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Review

Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states

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Abstract

The glucocorticoid hormone cortisol is essential for many forms of regulatory physiology and for cognitive appraisal. Cortisol, while associated with fear and stress response, is also the hormone of energy metabolism and it coordinates behavioral adaptation to the environmental and internal conditions through the regulation of many neurotransmitters and neural circuits. Cortisol has diverse effects on many neuropeptide and neurotransmitter systems thus affecting functional brain systems. As a result, cortisol affects numerous cognitive domains including attention, perception, memory, and emotional processing. When certain pathological emotional states are present, cortisol may have a role in differential activation of brain regions, particularly suppression of hippocampal activation, enhancement of amygdala activity, and dendritic reshaping in these regions as well as in the ventral prefrontal cortex. The coordinated actions of glucocorticoid regulation on various brain systems such as those implicated in emotional processing can lead to perceptual and cognitive adaptations and distortions of events that may be relevant for understanding mood disorders.

Keywords: Glucocorticoids; Emotion; Cognition; Amygdala; Medial prefrontal; Orbitofrontal; Depression

Contents

1. Introduction

Cortisol (corticosterone in rats) is a glucocorticoid hormone secreted by the adrenal gland into the bloodstream, and acts on numerous areas of the body. In some regions of the brain glucocorticoids have well-known inhibitory effects [1–3], such as restraint of the hypothalamic-pituitary–adrenal (HPA) axis and suppression of hippocampal glucose metabolism and blood flow [4,5]. It also appears that glucocorticoids increase activation in some other areas of the brain, such as the amygdala [2,6,7], suggesting

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site-specific effects of glucocorticoid activation that have implications for behavioral and cognitive functions subserved by these brain regions. This review highlights the accumulating evidence that glucocorticoid dysfunction may contribute to the pathology of mood disorders through activation in extrahypothalamic regions.

Distribution of mineralocorticoid (MR) and glucocorticoid (GR) receptors have been described in the primate amygdala, hippocampus, medial prefrontal and orbitofrontal cortical areas [8,9]. These same regions putatively underlie perception, memory and experience of emotional events. Cortisol serves a wide range of physiological, behavioral and cognitive functions and can be elevated in a number of contexts that may or may not be 'stressful' in the aversive sense of the term, such as territoriality, attachment behaviors, food intake, predatory behaviors, focused attention, social presentation, sustained effort and effortful thought (see Fig. 1) [10–12]. Therefore, it might be more accurate with regard to its influence on some brain regions to describe cortisol's effects in terms of 'readiness to behave' or as part of cognitive appraisal mechanisms. It is possible that the effects of cortisol on neurotransmitters and neuropeptides within various functional circuits can influence perception, attention and memory for environmental events.

In recent years, cortisol has been characterized as a 'stress hormone,' and elevated cortisol levels are sometimes considered synonymous with stress in certain areas of Ref. [13]. Indeed, cortisol is elevated in individuals under duress in order to allow physiological and cognitive response to stressful situations [14]. However, the characterization of cortisol as a 'stress hormone' is only partly accurate. Elevated peripheral cortisol levels are not necessarily an indicator of stress; subgroups of healthy individuals can have elevated basal cortisol concentrations [15,16], as can individuals with certain physical and psychiatric conditions [17–19]. Cortisol may differentially affect certain neurotransmitters and brain areas in both psychiatrically healthy individuals and patients with various mood disorders, and these effects may be distinct in healthy versus ill populations. The disparate effects of glucocorticoids on the various brain regions have potential relevance to

