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Chronic stress, cortical plasticity and neuroecology

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ABSTRACT

Prolonged psychological stress and accompanying elevations in blood cortisol are known to induce hypometabolism and decreasing synaptic density in the hippocampus and the prefrontal cortex (PFC). This article evaluates and explores evidence supporting the hypothesis that these, and other, selective effects of prolonged stress constitute a neuroecological program that adaptively modifies behavior in mammals experiencing adverse conditions. Three complementary hypotheses are proposed: (1) chronic stress signifies that the prevailing environment is life-threatening, indicating that the animal should decrease activity in brain areas capable of inhibiting the stress axis; (2) stress signifies that the environment is unpredictable, that high-level cognition may be less effective, and that the animal should increase its reliance on defensive, procedural and instinctual behaviors mediated by lower brain centers; and (3) stress indicates that environmental events are proving difficult to systemize based on delayed associations, and thus the maintenance of contextual, task-relevant information in the PFC need not be maintained for temporally-extended periods. Humans, along with countless other species of vertebrates, have been shown to make predictive, adaptive responses to chronic stress in many systems including metabolic, cardiovascular, neuroendocrine, and even amygdalar and striatal systems. It is proposed in this article that humans and other mammals may also have an inducible, cerebrocortical response to pronounced stress that mediates a transition from time-intensive, explicit (controlled/attentional/top-down) processing of information to quick, implicit (automatic/preattentive/bottom-up) processing.

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1. Chronic stress, cortical plasticity and neuroecology

Organisms throughout the five kingdoms retain certain capacities to adaptively modify their phenotype in order to better conform to their environment (Auld et al., 2010). Some of these changes are transient and reversible, whereas some are comprehensive and permanent. The studies of phenotypic plasticity, polyphenism and "predictive, adaptive responses" have shown that virtually all species can be reprogrammed by portending environmental cues, that the morphological changes are brought about by alterations in gene expression, and that the changes allow conformation to occasional but regularly recurring environmental pressures (DeWitt and Scheiner, 2004). These alternate environments typically involve stressors which demand different body types, behaviors, reproductive tactics, and life-history strategies (Pigliucci, 2001). Often the adaptive response to stress is conserved within groups of closely related organisms that inhabit similar ecological niches (Via and Lande, 1985). For instance, even though all organisms respond plastically to nutrient/energy deprivation, mammals exhibit a unique suite of physiological changes aimed at lowering the metabolism of specific organ systems in the interest of continued survival (Wells, 2009). This article discusses phenotypic changes in mammalian brain structure and neurochemistry, known to be largely mediated by alterations in gene expression, that occur in response to chronically high levels of the stress hormone cortisol. Herein, well-documented brain changes, and their behavioral correlates, are characterized as potentially adaptive responses to adverse ecological scenarios. Different lines of converging evidence will be considered in an exploratory and expository manner.

The mature mammalian brain can be reshaped by chronic or prolonged stress in two primary ways: (1) metabolic activity, dendritic growth and implicit memory are enhanced in the amygdala and caudate nucleus; and (2) metabolic activity, dendritic growth, explicit memory and inhibitory functions are reduced in the hippocampus and prefrontal cortex (PFC) (Cohen et al., 2007; Sapolsky, 2003). Many of the effects of stress on neural circuitry are mediated by the stress hormone cortisol which activates the numerous cortisol receptors present in the amygdala, hippocampus, and PFC (Morales-Medina et al., 2009). Once activated, these receptors trigger pathways that result in the expression or silencing of particular genes, which are the molecular antecedents thought to be respon-

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sible for a large proportion of the neurological remodeling (Petronis and Gottesman, 2000; Petronis, 2004; DeWitt and Scheiner, 2004). This remodeling, much of which has been shown to be epigenetic, may help stressed mammals to adapt to environmental adversity, with its particular set of recurrent and ecologically relevant threats and opportunities.

In the literature, the responses to stress in the amygdala and basal ganglia have been attributed adaptive significance (Sapolsky, 2003), but the responses of the hippocampus and PFC have mostly eluded the attention of evolutionary biologists (Reser, 2007). Increased activity in the amygdala is thought to help animals become more sensitive and responsive to threat (Radley and Morrison, 2005). Neural and dendritic hypertrophy in the basolateral amygdala potentiates the mechanisms dedicated to identifying stressors, and mobilizing the body to address them (Sapolsky, 2003). The amygdala stimulates the paraventricular nucleus of the hypothalamus (PVN) to release stress hormones, and hypertrophy of the amygdala increases its capacity to do this (Roozendaal et al., 2009). A different way to potentiate activity in the amygdala is to release it from the structures that tonically inhibit it (Mitra and Sapolsky, 2008). The PFC and hippocampus have long been identified in neurology as brain regions capable of inhibiting the autonomic and emotional responses to fear-inducing stimuli (Papez, 1937; MacLean, 1949; see LeDoux, 1987, for a review). This circuitry ensures that mammals can override the fear response if they make the determination that the stimulus may appear threatening but is not actually threatening (Morgan et al., 1993). Diminishment of activity in the PFC and hippocampus may ensure that the areas that incite stress, the amygdala and PVN, can function unimpeded during stressful times.

Decreased activity in the PFC and hippocampus may also adaptively influence the animal to be less cerebral and more impulsive (Reser, 2007). When facing lasting adversity, it may be advantageous to suppress the PFC and hippocampus because these areas put inhibitory pressure on defensive, instinctual, and dominant responses. When an animal experiences extreme stress, it is probable that its high-order behavioral strategies are proving relatively ineffectual (Boonstra, 2005). It may benefit such an animal to be less reliant on learned behavior, and more reliant on genetically programmed and species-specific behaviors. Hence, the changes in the hippocampus and PFC may protectively disinhibit innate and instinctual urges (Reser, 2007).

The present article will elaborate on three complementary hypotheses: (1) stress signifies that the prevailing environment is antagonistic, and that the animal should not suppress the stress response or inhibit conditioned fears; (2) stress signifies that behaviors that the animal has learned may be inefficacious or deleterious and that it should increase its reliance on innate behaviors over learned behaviors; and (3) stress indicates that environmental events are proving difficult to systemize on long time scales (using delayed associations) and thus the maintenance of contextual, task-relevant information in the PFC need not be maintained for temporally-extended periods.

Several neurological changes to areas including the amygdala, the caudate nucleus, the hippocampus, the mPFC, and the PFC in general will be discussed. Table 1 describes the general psychological consequences of these changes, the implications that they have for modern people as well as hypothetical implications that they may have had for prehistoric foragers. This table attempts to highlight the disparity between the limiting repercussions of these changes in the modern "information age" and their potentially adaptive significance in the prehistoric past.

