anhedonia and reduced energy are considered as the core symptoms of depression and at least two of them have to be present to confirm the diagnosis of major depressive disorder. Several models, related either to cognitive psychology or to biological psychiatry, have tried to explain, respectively, the underlying psychopathology and pathophysiology of major depression. However, few attempts have been made to integrate the two approaches [2,3]. This review tries to provide such a view. While focusing on clinical research,

the review is informed by a wealth of preclinical studies that, inter alia, address the processes underlying the role of current stress and ongoing predispositions in the initiation of a depressive episode [4••]. (These topics fall largely outside the scope of the current review.)

Schemata and self-referential processes

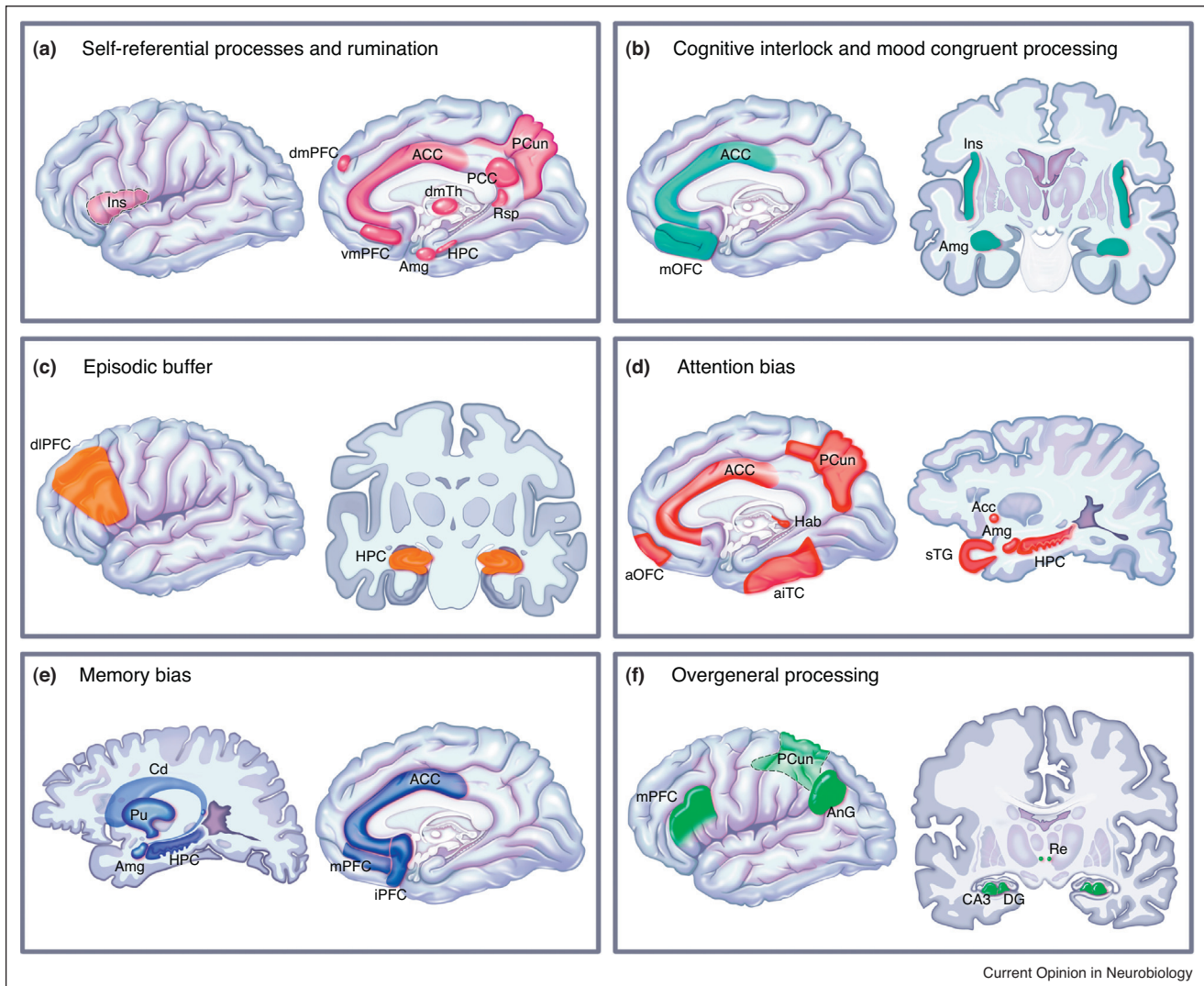
The seminal clinical model of Beck [5,6] has deeply influenced contemporary cognitive models of depression. Its basic assumption is that depressive individuals hold implicit (non-conscious) representations of their self, called ‘schemata’, which involve themes of loss, failure, rejection, worthlessness, and hopelessness.