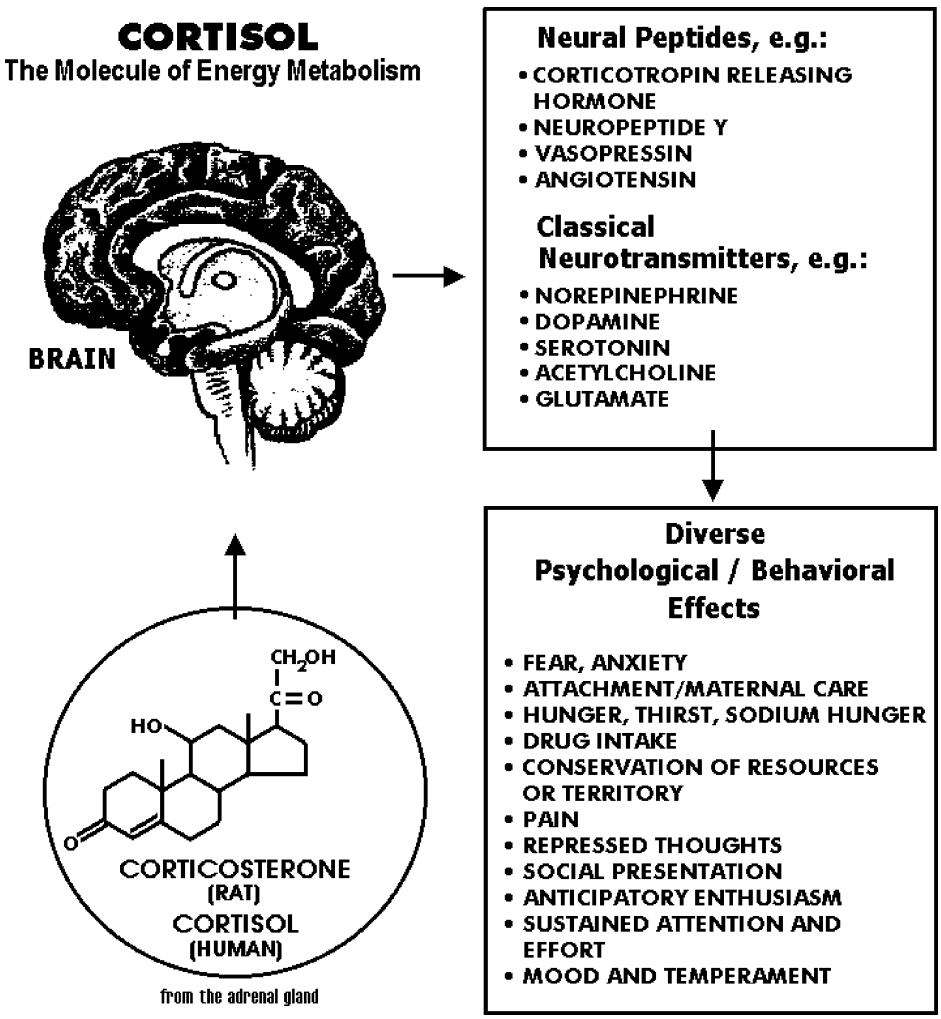

Fig. 1. The diverse effects of glucocorticoids on neuropeptides, classical neurotransmitters, and subsequent psychological and behavioral effects. The structural depiction in the lower left describes corticosterone in the rat.

understanding normal behavioral adaptation and the cognitive mechanisms underlying them, and may also have relevance to the pathophysiology of mood disorders. This paper overviews the interactions of glucocorticoids with neurophysiological, endocrine, behavioral and cognitive functioning, and discusses implications of these findings for mood disordered populations.

1.1. From systemic physiology to the organization of behavior

Regulation of glucose and mineral availability are necessary to sustain life. Glucocorticoids regulate glucose metabolism, while mineralocorticoids regulate sodium metabolism. In the brain endogenous cortisol acts on both MRs and GRs within various functional systems, with MRs displaying higher affinity for cortisol than GRs such that at basal conditions glucocorticoids primarily bind to MRs, and GRs become occupied when glucocorticoid levels increase [20]. Species differences in the distribution of MRs and GRs are prominent; receptor distribution tends to be limited to specific brain areas in lower animals [9] but are distributed widely throughout the primate brain [8,21–23]. Additionally, the primate hippocampus expresses fewer GRs than the rat hippocampus, and also expresses high levels of MRs [8].

At the cellular level cortisol exerts genomic actions through translation of mRNAs, and these genomic effects are important for the production of various neurotransmitters and neuropeptides [24]. A single GR gene has been identified in humans [25]. GR expression is regulated by a number of transcription factors through many unique binding sites (as many as fifteen) [25], which may allow the differential regulation of GR protein expression under varying conditions. Although these genomic effects are relatively slow, rapid steroid effects that could not be accounted for through genomic actions also exist, which presumably are effective when fast cognitive appraisals of the environment are needed [26–30]. Fast (msec) membrane effects of cortisol may be the result of rapid modulation of membrane-associated receptor proteins [31]. The functional roles of cortisol's membrane actions are less clear but some evidence indicates a link to rapid changes in monoamine levels [32].

Cortisol is part of a fundamental system engaged in a wide range of regulatory functions within various anatomical sites. Fig. 1 illustrates that, within the brain, cortisol apparently participates in the regulation of various neuropeptide systems such as corticotropin-releasing hormone (CRH) [2,33] and neuropeptide Y [12], and neurotransmitter systems such as serotonin [34], norepinephrine [35], dopamine [36], acetylcholine [37], and glutamate [38]. The effects on these systems influence psychological states that inform the animal of needs for preserving physiological homeostasis [39]. Through interactions with these neurochemical systems, glucocorticoids exert a wide range of effects on basic appetitive behaviors such as hunger, thirst, and drug intake. Finally, glucocorticoids may also influence the production of emotional and social behaviors such as attachment, temperament and mood.

The physiological, cognitive and behavioral effects of cortisol appear to act in a curvilinear, or 'inverted U-shaped,' fashion on many physiological and cognitive systems, in which moderate levels are optimal while extremely low or high concentrations each have distinct adverse behavioral or cognitive outcomes [28,40]. For example, when cortisol levels are extremely low or high the central state of hunger is reduced, while modestly elevated levels can induce the central state of hunger [12,41]. The central states influenced by the actions of cortisol on functional systems increases the likelihood of performing certain behaviors in suitable environments [12].