Interestingly, prenatal and early-life stress cause a pattern of changes that is strikingly similar to the changes that occur in response to chronic stress in adulthood (Weinstock, 2008). When pregnant rodent or primate mothers are stressed, they program highly analogous changes in the amygdala, hippocampus, and PFC of their offspring (Francis et al., 1999; Kapoor et al., 2006; Schneider et al., 1999). The behavioral changes in these offspring, which include increased vigilance, fearfulness and stress responsivity, have been interpreted by Michael Meaney and colleagues as constituting a predictive and adaptive response to early environmental adversity (Zhang et al., 2004). In this interpretation the amygdalar changes are attributed adaptive qualities. However, the role of the hippocampus and the PFC in contributing to this behavioral response has been neglected. Moreover, psychiatric disorders such as anxiety, depression, posttraumatic stress disorder and schizophrenia are associated with prenatal and postnatal stress, and involve the same pattern of changes to the hippocampus, PFC and amygdala (Axelson et al., 1993; Corcoran et al., 2001).

Elevated levels of noradrenaline and dopamine, such as occur during acute yet transient stress, impair PFC and hippocampus-dependent abilities such as working memory and attention regulation, but strengthen amygdala, caudate and subcortical-dependent functions such as fear conditioning, habitual behaviors and reflexes (Elliott and Packard, 2008; Packard and Teather, 1998). Thus, acute stress, chronic stress, prenatal stress and a number of major psychiatric disorders have all been shown to engineer a switch from thoughtful "top-down" control based on task-relevance to bottom-up control based on salience (Buschman and Miller, 2007; Hermans et al., 2014). This article focuses on these cortical corollaries of pronounced stress, and attempts to interpret them in terms of their ecological utility to mammals, from wild rodents to prehistoric humans. If the neurological changes that respond to stress were diffuse or only degenerative this might indicate that they do not represent adaptation. That the alterations are very selective, that they completely spare critical cortical and subcortical regions, that there are dozens of documented molecular pathways that converge toward these changes, and that arborization and neural activity in the amygdala (Francis et al., 1999; Radley and Morrison, 2005; Vyas et al., 2003) and caudate (Kim et al., 2001; Schwabe et al., 2008) is actually enhanced, suggests that these changes may not be pathological. To further explore the proposed evolutionary rationale for why these changes, in adulthood and in utero, might constitute an adaptive response we turn to the neurobiology of stress perception.

1.1. Stress perception

The recognition of an immediate physical stressor often takes place quickly and automatically in the amygdala, whereas the recognition of a delayed or abstract stressor takes place in the cerebral cortex (Bremner, 1999). The "low" and more direct pathway (sensory receptors to thalamus to basolateral amygdala to PVN) allows the animal to respond quickly to dangerous stimuli before they have fully identified the stimulus or assessed the situation (Dbiec and LeDoux, 2009). The high and more circuitous cortical pathway is far slower (around 24 milliseconds (at its fastest) as opposed to 12 milliseconds) because it passes through the cortex (from the thalamus), where it is informed by higher learning centers which allow context and formal thought to tailor the response (Pessoa and Adolphs, 2010). Quite often the cortical route serves to subdue or inhibit the amygdala's response to stress (Quirk et al., 2003). The fact that the cortex has this capacity to suppress the stress response may make it beneficial in a safe environment, but in an adverse environment its potential to convey false security may amount to an unjustifiable liability.

The amygdala, hippocampus, cortex, and several other areas of the brain have extensive connections to the hypothalamus, the brain center responsible for initiating the stress response (Bremner, 1999). Even transient signals from these areas (induced by fear, horror or helplessness) can induce the PVN of the hypothalamus

Table 1
The neurological effects of stress, then and now.

Neurological State	Psychological Consequences	Implications for Moderns	Implications for Foragers
Amygdala hyperactivity	Potentiation of conditioned fears	Anxiety, fear and excessive stress	Healthy caution, preparedness and mobilization
Caudate hyperactivity	Potentiation of procedural or habitual movements	Intrusion of habitual or procedural responses	Increased reliance on movements that have been proven effective
PFC hypoactivity	Behavioral disinhibition	Working memory and goal-setting problems	Increased reliance on instinctual and appetitive impulses
mPFC hypoactivity	Impaired inhibition of conditioned fears	Exaggerated stress responses to nonfatal threats	Enhanced awareness of potential threats
Hippocampal hypoactivity	Inaccessibility of contextual and episodic information	Explicit/declarative memory problems	Increased reliance on dominant and procedural responses

to secrete adrenaline and corticotropin-releasing hormone (CRH), which act throughout the brain, especially in the hypothalamus and the locus coeruleus (Dedovic et al., 2009). Both adrenaline and CRH affect cognition, stimulating anxiety and fear-related behaviors (Gold, 2005). If the stressor lasts long enough or if the CRH levels are sufficiently high, the release of adrenocorticotrophic hormone (ACTH) is triggered within the pituitary, which induces the release of glucocorticoids (GCs) by the adrenal cortex (Lovallo and Gerin, 2003). Cortisol, the GC in humans (rodents have corticosterone), moderates the physiological response to chronic or lasting stressors by inducing an array of effects throughout the body (Mastorakos et al., 2005). Long lasting stress can alter developmental trajectory and it is thought that the frequency and duration of stress exposure carries predictive information about environmental unpredictability and extrinsic morbidity/mortality. Natural variation (due to phenotypic plasticity or heritable variation) in stress reactivity is thought to reflect niche adaptation and be associated with individual differences in a range of life history-relevant domains including: affiliation, competitive risk-taking, parental investment, self-regulation, somatic effort, reproductive functioning and learning.

A heightened stress system is thought to enhance performance during stress-provoking or life-threatening situations (Wingfield et al., 1998) and facilitate fearfulness, vigilance and cautiousness, all traits that would have been highly adaptive during extended periods of dire stress (Marks and Nesse, 1994). Chronic stress is known to initiate up-regulation of the hypothalamic-pituitary-adrenal axis (HPA) in rodents, primates, and humans, causing the stress response to become more pronounced, and more easily triggered (Miller and O'Callaghan, 2002; Sapolsky et al., 1986; Lovallo and Gerin, 2003). This lasting up-regulation is thought to be an adaptation to sustained environmental demand (Petronis and Gottesman, 2000). Furthermore, enhanced amygdalar reactivity enables the animal to react to every seemingly threatening stimulus as if it were a full threat. This will inevitably lead to false alarms, but in terms of reproductive success, it is clearly better to overreact to a nonthreat than to underreact to a true threat (Nesse and Young, 2000). That the amygdala becomes hyperactive during prolonged stress has already been attributed adaptive significance (LeDoux, 1996). How are the changes in the hippocampus and the PFC to be understood though?