At the neurobiological level (Figure 1a), activation of a self-referential schema requires two different systems: a network activated during functioning in a self-referential mode, and a system giving a negative label to this network. Recent research has highlighted that self-referential processes such as inward attention to personal thoughts and feelings [7••], are associated with recruitment of a default mode network (DMN) that is active in the resting state and becomes deactivated during externally oriented processes such as goal-directed tasks [8,9]. The DMN consists of a set of interconnected brain areas including the ventral and dorsal medial prefrontal cortex (mPFC), anterior and posterior cingulate cortex (as well as the precuneus and retrosplenial cortex), insula, dorsomedial thalamus, hippocampus and amygdala. In depressed patients, there is a failure to de-activate this circuit, which interferes with performance in cognitively demanding tasks [10•]. However, self-focus is not a monolithic process, as it can for example focus on positive or on negative aspects: only the latter might relate to depression. Depressed patients fail to reduce DMN activity particularly when they are reappraising negative images [12]. Self-referential processing of negative personality traits is associated, in depressed patients, with an increased functional connectivity between parts of the DMN, including the ACC, the dorsal mPFC and the amygdala [13], further suggesting increased synchronization in this network during depressive states. Interestingly, a recent study showed that increased negative self-image is also related to decreased activity in the left ventro-lateral prefrontal and anterior cingulate cortex (ACC) [11], which exhibit altered functioning in depression.

Cognitive interlock and mood congruent processing

Schemata bias information processing by favoring information congruent with their content. Such biases contribute to the installation and maintenance of depressive

Figure 1



Brain networks involved in **(a)** self-referential processes and rumination, **(b)** cognitive interlock and mood congruent processing, **(c)** episodic buffer, **(d)** attention bias, **(e)** memory bias, **(f)** overgeneral processing. dmPFC: dorsomedial prefrontal cortex, vmPFC: ventromedial prefrontal cortex, mPFC: medial prefrontal cortex, iPFC: inferior prefrontal cortex, mOFC: medial orbitofrontal cortex, aOFC: anterior orbitofrontal cortex, dlPFC: dorsolateral prefrontal cortex, aiTC: anterior inferotemporal cortex, STG: superior temporal gyrus, AnG: angular gyrus, Ins: insula, ACC: anterior cingulate cortex, PCC: posterior cingulate cortex, PCun: precuneus, Rsp: retrosplenial cortex, dmTh: dorsomedial thalamus, HPC: hippocampus, Amg: amygdala, Hab: habenula, Acc: nucleus accumbens, Cd: caudate, Pu: putamen, Re: nucleus reuniens, DG: dentate gyrus of the hippocampus.

mood. This effect would be reinforced by a phenomenon called cognitive interlock [14].