1.2. Glucocorticoids, dopamine, salience and the prediction of reward

The interactions of the glucocorticoid and dopamine systems illustrate the diverse effects of glucocorticoids on neurotransmitter systems. Glucocorticoids can influence dopamine activity in the brain, and both glucocorticoids and dopamine appear to work in concert across various functional systems. Modest glucocorticoid elevations can have facillitory effects on appetetive systems, in part through influencing dopaminergic neurons [42–44]. Rats will exert modest effort (via bar press) in order to self-administer corticosterone, suggesting that glucocorticoid effects may be intrinsically motivating [45]. Some healthy human subjects initially report feelings of euphoria following cortisol and dexamethasone injections, similar to receiving a dose of adrenaline [46,47], and glucocorticoids can induce euphoria and hypomania during chronic treatment [46,48,49]. A small subset of people report mood elevation or 'giddiness' after 5-day prednisone treatment [50].

The cortisol elevation in animals during search and subsequent reward suggests that glucocorticoids are likely acting on a number of experiential aspects, which encompass arousal, orientation in the environment, and memory for previous sources of reward [51,52]. Rats that are 'high responders' in drug self-administration paradigms tend to have higher levels of endogenous glucocorticoids than those that are 'low responders', despite a high rate of variability between animals [53]; adrenelectomy reduces the rates of drug self-administration [54]. Glucocorticoids may alter dopamine transmission in specific sites, potentially generating these behavioral effects of drug administration [53] because of dopamine's role in signaling the salience for and learning of rewarding objects [55,56]. In rats who are 'high responders' glucocorticoids apparently increase dopamine synthesis in the nucleus accumbens, where dopamine release plays a role in modulating both reward-related learning and psychomotor activity [57]. In adrenaliectomized rats, extracellular dopamine is decreased

in the shell of the nucleus accumbens [42]. Also, in the medial prefrontal cortex, chronic corticosterone administration can increase dopamine turnover, as demonstrated by homovanillic acid levels [58].

2. Glucocorticoids and cognition

2.1. Arousal, attention and cortisol

Subjective reports and behavioral observations of arousal and energy levels correlate with cortisol measures in humans, providing support for cortisol's role in sustaining and facilitating cognitive functions. Administration of glucocorticoids generally leads to increased subjective arousal in humans [47,59]. Cortisol release is inhibited during sleep [60] and increased in the morning hours [12]. The normal elevation of morning cortisol concentrations in children and adults suggests a 'wake up' energy-enhancing role for cortisol, and levels then decline as the day progresses showing a nadir during evening hours.

The relationship between cortisol and psychological state is reflected in the association between higher morning cortisol levels and increased anticipatory states that require enhanced glucose metabolism [15]. Moderately elevated cortisol is advantageous for increased arousal and energy expenditure in the organization of behavior. For example, adults who report having high self-esteem had higher cortisol levels and lower psychological distress than did those with lower self-esteem [16]. Among children, those who were described as bold and energetic had higher cortisol levels than other children [61,62]. Extroverted children, at the start of a new school year, tended to show larger increases in cortisol than did more introverted children [63]. This might reflect enhanced arousal levels and increased 'readiness to behave' in these extroverted children, who may be happily anticipating increased challenges and social interaction with peers. Nevertheless, the cortisol effect appears nonspecific; children described as behaviorally inhibited also tended to have higher cortisol concentrations, perhaps reflecting chronically enhanced anticipatory anxiety for upcoming events [64,65]. The unifying feature of the glucocorticoid elevation in these apparently diverse personality subtypes may conceivably be a state of heightened arousal and attention to the social environment.

The relationship between cortisol and attention is supported by self-report; for example, self-reported concentration improves with acute, periodic increases in plasma cortisol concentrations [59]. Although chronic cortisol elevations have detrimental effects on attention, short-term moderate and high doses of glucocorticoids appear to have no negative effects on sustained or selective attention in humans [66,67]. Additionally, results of animal studies suggest that periodic glucocorticoid elevations may enhance focused attention toward an emotionally arousing stimulus [68,69] by increasing the availability of norepinephrine [70,71]. Increased glucocorticoid concentrations may consequently allow mobilization of cognitive resources and increase the chance of survival through enhanced memory for these emotionally arousing events [72]. When glucocorticoid concentrations increase, occupation of GRs appears to influence perceptual detection thresholds to aid in focused attention on the perceived stimulus, to the exclusion of irrelevant stimuli [73]. Anticipation is one cognitive arousal state that allows enhancement of focused attention towards an event, and is also associated with cortisol elevations [74]. Presumably, the cortisol elevation may allow the animal to prepare cognitive resources for engagement toward the anticipated situation. When optimal arousal levels and attentional systems are established, higher-order cognitive mechanisms can proceed.