2. The effects of stress on the hippocampus

The response to acute stress, which is mediated by adrenaline, and the response to prolonged stress, mediated by cortisol, increase energy use in the brain; heightening both memory and processing speed. However, when cortisol levels are sufficiently high, the opposite occurs, and energy usage in some areas of the brain can be cut drastically (Foy et al., 2005). After about 30 min of intense stress this "inverted U" relationship becomes apparent and PFC and hippocampus-dependent mental functions begin to decline rapidly (Alexander et al., 2007; Dolcos and McCarthy, 2006; Luethi et al., 2009; Liston et al., 2009; Sapolsky, 1994). In fact, if the cortisol levels are elevated over many hours, neurodegenerative processes commence in the forebrain, primarily in the hippocampus and PFC (Kim and Yoon, 1998; Zhu et al., 2007). Hippocampal volume is known to decrease in response to prolonged environmental stress in rodents, monkeys, humans and presumably most other mammals (Lambert and Kinsley, 2004). The damage to the hippocampus can progress to the point of neuron loss, apoptosis, and memory impairment in humans and also across mammalian species (McEwen, 2007). This wide taxonomic susceptibility makes the hippocampal neurodegenerative response to stress appear to have been naturally selected and conserved.

The hippocampus, an area within the medial temporal lobe of the brain plays the role of modulator to the hypothalamic-pituitary-adrenal response to stress. It does so by inhibiting the actions of the hypothalamus. The PVN of the hypothalamus receives extensive inhibitory collaterals from the hippocampus (Radley and Morrison, 2005). In fact, activity in the PVN can be both tonically and phasically overridden by these inhibitory inputs (Mitra et al., 2005). The hippocampus has many cortisol receptors, is very sensitive to fluctuations in cortisol levels, and is well-suited for its job of creating negative feedback for CRH release (Diorio et al., 2000). When blood cortisol concentrations reach sufficiently high levels, the hippocampus sends inhibitory messages through its projections to the PVN of the hypothalamus, signaling that the stress response has gone on for too long and must be diminished (Bao et al., 2007). However, lasting elevations of cortisol are toxic to the hippocampus and lead to volume reduction as well as hippocampal dysfunction (Kim and Yoon, 1998). Decreased volume of the hippocampus results in diminished ability to generate negative feedback on cortisol release, and this is a driving element in the lasting, autocatalytic potentiation of stress known as the "stress cascade" (Sapolsky, 1996).

The high-affinity mineralocorticoid receptors for glucocorticoids, when activated, serve to enhance learning and LTP, whereas the low-affinity glucocorticoid receptors (which are 10 times more difficult to bind to and are only occupied heavily during major stressors) strongly inhibit both LTP and primed burst potentiation (PBP) (de Kloet et al., 2005; Herbert et al., 2006). When the glucocorticoid receptors are activated heavily, their occupancy leads to prolonged opening of calcium-dependent potassium channels resulting in decreased neuronal excitability (McEwen and Sapolsky, 1995). Prolonged GC elevations have been shown to lead to excitotoxicity, cytoarchitectural damage, the inhibition of neurogenesis and atrophy of dendritic branch points in the CA1 and CA3 cell fields of the hippocampus (Sapolsky, 2003). Apart from the PFC, other areas of the brain are not insulted by stress in this way. Why not? It is certainly possible that these changes are truly pathological and maladaptive and that they occur due to some cur-

rently unknown tradeoff, where hippocampal neurons retain some advantage despite an accompanying susceptibility to cortisol. However, given that hippocampal degeneration liberates activity in the PVN of the hypothalamus, the response may alternatively represent an effort to increase responsiveness to threat, a process that can be seen as complementary to the neuroproliferation in the amygdala.

Aside from its function in inhibiting the hypothalamus, the hippocampus is also crucially involved in encoding and retrieving declarative or explicit memory which includes: episodic (contextual), and spatial memories (Eichenbaum, 2004). Moreover, aside from reducing its ability to send negative feedback to the hypothalamus, chronic stress is known to impair explicit (otherwise known as declarative or hippocampus-dependent) memory (Diorio et al., 2000; Sapolsky et al., 1986) which is central to high-level mental functioning. Why should both functions share the susceptibility to neurodegeneration? Could it be because explicit memory plays a role in inhibiting defensive responses? Perhaps episodic memory provides information about when not to be afraid but is also subject to making fatal errors. Perhaps during adversity the animal should not trust hippocampal inhibitory schemas based on isolated autobiographical events but should instead act on general, semantic knowledge (averaged over many autobiographical events) held in early/lower cortical areas. As it happens, the area of the PFC that is most extensively connected with the hippocampus – the medial prefrontal cortex (mPFC) – is thought to mediate hippocampal-dependent aspects of episodic memory, is instrumental in suppressing the stress response, and is also the cortical area damaged the most by chronic stress (Quirk et al., 2003).

2.1. The effects of stress on the PFC

It is widely accepted that the mPFC has a commanding capacity to diminish the stress response (Figueiredo et al., 2003). In fact, the amygdala receives extensive inhibitory collaterals from the PFC (Radley and Morrison, 2005). Like the hippocampus, the mPFC is a target of both acute and repeated stress (Cerqueira et al., 2007). For instance, acute stress from social speaking has shown to diminish cognitive flexibility, the regulation of attention, and working memory (Luethi et al., 2009). Also emotionally upsetting movies have been associated with significantly reduced PFC activation. Neuroimaging work has demonstrated that acute stress negatively affects working memory-related activation of the dorsolateral PFC (Qin et al., 2006). Chronic stress leads to dendritic retraction and debranching in many areas throughout the PFC, in rodent, and primate models (Brown et al., 2005; Patel et al., 2008). The volumetric reductions in rat mPFC due to stress are confined to the upper layers, where most hippocampal projections terminate (Jay and Witter, 1995). Synaptic density has also been shown to be significantly diminished in a variety of PFC regions including the mPFC, and dorsolateral PFC. Interestingly, data indicate that neurons in the rat infralimbic PFC that project to the amygdala do not lose dendritic material in response to stress (Shansky et al., 2009), highlighting the distinct preservation of amygdala circuits. Interestingly, as in the hippocampus, PFC dendritic damage interferes with the ability of the mPFC to suppress the stress response (Mizoguchi et al., 2003).