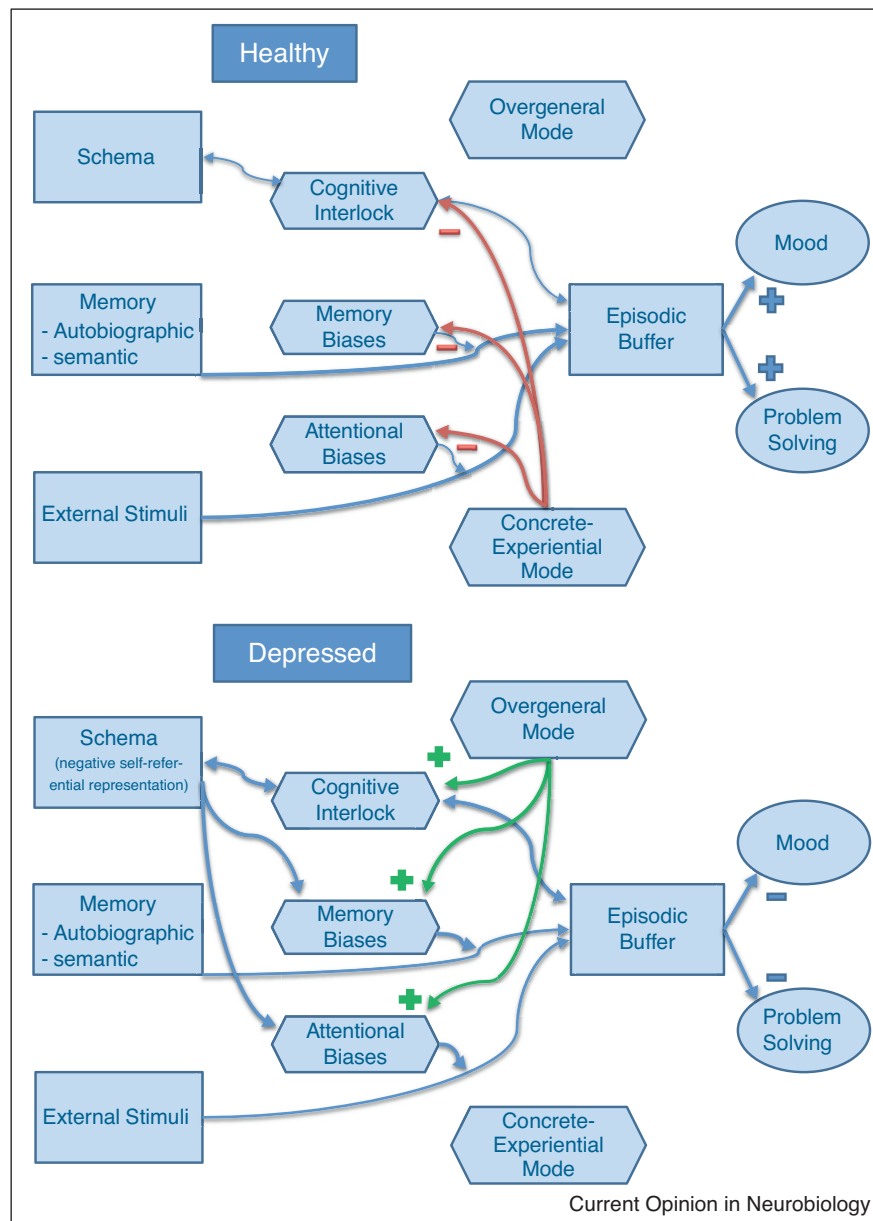
Recent data have shown that the medial orbitofrontal cortex (OFC) may underlie emotion-congruent judgment [15] and thus be crucial for the mood-congruent information processing underlying the cognitive interlock. Interestingly, in depressed patients OFC and ACC are associated with processing of negatively valenced stimuli that are congruent with the depressed state [16]. Other lines of evidence have associated emotion-congruent judgment with additional brain areas including the amygdala, insula and ACC [16,17], which are all dysfunctional

in depressed patients [3,4] confirming that depression is associated with altered functioning of the brain system underlying mood-congruent processing (Figure 1b).

Episodic buffer

Schema-congruent information activated in the episodic buffer (a component of working memory integrating multimodal information) would increase the activation of depressive schemata via a feedback loop, and further increase the bias toward processing of schema-congruent information. The mind would then be trapped in a depressive loop, completing and reinforcing the pattern of information primed by the schema (Figure 2).