2.2. Perception, memory and cortisol

In general, engagement of any cognitive process requires energy expenditure, which, in turn, is facilitated by glucocorticoids through their role in glucose metabolism. These operations are dependent on the coordination of various brain areas within functional anatomical systems. When emotionally arousing stimuli are processed, the amygdala, medial temporal regions, and prefrontal cortex, particularly medial and orbitofrontal cortices, appear to be important for perception of and episodic memory for this type of stimuli [75,76]. These brain regions also have functional connections with brainstem areas important for arousal and attention [77,78].

The amygdala plays major roles in the evaluation of a variety of emotionally salient stimuli [79–82], and electrical stimulation of the amygdala results in increased cortisol concentrations [83]. Human studies illustrate that perception of negative affective stimuli can result in elevated cortisol levels [84], and cortisol administration can influence response to negative stimuli in a dose-dependent manner [85]. For example, the enhancing effects of glucocorticoids on acoustic startle reflex differ depending on dose; 5 mg of hydrocortisone can enhance acoustic startle eyeblink reflex magnitude, while 20 mg can reduce the magnitude [85]. Both low and high glucocorticoid levels are also associated with deficits in memory performance, indicating that glucocorticoid effects on this cognitive domain follows the 'inverted U-shaped' curve such that certain concentrations of cortisol are necessary for optimal memory consolidation [30,86–89]; these effects appear to complement glucocorticoids' effects on electrophysiological functioning in the hippocampus in which moderate, but not low and high, glucocorticoid concentrations are optimal for long term potentiation and primed burst potentiation [90,91]. The circadian rhythm of cortisol can also influence the effects of exogenous cortisol administration on memory consolidation. Although elevated cortisol concentrations resulting from glucocorticoid administration or stress are

typically associated with declarative memory deficits [66,92–94], glucocorticoid administration (35 mg hydrocortisone) during the afternoon, when cortisol concentrations are substantially lower than morning concentrations, can enhance declarative memory performance [95]. Finally, varied findings of glucocorticoid modulation of memory may be due to different effects on memory consolidation and memory retrieval. Glucocorticoids administered 30–60 min prior to retention testing impairs long-term memory performance [30,96] while having no discernable effect on performance when administered prior to or following initial learning when the stimuli are non-arousing [96].

Regions of the amygdala and hippocampus, which contain GRs and MRs [8,9], participate in a memory system specific to autobiographical (episodic) events [97]. Cortisol's facilitory effects on memory at moderate concentrations have been shown to involve interaction between the basal lateral amygdala, basal ganglia and hippocampus [75,98]. Acute glucocorticoid administration can lead to increased spontaneous cell firing in the amygdala [99] and decreased glucose utilization in the hippocampus [4]. Glucocorticoid administration can increase startle reflexes in humans at low doses [85], can decrease startle reflexes to emotional stimuli at larger doses, and can enhance memory for emotionally-valenced, compared to neutrally-valenced, pictures [100]. In the case of memory consolidation for a particular event, glucocorticoids appear to broadcast the salience of the event to diverse brain regions, such as the hippocampus [98], via activation of the basal lateral amygdala, due in part to interactions with the noradrenergic system, amplifying these signals [86,98,101–103]. Neurochemical lesions of the basal lateral nucleus blocks the memory-enhancing properties of glucocorticoids [104]. Cholinergic mechanisms are equally important to the consolidation of emotional memory; administration of muscarinic antagonists block the facilitatory effects of glucocorticoids on emotional memory consolidation [103]. Both human and animal research suggests that the memory-enhancing effects of glucocorticoids may be especially relevant to *emotional* memory [86,100].

3. Consequences of glucocorticoid elevation

3.1. Cortisol, fear and anxiety

During states related to fear or anxiety, glucocorticoids are generally elevated [105], and if an animal is already fearful, glucocorticoid administration can lead to increased response to and memory of the experience of fear, as measured by increases in freezing behavior [68,69]. For example, freezing responses to conditioned stimuli were potentiated by high-dose corticosterone treatments in rats [69]. Cortisol is important for sustained fear-related responses, for efficient cognitive appraisal of events, and for the normal development and expression of behavior [106,107]. Glucocorticoids also facilitate physiological responses to other types of stressors. For example, when glucocorticoids are not available, as in the case of adrenalectomized animals, physiological stressors such as hemorrhagic, hypoxic or surgical stress result in lower survival rates [108–110]. Such animals cannot mobilize or sustain protective, compensatory, physiological responses to these stressors.