In rodents, even short intervals of stress are capable of reversing the extinction of fear conditioning (resulting in the resurrection of old fears), and this is thought to be caused primarily by stress dysregulation of the mPFC (Izquierdo et al., 2006). Cell fields of the mPFC attenuate emotional responsiveness by directly inhibiting the basolateral amygdala (Figueiredo et al., 2003). Regions of the mPFC also inhibit the stress response by acting on the hypothalamus indirectly, through the hippocampus (Mizoguchi et al., 2003). The PFC is connected to the hippocampus by axons originating in the subiculum and ventral CA1 subfields (the same cell field that shows the most pronounced dendritic atrophy during chronic stress). These efferents travel from the hippocampus through the fimbria-fornix system and terminate in glutamatergic contacts with pyramidal cells and interneurons of the mPFC (Liston et al., 2006). The connections between these two areas are thought to modulate both learning and memory processes as well as the regulation of the stress response, ultimately through inhibition of the release of corticotrophin-releasing hormone (CRH) in the PVN of the hypothalamus (Cerqueira et al., 2007). That these affected areas are both involved in explicit memory, stress diminution and the stress cascade is probably not coincidental.

Modern cognitive neuroscience has identified conflicts of interest between the cortex and the amygdala where they often contradict and even inhibit one another (McEwen, 2007). In fact, the cortex tonically inhibits the amygdala, and only when a fear stimulus is very powerful can the amygdala override the suppressive effects of the cortex (LeDoux, 1996). Many studies, including research with humans have shown that the mPFC, especially the ventromedial PFC (vmPFC), plays a large role in inhibiting defensive and emotional responses (Phelps et al., 2004) (Fig. 1).

To extinguish fear behaviors the vmPFC suppresses amygdala function by engaging a network of inhibitory interneurons that synapse on the amygdala (Sotres-Boyen et al., 2004). The vmPFC is also the subsection of the mPFC that exhibits the greatest reduction in activity in response to chronic stress (Koenigs and Grafman, 2009). Studies have shown that rats with lesions in the vmPFC continue to act fearful in the presence of discontinued, conditioned fear stimuli long after rats without lesions learned to ignore these stimuli (Morgan et al., 1993, 2003; Morgan and LeDoux, 1995). Destruction of the vmPFC abolishes the ability to suppress fears and causes animals to react fearfully to fear conditioned stimuli, even if they are vastly reduced in intensity (Milad and Quirk, 2002). It seems that natural selection "acted" on this phenomenon and selected the mPFC (and especially the vmPFC) to be susceptible to chronic stress for functional reasons.

2.2. Why inhibiting stress reactivity is maladaptive in an adverse environment

In a safe environment the explicit processing of the hippocampus and PFC is likely beneficial because it helps the animal to draw inferences about, systemize, and understand complex variables in its environment. This is a time-intensive process that involves creating and testing hypotheses. In a safe environment, faulty associations or examples of unwarranted inhibition are not punished heavily. Explicit processing may take the emphasis away from threat, and allow the animal to pursue things that it finds rewarding and interesting. In an unsafe environment though, an animal should be less concerned with secondary and tertiary reinforcers, and instead, should rely on age-old, instinctual behaviors that are less susceptible to error.

The basolateral amygdala bases its decisions (whether to incite stress or not) on implicit, nondeclarative, acontextual memories (Fanselow and Gale, 2006). This suggests that the amygdala is largely a co-occurrence detector. The amygdala warns us of simple associations without respect to how, where, when or why (Eichenbaum, 2004). In contrast the cortical-hippocampal complex employs explicit memories that use context and episodic events to make inferences about the how, where, when and why (Manns and Eichenbaum, 2006; Labar and Cabeza, 2006; Reber, 2008). This type of inferential thinking must be susceptible to all of the pitfalls and hazardous heuristics of cognition identified by cognitive psychologists (Kida, 2006).

The memories for co-occurrences that exist in the PFC, relative to those in the amygdala, involve higher-order associations because they involve neurons that are capable of sustained firing

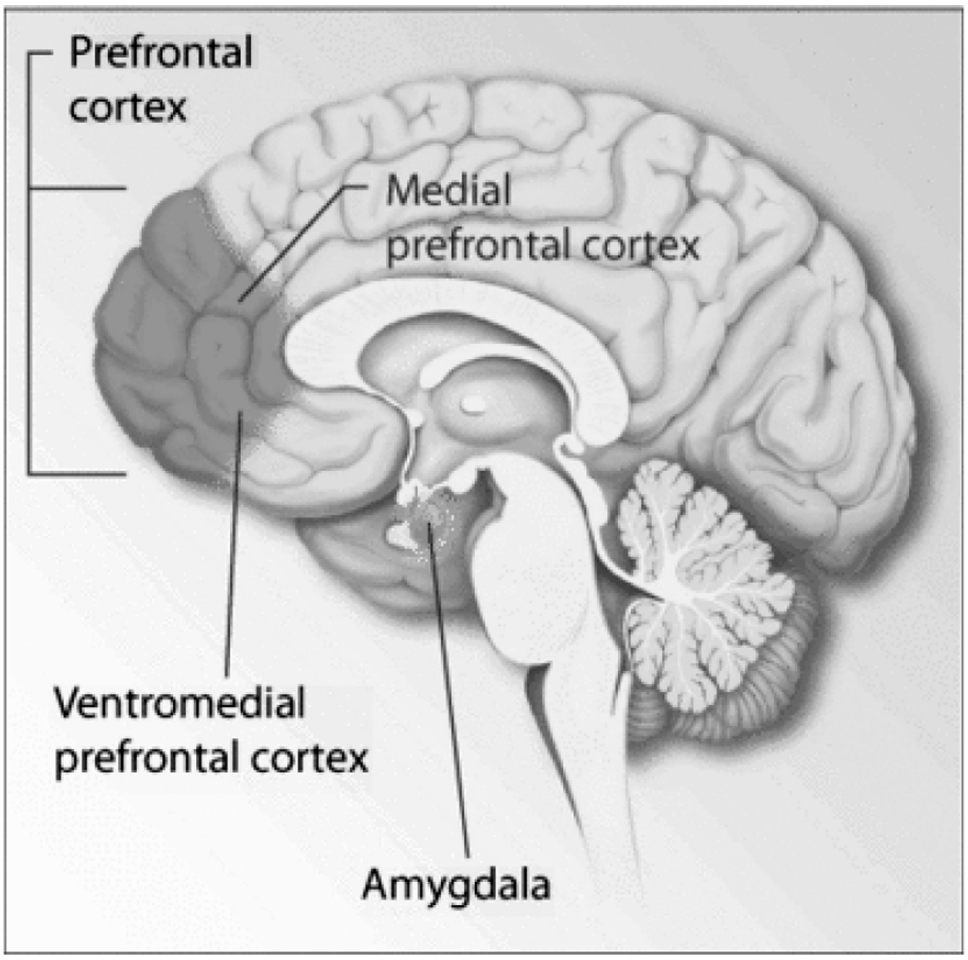

Fig. 1. Depiction of the anatomical location of the amygdala, the PFC, the mPFC, and the vmPFC.