Figure 2



Cognitive functioning in a healthy (a) or depressed (b) individual. In a depressed individual, a negative self-schema and an over-general mode of processing concur to automatically prime and activate information that is congruent with the negative self-schema, via a cognitive interlock (resulting in rumination), biased memory and attention. In a healthy individual, a concrete mode of processing counteracts these automatic activations.

The episodic buffer relies on two different brain areas: the hippocampus and the PFC (Figure 1c). The involvement of the PFC [18] is coherent with data obtained via neuroanatomical tracing methods in non-human primates showing that the PFC receives and integrates polymodal sensory information from posterior cortical areas [19]. Activation of prefrontal areas during the integration of information from multiple, specialized processing pathways has been confirmed by neuroimaging studies revealing that the right PFC, particularly the right middle

and superior frontal gyri, is activated during the integration of verbal and spatial information [20]. Conversely, transient inhibition of the right dorsolateral PFC reduced feature binding [21]. Neuroimaging studies also implicate hippocampal activity in relational encoding and sensory binding [22] which is consistent with the fact that the hippocampus also receives input from multimodal cortices such as the entorhinal cortex, and with its involvement in encoding of episodic memory. Defects in the function and morphology of the dorsolateral PFC and

hippocampus in depressed patients have repeatedly been reviewed [3,4**].

Another factor in this model is the imbalance between implicit and explicit processes described in dual process theories [23]. Schemata would automatically activate implicit processes that gather congruent information (pattern completion), so maintaining and exacerbating mood. In non-depressed individuals, as mood worsens, explicit voluntary processes re-balance mood by seeking mood-incongruent information (differentiation from the pattern primed by the schema). In depression, however, there is a failure of explicit processes to counter-balance implicit processing biased by depressive schemata [24] (Figure 2).

Cognitive bias

A meta-analysis has confirmed that implicit cognition is biased in depression, favoring negative implicit self-referential cognition [25]. Specifically, although significant biases were evidenced for implicit attention and memory, the strongest effects were observed for negative interpretative biases and implicit beliefs about the self. The effect sizes for specific biases are small, rarely exceeding 5% of the variance, stressing the importance of considering all biases and their cumulative impact.

The increased attention to negative stimuli by depressed patients results in an increased processing of stimuli with negative valence, and a decreased processing of stimuli with positive valence. For example, functional neuroimaging studies report exaggerated activity in the amygdala, in depressed patients, in response to negative stimuli, including sad faces or words [26,27]. This involves both infraliminal and supraliminal stimuli, and also involves other brain areas: depressed patients show greater activity than non-depressed controls in the left hippocampus, right anterior inferotemporal cortex, bilateral rostral superior temporal gyrus and right anterior orbitofrontal cortex, in addition to the left amygdala, when processing masked-sad versus masked-neutral faces [28*]. Further, in contrast to control subjects, depressed patients do not show increased activity in the putamen and in the fusiform gyrus in response to happy faces [29] or the BOLD signal in the nucleus accumbens and in the hippocampus during positive reward or words tasks [30**] (Figure 1d).

The lateral habenula (LHb) may be a key subcortical structure in the generation of negative cognitive biases. The LHb encodes aversive states [31] such as omission of an expected reward [32] leading, on the one hand, to increased processing of negative information by the amygdala and, on the other, to decreased processing of positive information by the nucleus accumbens [30**]. The LHb exhibits hyperactivity during depressive-like states [33,34*], and antidepressant effects have been reported following Deep Brain Stimulation (DBS) of the LHb [33].

Negative cognitive biases can also result from reduced top-down regulation. For example, in depressed individuals, processing of negative words is associated with increased activation in the rostral ACC and precuneus [35,36], which probably relates to compensatory mechanisms (greater activation being required to achieve top-down inhibition) (Figure 1d). Inactivation of the rostral ACC by DBS also elicits rapid and long-lasting antidepressant effects [37].