The experience of fear generally precedes the rise in cortisol. Corticotropin-releasing hormone (CRH) is one mechanism through which glucocorticoids may mediate behavioral responses; CRH is well-known to mediate a variety of fear-related behaviors [111–114]. Elevated cortisol concentrations promote the facilitation of CRH gene expression in the amygdala and the bed nucleus of the stria terminalis, which consequently can enhance the perception of fear- and anxiety-inducing stimuli and fear-related behaviors (see Fig. 2) [7,114–116]. Exposure to a stress- or fear-eliciting stimulus, associated with increased plasma cortisol concentrations, can lead to increases in cortisol and CRH in the amygdala [117] which, in turn, can promote increased norepinephrine cell activity in the locus ceruleus [111,118,119]. The arousal produced by this combination of effects appears to enhance memory for fearful or anxiety-inducing events. The induction of CRH gene expression in the central nucleus of the amygdala, along with the facilitation of norepinephrine in the basal lateral region of the amygdala [86] thus appear to subserve an important mechanism for sustained fear and memory for fear-inducing events. The role of the amygdala in cognitive appraisal has been characterized as detection of discrepancy or uncertainty in the environment [120]. Recruitment of cognitive resources when presented with ambiguous, discrepant, or potentially threatening stimuli may be an important role of the amygdala in particular and glucocorticoid actions within the context of the extra-hypothalamic system.

3.2. Negative consequences of cortisol elevation

Constant elevation of glucocorticoids can lead to adverse physiological and cognitive consequences [121]. Prolonged exposure to elevated cortisol concentrations can result in fatigue, depression, apathy, and impaired concentration [47,50,122]. Long-term consequences of continued cortisol elevation within the context of repeated stress includes neural atrophy in the hippocampus [123,124] and medial prefrontal cortex [125], decreases in bone mineral density [126] and compromised immune system function [121].

Cognitively, prolonged high levels of cortisol can exert deleterious effects on certain types of memory, but the performance effects are dependent on the timing and length of exposure. Short- and long-term effects of glucocorticoid elevation on spatial and visuospatial memory are complex and appear to differ for acute and chronic exposures. Acutely increased endogenous glucocorticoids resulting

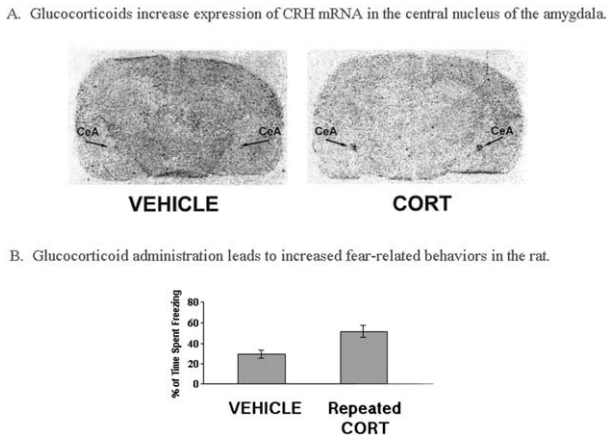

Fig. 2. Cortisol, CRH and amygdala in fear/anxiety. (A) Digitized images of CRH mRNA in the CeA in corticosterone- (4 mg) or vehicle-treated rats. (B) Freezing responses of rats in the retention test in corticosterone-treated and vehicle-treated rats. Corticosterone administration was associated enhanced emotional memory, with increased duration of freezing behavior. Thompson et al., 2001, Society for Neuroscience abstract.

from a stressor can enhance spatial memory [127], while chronic glucocorticoid administration can lead to deficits in spatial memory performance [128]. Studies consistently report deficits in verbal and declarative memory when high concentrations of glucocorticoids are present [66,129]. In contrast, lower elevations of cortisol for brief time periods (e.g. a dose administered during afternoon hours when endogenous circadian secretion is low) do not significantly affect memory functioning, and enhanced memory performance [95]. Additionally, higher concentrations do not appear to significantly impact procedural memory, arousal, attention, or executive functions unless extreme cortisol levels are sustained over a prolonged period of time [130].

It has been hypothesized that the disruption of cognitive functions, particularly certain types of memory, from chronic glucocorticoid elevation during repeated stress may result from neural atrophy [121] via facilitation of excitatory amino acid-mediated toxicity [28,123]. The primary region of interest in rat studies of glucocorticoid-induced neural deterioration has been the hippocampal formation [5,124]. However, neuronal atrophy in the hippocampus may not be directly responsible for cognitive impairments observed in those chronically exposed to elevated glucocorticoids. Damage to the hippocampal CA3 region results in elevated corticosterone levels and memory impairments. Administration of metyrapone, a glucocorticoid-synthesis inhibitor that reduces glucocorticoid concentrations to basal levels, reverses the memory impairments associated with CA3 lesions [131]. The impairments apparently are dependent on elevated glucocorticoids, as animals with both CA3 lesions and metyrapone treatment who also received corticosterone supplementation displayed memory impairments similar to lesioned animals without metyrapone treatment [131]. Because glucocorticoid activity in the amygdala has been shown to play a role in memory impairments, this study suggests that the memory impairments associated with hippocampal atrophy may also be dependent on glucocorticoid activity in the basolateral amygdala [131,132].

3.3. Cortisol, brain and psychopathology

The perception and experience of emotionally evocative stimuli can increase cortisol concentrations [133,134] and activate circuits that are, by inference, important for effectively processing and experiencing emotion in healthy individuals [76,135,136]. Cortisol also is known to facilitate neural processing in regions of the brain that underlie information processing of emotional events, perhaps via the induction of CRH gene expression in the central nucleus of the amygdala [137,138]. Importantly, the induction of these central states can be long lasting, so that the central activation (elevated levels of CRH) and the experience of fear, anxiety, or other negative emotional states may persist even while systemic cortisol concentrations decrease to basal levels [137,139].