(Goldman-Rakic, 1995). Neurons in the PFC can span a wider delay time or input lag between associated occurrences (Zanto et al., 2011). Thus close temporal contiguity between two stimuli is not necessary for them to become associated. Thus, PFC processing can involve subjective inferences about causality based on prior experience. The response properties of neurons in the amygdala; however, limit the amygdala to encoding information about the objective association of two, near simultaneous events (LeDoux, 1996). Therefore, the amygdala is susceptible to making false alarms and misses, but the hippocampus and cortex can formulate associations (from inductive reasoning) that are illusory and not representative of veridical relationships in the environment.

3. Stress and alterations in dopamine neurotransmission

The mesocortical dopamine system is heavily impacted by stress. Both acute and chronic stress have been shown to dysregulate dopamine transmission in the ventral tegmental area VTA (Patel et al., 2008). The mesolimbic system (activated by situations requiring motivation and physical effort) in contrast, is not adversely affected by stress. Acute stress is associated with increases in dopamine levels, excessive D1 (Vijayraghavan et al., 2007) and D2 (Gibbs and D'Esposito, 2005) dopamine receptor stimulation and accompanying reductions in sustained firing and correct tuning of PFC neurons (Vijayraghavan et al., 2007). This effect has been observed in humans (Gibbs and D'Esposito, 2005) and other mammals (Druzin et al., 2000). The case is similar for chronic stress. Whereas elevated levels of glucocorticoids increase dopaminergic transmission in the mesocortical system in the short-term, long-term elevations in GCs decreases dopaminergic transmission causing comparable reductions in sustained firing and correct tuning of PFC neurons (Mizoguchi et al., 2000). This has been taken to underlie the "inverted-U" relationship between working memory and stress (Gibbs and D'Esposito, 2005) mirroring that seen in hippocampus-dependent memory.

Dopamine sent from subcortical VTA neurons modulates the activity and timing of neural firing in the PFC acting to sustain ongoing neural activity. Dopamine neurotransmission in the PFC is thought to be instrumental in the ability to internally maintain, and update contextual information. Seamans and Robbins (2010) suggest that the DA/PFC system may play a major role in the way attentional resources are allocated in the effort to understand the meaning of patterns of stimuli and the strategies to cope with or take advantage of them. It is important for mammals to identify and capture information about unexpected occurrences and systemize them in an attempt to identify systematic patterns. It is crucial that this effort is focused on the contextually unique features of the novel scenario, and for this to happen those features must be maintained in working memory through sustained firing over elapsing time so that the cognitive modeling taking place can analyze their significance. By reducing sustained firing in PFC neurons chronic stress may reduce the frequency of associations made between temporally distant stimuli. During stressful times, associations made between temporally distant stimuli may lead to misinformed or ineffective behavior. Interestingly, neurons in the vmPFC have been shown to be instrumental in the tendency to

falsely perceive coherent patterns in random events (Clark, 2010). Perhaps in adverse environments it is less helpful to search memory for relationships between stimuli that occur in delayed succession and instead to focus on those occurring in quick succession. The dopaminergic dysregulation may also suggest that chronic stress takes emphasis from top-down modeling and instead places emphasis on bottom-up responses.

4. Why inhibiting instinctual impulses is maladaptive in an adverse environment

The hippocampus and especially the PFC, are involved in inhibiting innate and instinctual drives, other than fears, and the neurodegeneration that takes place in response to stress may adaptively disinhibit reliable and valuable impulses (Reser, 2007; Wirth, 2015). Highly encephalized vertebrates like mammals have the ability to inhibit impulses, delay gratification and prolong anticipation when it is clear that this will be beneficial in the long run. Mammals and primates in particular employ this kind of restraint in order to wait for an opportunity, to deceive a competitor, to cooperate or reciprocate with a conspecific, to submit to a dominant individual or to acquiesce to their own offspring (Kappeler and van Schaik, 2006). When times are difficult, resources are sparse and predators are numerous, restraint, deference and acquiescence are probably ineffective tactics. In the wild, when times are tough, temperance, discipline, hesitation and forethought may often be handicaps.

Neurodegeneration in the PFC and hippocampus caused by stress are known to create deficits in executive function as well as in learning and memory (Arnsten, 2009). For instance, LTP disruption in the hippocampus-mPFC pathway, which significantly impairs working memory, can be induced after only a single episode of acute stress in rats (Rocher et al., 2004). Chronic stress-induced dendritic atrophy in the mPFC has been shown to correlate with severe functional deficits in attentional control and higher-order cognitive function (Liston et al., 2006). These deficits in working memory and executive function have been speculated to be maladaptive in the literature, because they reduce representational flexibility and preparatory set (Cerqueira et al., 2007). This is certainly true, but working memory probably involves particular costs in addition to its advantages. For example, working memory allows the generation of alternatives to innate tendencies. Overriding innate tendencies can be adaptive or maladaptive, ultimately depending on context.

The PFC is notorious for suppressing urges from lower, instinctual regions. It sends projections to many subcortical areas, allowing mammals to inhibit the things that come naturally (Fuster, 2009). Humans constantly inhibit lower order drives. For example, it is largely thought that anorexia nervosa is an example of the frontal lobe suppressing the hunger drive created by lower brain centers such as the hypothalamus (Spinella and Lyke, 2004). Hunger is a fundamental instinctual drive that, at least in humans, can be vastly overridden by PFC function. Clearly, the cortex has the ability to formulate its own plans and use its inhibitory capacities to create behavior that can be at odds with reproductive success.