The brain network underpinning depression-related memory bias (Figure 1e) involves the same set of brain areas, including the amygdala, the hippocampus, the ACC and PFC, but also the caudate-putamen. Indeed, increased memory sensitivity for negative material in depressed individuals is associated with greater activity in the right amygdala during successful encoding of this material, which correlated with the severity of depression. This is accompanied by increased functional connectivity between the amygdala and the hippocampus, caudate and putamen, suggesting that when encoding negative material, depressed individuals over-recruit a network involved more generally in enhancing memory for affective stimuli [38]. Memory bias in depressed individuals also involves decreased memory for positive stimuli, which is related to greater activity of the cingulate cortex, right inferior and left medial PFC, right hippocampus and amygdala [39].

Rumination and overgeneral processing

Another important cognitive feature of depression is rumination, defined as a tendency to repetitively analyze one's problems, concerns, feelings of distress and depressed mood states [40,41]. Research has demonstrated that depressive rumination is the most significant cognitive factor accounting for mood depletion, relapse and maintenance of depression [41]. Depressive rumination is characterized by an abstract and over-general mode of thinking, centered on the causes and consequence of one's present state, as opposed to experiential, concrete thinking that focuses on the direct perception of immediate experience. The over-general mode favors the completion of patterns determined by abstract representation (such as a schema), while the experiential mode discriminates the uniqueness of each experience. Under certain learning experiences, rumination might become a cognitive habit that maintains depression [42**]. Empirical evidence suggests that depressive rumination is sustained by basic cognitive impairments, such as difficulties in inhibiting negative information at the attentional level [43,44], and especially the inability to disengage from negative information [45,46]. These impairments of attentional control provide a further explanation of biases in perception, judgment and memory. However, there is uncertainty about the relationships and combined influences of these cognitive biases and impairments [47**].

In structural and functional neuroimaging studies, the brain network underlying rumination overlaps the network recruited during negative self-referential processes (Figure 1a). Indeed, rumination has been associated with increased activity of the DMN [48**], including regions processing emotional recall such as the hippocampus [3], but also with decreased activity within a network involved in the process of inhibiting unwanted thoughts. The latter network includes the bilateral inferior frontal gyrus, the ACC and the mid-cingulate cortex. In depressed patients, levels of rumination correlate positively with activity in parts of this system, particularly the vmPFC and ventral ACC [48**].

Over-general processing of sensory information can relate to two different processes: either a decrease in pattern separation or an increase in pattern completion. Pattern separation enables the dissociation of similar stimuli conveyed from the external world in distinct non-overlapping neuronal representations, while pattern completion enables accurate generalization in case of a partial sensory input [49]. Converging data from computational models, human neuroimaging, animal *in vivo* electrophysiology and animal lesion studies all indicate that the granule cells of the dentate gyrus (DG) of the hippocampus are strongly involved in pattern separation [49]. This has been attributed to the sparse coding seen in this region that renders overlap between two different activations very improbable. On the other hand, the CA3 region has been implicated in pattern completion [50]. The contribution of the DG to pattern separation has received much interest due to the observation that the granule cell layer of DG is one of the few brain regions in which new neurons can be born and survive during adulthood. Specific depletion of hippocampal adult neurogenesis (AN) decreases pattern separation [51,52], while a specific increase of AN has the opposite effect [51]. Interestingly, antidepressants increase AN, while specific suppression of AN induces depressive-related phenotypes and suppresses antidepressant-related effects [53,54**], indicating that this process is closely related to vulnerability to depression and to remission after a depressive episode [55**]. Nevertheless, other brain regions are also involved in pattern separation and in over-general memory (Figure 1f), including the nucleus reuniens and the medial prefrontal cortex [56**]. Further, in depressed patients over-general memory is also associated with activity in the precuneus and in the angular gyrus [48**].

Conclusions

In sum, research has established that depression is characterized by attentional control impairments and biases that seem to be sustained by implicit processes arising from negative self-schemata. These impairments and biases result in a ruminative style characterized by over-generalization and a failure of analytic thinking that depletes mood and maintains depression. The neurobiology of depression

reveals functional alterations in specific brain networks that fully overlap with predictions from this theoretical model. This convergence further supports the cognitive model of depression and also provides a functional account of the features described by neurobiologists in the depressed brain.

Conflict of interest statement

Nothing declared.

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