Many individuals who suffer from depression show abnormalities in cortisol secretion when the system is challenged [140–142]. Increases in cortisol concentrations in depression are associated with impaired cognitive functioning [143–146]. Abnormalities in cortisol reponse under stress conditions described in dysphoric individuals have been associated with performance deficits on tests that employ emotional stimuli [147]. Behaviorally, excessive perceptual bias toward perceiving negative stimuli is influenced by normal mood changes and by pathalogical mood states [148–150]. In healthy adults, induced depressed mood results in a sad interpretation of facial expressions that are normally perceived as neutral or ambiguous [151,152], and evidence exists that patients with depression tend to judge faces as expressing more negative emotion when compared to healthy, nonpsychiatric subjects' judgments [153–155] and to show increased attention toward negative emotional stimuli [150]. Patients

with depression also show autobiographical memory deficits in which negatively-valenced memories are available for recall but positive memories are less accessible [156,157] suggesting altered attention to negative events at the time of encoding and/or restricted access to positive memories at the time of retrieval.

Imaging studies reveal that several regions of the brain implicated in these emotional processes have abnormal glucose metabolism and, in some cases, significant relationships between cortisol secretion and metabolic activity during major depression have been described [158,159]. For example, in unipolar and bipolar depressed subjects, glucose metabolism is elevated in the amygdala, and stressed plasma cortisol concentrations were correlated positively with this activation in the same depressed patients, as Fig. 3 illustrates [158,159]. Additionally, functional imaging studies of mood disordered subjects described abnormal amygdala responses to affective stimuli [160–162]. The effects of cortisol may influence a limbic-thalamo-cortical circuit through its influence on amygdala activation, orbitofrontal cortical regions, and ventral prefrontal cortical areas such as the ventral anterior cingulate cortex [159,163,164]. Structural abnormalities in the hippocampus [165–167] of mood disordered patients have also been described, and can potentially be attributed to cortisol hypersecretion [165].

Glucocorticoid levels may alter functioning of the amygdala and prefrontal cortex during states of depression,