The hippocampus is probably also involved in inhibiting innate behavior, even if indirectly. The first functional conceptualization of the hippocampus claimed that it was an area responsible for "behavioral inhibition" (Nadel et al., 1975). Since this time, the focus has moved to its importance in spatial abilities and episodic memory, but there is still a good deal of evidence that it is involved in inhibiting impulses. For instance, animals with hippocampal damage tend to be hyperactive and tend to have difficulty learning to inhibit responses that had previously been reinforced (Best and White, 1999). Thus the neurodegenerative changes that occur within the hippocampus in response to stress might also result in behavioral disinhibition. In contrast, amygdala activation causes an animal to neglect what it was thinking about earlier, arresting its ongoing activity, and orienting it to a new stimulus (Morgan et al., 1993). Animals with amygdalar lesions are less responsive to external stimuli and exhibit a predisposition towards internal stimulation (Kandel et al., 2000). This may be why stress causes the amygdala to become hyperactive, and the hippocampus and PFC to become hypoactive, because stress signifies that the focus should be on the external world not the internal world.

The neurodegenerative effects of chronic stress may be revolting against a hidden danger, the "tyranny" of the prefrontal cortex. Hyperfrontality is a nonclinical but documented syndrome characterized by excessive prefrontal domination of behavior. Hyperfrontal individuals can be stoic, reserved, obsessive, repressive, neurotic, detached and dispassionate. They are able to quell and override subcortical impulses by mobilizing past learning and beliefs. This kind of behavior can surely be adaptive but probably only in specific ecological contexts. Hyperfrontality and hypofrontality may represent opposite strategies on a behavioral continuum that have been maintained through "environmental heterogeneity," a form of balancing selection. The hypofrontality seen in traumatized individuals and in those with schizophrenia or PTSD (Buchsbaum, 1991) may be an effort to reduce tyrannical prefrontal supervision, making them less "susceptible" to temporally distant or conceptually abstract rewards. Patients with prefrontal damage engage in behaviors aimed at immediate gratification despite the fact that they can appreciate that the long-term results of their actions are often self-defeating (Eslinger et al., 2004). Perhaps during adversity in the ancestral past behaviors aimed at immediate gratification were not self-destructive as they often prove to be today.

It is important to point out that what the PFC and hippocampus are allowing animals to inhibit is often what their genes are "recommending." The brainstem along with the diencephalic and limbic areas are hard-wired with a huge number of ethologically appropriate responses that have been engendered by natural selection over geological time (hundreds of millions of years). Environmental stimuli are constantly activating these inclinations, and in lower animals this almost always results in outward behavior. In animals with large cortices though, the subcortical predispositions are merely suggestions, not commands, because of their capacity to inhibit them, and to try something more complicated or difficult. Motivational impulses originate subcortically (e.g., midbrain reticular formation and hypothalamus), are sent via the anterior thalamus to higher structures (e.g., amygdala, cingulate cortex, PFC and hippocampus), which provide feedback regulation that may reinforce or inhibit the generation of the impulse. Some of the projections carrying this feedback travel directly to the originating structures, others regulate the ascending subcortical inputs through the thalamus by way of the pallidum. This process may involve the well-known cortico-striato-pallido-thalamic loop (Swerlow and Koob, 1987). PFC and hippocampus-dependent, explicit memory determines what this feedback to the subcortex will be and provides the behavior that may supplant the subcortical recommendations. If the environment is barbaric and irrational, then perhaps contrived and complicated behavior is less adaptive than time-tested, instinctual behavior. This seems especially true when one considers the fact that explicit behaviors require much more processing time before a reaction can occur.

4.1. Chronic stress, the caudate nucleus, and reaction time

Several well-received studies have found that acute stress biases processing toward caudate-dependent learning strategies (Kim et al., 2001), and improves performance on habitual and/or well-

rehearsed tasks (Broadbent, 1971; Wickens et al., 2007). In both humans and rodents, chronic stress has been associated with a substantial decrease in the use of hippocampal-dependent learning strategies and a dramatic increase in the use of caudate-based learning strategies (Schwabe et al., 2008; Hartley and Adams, 1974; Packard and Cahill, 2001). This stress-induced shift from top-down, explicit information processing to automatic, implicit processing has been well characterized experimentally (Packard and Wingard, 2004). Many researchers have concluded that this is due to the fact that stress impairs PFC operation but spares ingrained habits dependent on the basal ganglia, as well as late motor and early sensory cortices (Arnsten, 1998; Elliott and Packard, 2008). Robert Sapolsky, a leading researcher of stress neuroscience, has concluded that the stress cascade may adaptively recalibrate the brain to put emphasis on regions responsible for habitual or procedural responses, such as the caudate nucleus (1994).

Humans under intense chronic stress have been shown to exhibit potentiated reflexes and increased speed for habitual movements (Pfaffman and Schlosberg, 1930; Vasterling et al., 2006; Vedhara et al., 2000). Combat veterans with PTSD, especially those who were using the caudate heavily in life-threatening situations (such as riflemen), exhibit hypertrophic caudate nuclei and atrophic hippocampi (Bremner, 1999). Since the processes of the hippocampal and caudate systems work antagonistically at times (Voermans et al., 2004), hypoactivity in the hippocampus and PFC may permit subcortical movement areas more autonomy and ensure that the thinking mind cannot easily interfere with their responses.

Reaction time or the delay between the input and output seen in an animal's behavior is an indication of the amount of neural processing taking place, where more processing equates to longer delays (Bogacz et al., 2009). The least encephalized animals have the fastest responses (Chittka et al., 2009). For example, animals such as insects display reaction times that are hundredths of those observed for mammals (Dean, 2005). In fact, reaction time slows with the number of synapses interposed between input and output (Kandel et al., 2000). The neurodegenerative effects of stress on the PFC likely act to adaptively potentiate instinct, but may also speed up reaction to the environment as it is known that explicit movements trade speed for informedness.

5. The hippocampus and neuroecology

Behavioral strategies based on hippocampal learning probably work well in a predictable and ordered environment. An environment that sends clear, honest signals about the interrelationships between complex variables allows animals to formulate ecologically meaningful knowledge. Chaotic and violent environments; however, may not be amenable to hippocampal-based strategies. In a stressful environment many of these signals are probably muddled and misleading. Psychologist George Kelly has argued that in a stressful or anxiety-provoking environment is it usually very difficult for humans to understand the important variables and how they interrelate (1991). Stress is known to be exacerbated when the human or rodent cannot figure out how to make things better, feels helpless or feels like it has no control (Glass et al., 1971; Minor et al., 1984). In fact, an experimental animal that is subjected to numerous stressors will liberate significantly less cortisol if it is made to think that it has some control over the frequency of the stressors, even if it does not actually have any control at all (Sapolsky, 1994). If the animal has no control over environmental variables then why should it expend energy attempting to understand and systemize them? Top-down regulation of behavior may only be beneficial for reproductive success if the animal has the capacity to use its systemizations to exert meaningful control. When environmental variables are incomprehensible and the animal has little influence over its state of affairs, then explicit thinking may be as extraneous as it is in less encephalized animals; specifically because there is no "correct solution" for higher cognition to arrive at.