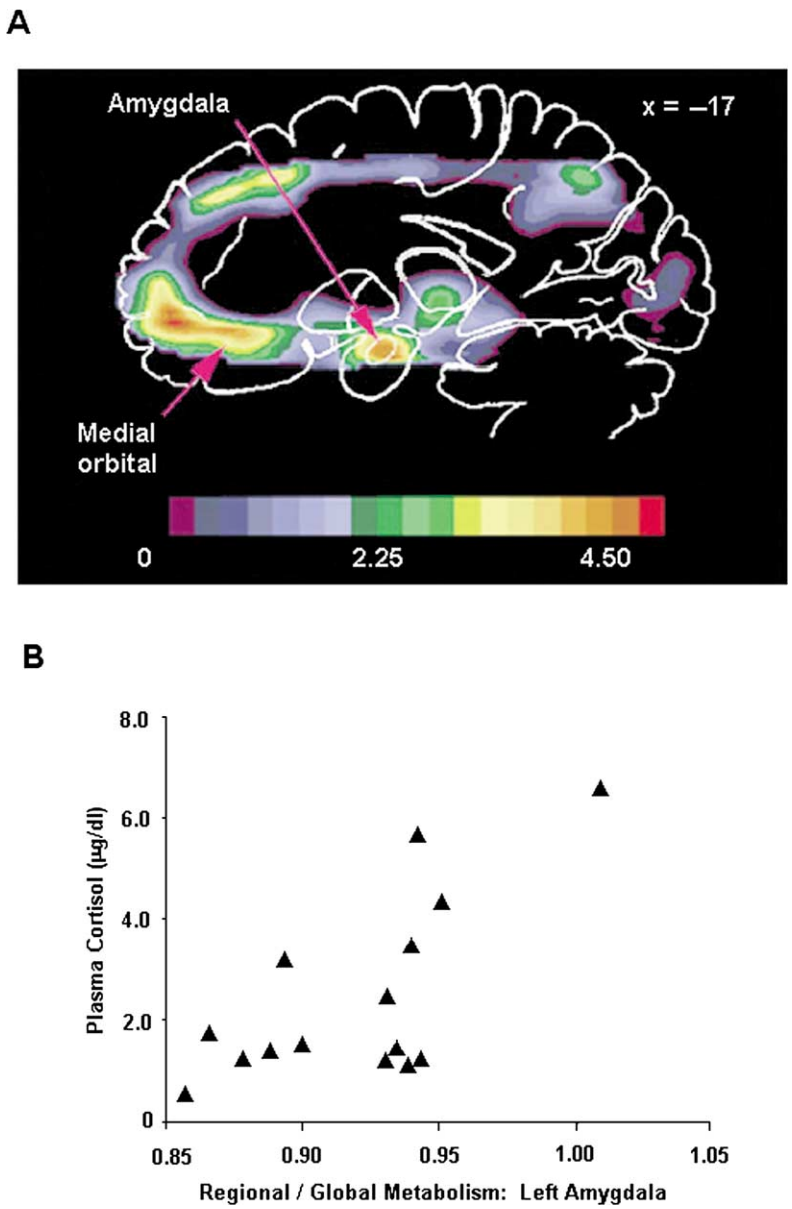

Fig. 3. Amygdala and prefrontal cortex activation in depression [168]. (A) Areas of abnormally increased CBF in familial MDD. Analyses show areas of increased CBF in depressed patients relative to controls in the amygdala and medial orbital cortex. Anterior is to the left. (B) Relationship between plasma cortisol concentrations measured immediately prior to the PET radiotracer injection and normalized glucose metabolism in the left amygdala for an MDD sample ($n = 15$) [159].

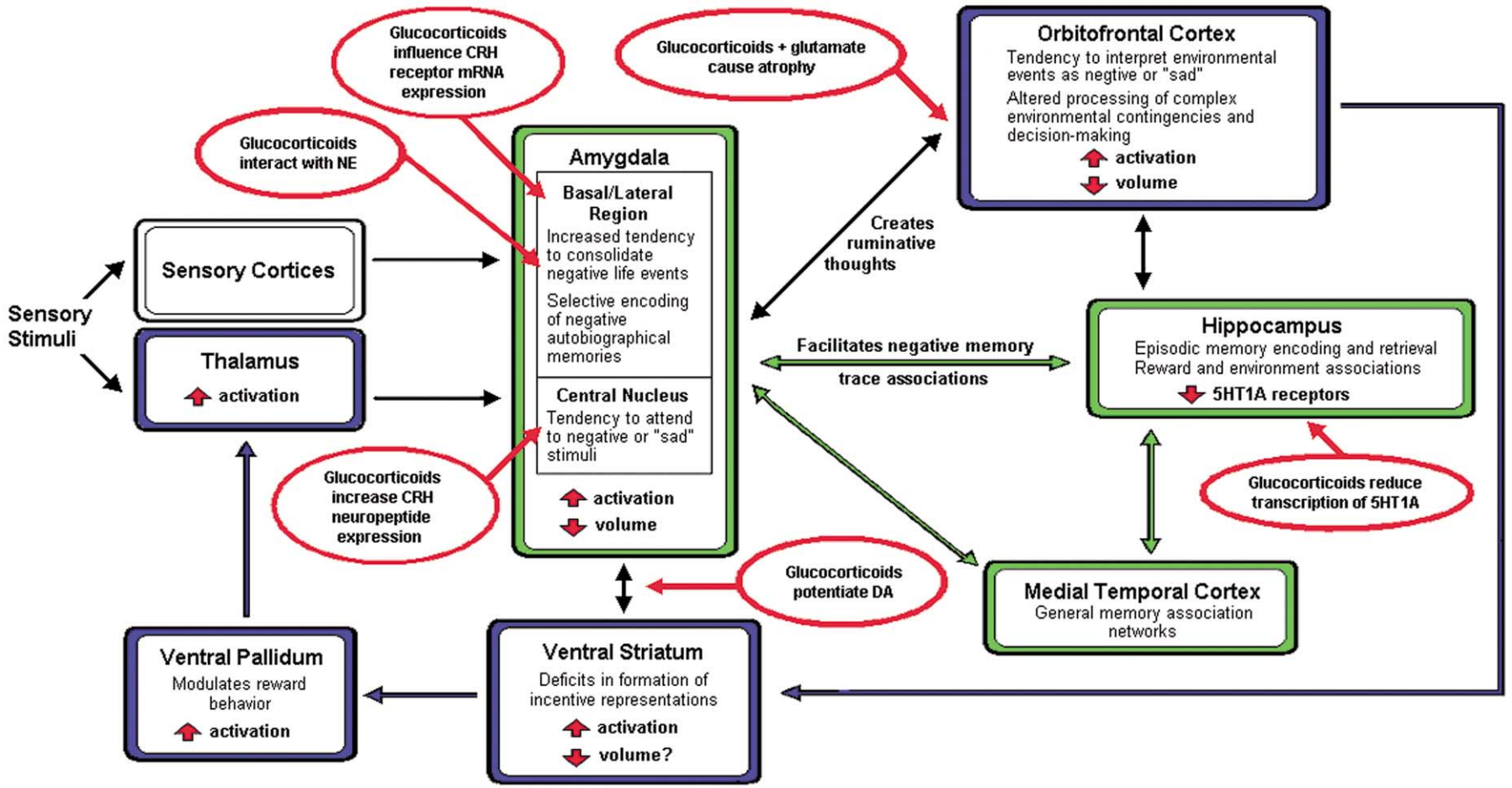

Fig. 4. Neurobiological systems underlying perception, memory and experience of emotion in depression. This model combines findings from neurophysiological and neuroimaging studies and superimposes hypothesized roles for these structures in the cognitive experience of depression. Brain abnormalities in depression include areas from the frontal-subcortical circuit (outlined in blue) and the hippocampal-amydala complex (outlined in green, along with medial temporal cortex). Effects of glucocorticoids on these systems are outlined in red.

which has implications for cognition and behavior. The amygdala, particularly the left amygdala, and the medial orbitofrontal cortex both show abnormal elevations in cerebral blood flow and metabolism in depression [163,164]. Additionally, the amygdala activation observed in depressed patients does not habituate normally to faces expressing sadness, when compared to healthy subjects [168]. Decreases in ventral prefrontal cortex metabolism are associated with decreases in depressive symptoms during antidepressant treatment [163,164,169–171]; the abnormalities of the ventral prefrontal cortex are not observed during remission from depression and are presumably state-dependent [170]. Postmortem studies revealed a variety of histopathalogical changes within the orbitofrontal cortex, ventral anterior cingulate cortex and subiculum of the hippocampus during depression, which include glial cell and neuropil reduction [172,173] which may result from an interaction of glucocorticoids in the presence of glutamate transmission during recurrent stress [38,123].

Though much of the evidence from human research is correlational, the converging evidence from the cognitive, neuroendocrine, psychiatric and neuroimaging literature supports the potential role of glucocorticoids in both normal and abnormal emotional cognition, experience, and behavior. Fig. 4 illustrates functional connections between brain regions important for episodic memory and those that are part of frontal-subcortical circuits, and how these circuits may be dysfunctional in mood disorders to create observed deficits in perception, memory, and experience of emotional events.

The amygdala and hippocampus show abnormalities in mood disorders described above that may be partially attributed to the actions of glucocorticoids. Glucocorticoid effects shown in the figure have been observed in vivo in animals and in vitro in tissue culture preparations. Mood disordered patients have decreased 5HT1A receptors in the hippocampus [174–176], and elevated glucocorticoid concentrations can reduce the transcription of 5HT1A mRNA [177–179]. Glucocorticoids can influence dopamine activity in the striatum, and can result in increases in dopamine transmission in the nucleus accumbens shell [180–182]. Dopamine activity in the striatum has been associated with anhedonia, reversible with antidepressant treatment [183–185]. Glucocorticoids interact with the noradrenergic system [102,132,186], and in the amygdala this interaction is important for consolidating emotional memories [102,132] and for optimally signaling the hippocampus [91,98]. Increased CRH mRNA expression in the central nucleus of the amygdala has been linked to increased glucocorticoid concentrations [7,33,114,116], and to enhanced emotional memory [68,69,114,116,187]. Attentional, perceptual and memory deficits for emotional stimuli associated with depression can be attributed at least in part to an amygdala-hippocampal dysfunction. It has been hypothesized that the reciprocal connections of the amygdala-hippocampal formation with the frontal-subcortical circuit can contribute to observed deficits in emotional cognition and behavior in depressed patients, such as negative interpretation of events and deficits in reward-based decision-making.

Abnormalities in regional brain activation, cortisol regulation, and cognitive processing in mood disorders, when considered within the framework of both animal and human neuroendocrine studies, demonstrate that the relationship between depression and cortisol plays a critical role in the morbidity of depression [188].

4. Conclusions

Glucocorticoids participate in sustaining circadian energy levels in mammals. They facilitate cognition and behavior pertaining to fear and anxiety responses by initiating changes in various functional brain systems that underlie cognitive mechanisms. These effects are produced via interactions with classical neurotransmitter and neuropeptide systems. Cortisol is necessary to sustain behavior and plays a protective role, but has deleterious effects on physiology and cognition during chronic long-term release [123].

Various cognitive domains contribute to the interaction between the animal and its environment, and glucocorticoids influence these cognitive operations. Enhanced arousal, through the interaction of glucocorticoids with norepinephrine and dopamine, allows the animal to orient, focus and sustain attention on perceived events and mobilize resources for necessary decision-making and action. Glucocorticoids participate in attention and emotional memory processes through interactions with norepinephrine, while decision-making based on salience requires glucocorticoids and dopamine. Cortisol can potentiate the experience of fear and anxiety through the activation of extrahypothalamic CRH. Chronic high cortisol levels are detrimental to a number of cognitive domains, and this has implications for cognitive/emotional processing and behavior.

Overactivation of the amygdala and associated cortical areas during depression may alter the experience of these patients across a number of cognitive domains, involving attention, perception and memory systems normally recruited by cortisol. For example, information relayed to the amygdala may be influenced by amygdala overactivity potentiated partly through excessive glucocorticoid activity. The abnormal expression of serotonin 1A receptors found in depressed patients may also be linked to abnormal cortisol regulation. Ongoing research has a major goal to better understand the specific roles of glucocorticoids in mood disorders and whether the contributions of glucocorticoids are premorbid or emerge following symptom presentation.

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