The glucocorticoid stress hormones generally cause different tissues and organ systems to put off long-term, expensive building projects like growth, most forms of anabolism, digestion, tissue repair, sexual reproduction and immune function. They do this to redirect the body's energy toward fighting and flight. In much the same way, PFC and hippocampal-dependent learning (unlike caudate and amygdalar learning) are very much slow and cumulative processes that represent long-term efforts at informing behavior in the distant future (Eichenbaum, 2004). If supply lines toward provident but expensive long-term somatic efforts are cut off when cortisol is elevated, it seems sensible that the PFC and hippocampus would fall into this category. Hippocampal-dependent memory, in the sense that it is contextual and episodic, represents new, untested learning, and for this reason, relative to other brain areas, it may be expendable in adverse situations.

Importantly, there are other examples of natural selection favoring altered processing priorities, and these also involve neurodegeneration. The study of neuroecology has shown that hippocampal size can vary dramatically in individual animals over the course of a single season. In fact, neuronal fluctuations in the hippocampus are known to occur in a wide variety of food-caching mammals (Kempermann, 2002) and birds (Garamszegi and Eens, 2004). The hippocampus increases significantly in volume during seasons where the animal must remember where it hid its food, and then decreases when the season ends (Clayton, 2001). In fact, neurogenesis in the hippocampi of individual adult mammals is known to increase with environmental stimulation and enrichment (Kempermann et al., 1997, 1998), and decrease along with the diminishment of body size, metabolic rate and need to forage (Jacobs, 1996). This relationship, between environmental demands and investment in hippocampal neurons is commonly interpreted to be an ecological strategy focused on the tradeoff between saving energy, and reliance on hippocampus-dependent memory (Dukas, 2004). The similarities here suggest that the stress cascade, which occurs in a wide variety of animals, may also be an example of a neuroecological response.

6. Stress, cognition and evolutionary medicine

Evolutionary medicine is the field of study that attempts to understand disorder and disease in terms of evolutionary biology. It has clarified the evolutionary origins of many of the most prevalent diseases including atherosclerosis, cancer, cardiovascular disease, cystic fibrosis, diabetes mellitus, obesity, sickle cell anemia and many others (Nesse and Williams, 1995; Williams and Nesse, 1991). Following the pioneering work of Panksepp (2006) there has been a movement to understand psychiatric disturbances in terms of the underlying evolutionary mechanisms that they may represent. Many articles have analyzed various forms of psychopathology in terms of evolutionary theory and evolutionary medicine (e.g. Baron-Cohen, 1997; Marks and Nesse, 1994; Reser, 2009), and this area of research has been referred to as "evolutionary psychopathology," or "Darwinian psychiatry".

Researchers in the field of evolutionary medicine view stress and anxiety as adaptive when they permit animals to effectively escape danger (Marks and Nesse, 1994). It has been shown that animals that have a genetic susceptibility to being highly stressed or anxious are more likely to avoid being eaten by predators (Dugatkin, 1992). In fact, Williams and Nesse (1991) have pointed out that a proclivity for enhanced stress responsiveness may be highly beneficial in terms of reproductive success, especially in adverse environments.

Table 2
The neurological effects of stress associated with different conditions.

Condition	Hippocampus Hypoactivity	PFC Hypoactivity	Amygdala Hyperactivity
Acute Stress	de Kloet et al. (2005), Herbert et al. (2006), Elliott and Packard (2008)	Rocher et al. (2004), Patel et al. (2008)	Radley and Morrison (2005), Roozendaal et al. (2009)
Chronic Stress	Kim and Yoon (1998), Lambert and Kinsey (2004)	Liston et al. (2006), Zhu et al. (2007)	Francis et al. (1999), Radley and Morrison (2005), Vyas et al. (2003)
Prenatal Stress	Weinstock (2008), Schneider et al. (1999)	Francis et al. (1999), Kapoor et al. (2006)	Zhang et al. 2004, Diorio et al. (2000)
Anxiety Disorder	McEwen (2007)		Francis et al. (1999), Vyas et al. (2003)
Depression	Lambert and Kinsley (2004)	Corcoran et al. (2001), Axelson et al. (1993)	
PTSD	Bremner (1999)		Panksepp, 2006
Schizophrenia		Goldman-Rakic (1995)	

In fact, it is widely accepted that diverse animal species use the neuroendocrine stress axis to integrate sensory input regarding habitat quality to inform the appropriate level of fear, withdrawal, avoidance, paranoia and other defensive behaviors (Diorio et al., 2000).

Articles written in evolutionary medicine have examined clinical syndromes such as anxiety, posttraumatic stress disorder (PTSD) and depression, and characterized them as beneficial responses to dangers such as predator pressure, scarcity and conspecific conflict (Baron-Cohen, 1997). Each of these disorders has been hypothesized to respond to different ecological scenarios. Depression has been conceptualized as a permissive strategy that emphasizes appeasement of dominant individuals, and low risk-taking (Allen and Badcock, 2006). Anxiety is thought to represent a careful, cautious strategy where fears and aversive drives are emphasized over appetitive drives (Marks and Nesse, 1994). PTSD has been conceptualized as a threat-avoidant strategy where the individual is particularly sensitive to stimuli that it found traumatic in the past (Panksepp, 2006). Schizophrenia has been conceptualized as a response to severe stress that is characterized by disinhibition, hypervigilance, and high emotional reactivity (Reser, 2007). These and other psychological disorders may represent compartmentalized suites of psychophysiological symptoms that become adaptive, when they present together, in particular environmental contexts. Many "behavioral syndromes" have been discovered in mammalian species and these are thought to represent adaptive responses to particular scenarios, despite the fact that they appear maladaptive when taken out of their ecological context (Sih et al., 2004). There is an emerging consensus now in ethology that when traits are correlated, they should be studied together as an ecological package rather than as isolated units (Sih et al., 2004).

The three major traits of the stress cascade, cortisol dysregulation, reduced hippocampal volume, and impairment in hippocampus-dependent memory, are also major components of depression, anxiety disorders, PTSD and schizophrenia (Lambert and Kinsley, 2004). Moreover, each of these four disorders are linked with prolonged stress, traumatic past experience, exaggerated stress response, PFC dysregulation, attentional deficits, startle potentiation and increased heart rate responsivity (Corcoran et al., 2001; Axelson et al., 1993). Disorders like schizophrenia, PTSD, anxiety and depression could perhaps each represent behavioral syndromes that employ the defensive benefits of the stress cascade as identified in this article. See Table 2 below.

Evolutionary perspectives regard diseases as adaptations that are no longer beneficial because of a "mismatch" between the ancestral environment and the modern environment (Williams and Nesse, 1998; Neel, 1999). In modern times, the cognitive repercussions of excessive stress impair our ability to function professionally and decrease quality of life in the workplace and at home, despite the fact that our stressors are rarely life-threatening or even physical. Because of this mismatch, the stress cascade (and associated disorders) appears to be out of place in time; yet another example of an "ecological anachronism."

Table 3
Features of the stress cascade that are interpreted in an evolutionary context.

- Wide taxonomic susceptibility with highly conserved features
- Dozens of molecular pathways that converge toward the neurological changes
- A high degree of neuroanatomical specificity within and between species
- Most brain areas are completely spared
- Some brain areas are up-regulated rather than down-regulated
- Neural remodeling resembles known neuroecological changes
- Acute stress, chronic stress and prenatal stress share neuropathological symptomatology
- Anxiety disorder, depression, PTSD and schizophrenia also share these symptoms
- Enrichment, stimulation, and maternal care have opposite effects on the hippocampus and PFC

7. Conclusions

After an exploratory review of relevant literature this article concludes that the 3 hypotheses presented in the introduction cannot be accepted or rejected, but have been met with supporting evidence (Table 3). In addition to the benefits of disinhibiting the stress response and defensive and evasive responses, the stress cascade may also allow the animal to disinhibit appetitive drives and help it to be opportunistically nearsighted. Perhaps during stressful times PFC functions such as the temporal organization of behavior, inhibition of spontaneous activity, long-term goal setting, and flexibility with regard to novelty, all take a back seat to the more primal cognitions involving brainstem impulses, hypothalamic inclinations, limbic drives and striatal urges. Delaying gratification, thinking twice, and creating elaborate mental models of one's environment may be unattractive modes of operation during stressful times when it may be better to employ Occam's razor and simplify, streamline, and expediate. The PFC and hippocampus strong-arm behavioral control of the animal from its hard-wired instincts to the beliefs and associations that the animal contrived based on its unique and eccentric interaction with the world. These may give the animal means to subdue, pervert, and incapacitate the prime directives of nature.

Dawkins (1976) has argued that the cortex has not been allowed tyrannical autonomy over behavior in any species because such animals would develop motivations that are inconsistent or conflicting with the motives of its genes. Dawkins points out that the

Table 4
Hypothesized benefits of hippocampal and PFC neurodegeneration during stress.

- Reduced inhibitory pressure on the amygdala and PVN
- Increased reaction time and disinhibition of lower motor centers
- Increased innate, instinctual, and species specific behaviors
- Increased defensiveness, withdrawal, avoidance, vigilance, and opportunism
- Increased resistance to delayed gratification, temporal discounting and delayed or abstract rewards
- Stress may signify that higher-order strategies are failing or perceiving false patterns
- Untested episodic memories may be tenuous during times of stress
- Associations between temporally distant stimuli maybe tenuous during times of stress

highly evolved human mind allows us to temporarily escape the direction of "selfish" genes by allowing us to reprogram and even override our instinctive behavior. Today humans can choose not to have children or choose to commit suicide, decisions that few animals are granted the authority to make. The reason that humans have this degree of "free will" is because their ancestral ecological niche was highly cognitively demanding and necessitated ingenuity, insight, tolerance and restraint. However, evolution only allows animals intellectual abilities to the extent that they will help them to live and to pass on their genes. When we take a "gene's eye view" of the stress cascade phenomenon it becomes apparent that our "selfish" genes are not "concerned" with our higher-order intellectual abilities. Hippocampus-dependent explicit memory and PFC-dependent working memory may thus be expendable from a gene's perspective when these abilities interfere with the propagation of germ cells.

Explicit memory (hippocampal-dependent) and working memory (PFC-dependent) may have evolved under relatively favorable circumstances over the last 300 million years. These two forms of memory may have been largely pioneered in early mammals during the Mesozoic and then expanded in primates during the Cenozoic in order to inhibit and modify lower impulses and fears in accordance with what the animal has come, by experience, to know or believe (Dunbar and Shultz, 2006). The large frontal lobe in primates makes it so that subcortical structures participate in but do not dominate the decision-making process, though during panic they may (Panksepp, 1998). Primates have a voluminous and richly connected frontal lobe because their environments require a tremendous capacity to learn and integrate. The slow process of "cortical civilization" that has taken place over the last several hundred thousand years has allowed the human brain to develop further. Our PFC allows us to be civilized, self-disciplined, polite and reserved – strategies that are probably only apposite during times of civility. When the environment cannot be controlled, rationalized or systemized; however, implicit, procedural, caudate and amygdalar behavioral strategies may be preferable to explicit, declarative, cortical ones. That even humans have this vulnerability says something very specific about the adaptive value of intelligence. The hypothesized benefits of this vulnerability are listed in Table 4 below.

It will be difficult to determine irrefutably if what we know as the stress cascade was in fact an adaptive process in the ancestral past. The hypotheses presented here are largely exploratory, and rely on convergent, comparative evidence. This is partly due to the paucity of related research. Furthermore, the present article has made some unsupported assumptions about stress-ecology and the nature of advanced cognition in the wild. However, this type of exploratory analysis is generally thought to be progressive as it is thought that analyzing disease states from an evolutionary perspective may ultimately do much to inform and influence medical theory, clinical research and ultimately even intervention strategies.

One way to test or falsify the present hypotheses would be to expose animals to artificial but ecologically valid environments, and assess their behavior. Rats reared in a stress free, enriched, and nurtured environment could be analyzed relative to rats that have been stressed pre and postnatally. Both groups could be introduced into an environment that is high in predation, social defeat, or low in resources. The ability of each group to negotiate the stress-filled environment, avoid threats and attain reproductive success could be quantified and compared and the specific hypotheses listed in Table 4 could be tested. A different way to test these hypotheses would be to look for allelic or phenotypic variants in low stress populations. For example, the glucocorticoid receptor in mammals found on islands without natural predators could be expected to exhibit lower binding affinity or present in the hippocampus in lower density because of their inhibitory effects on LTP. Mineralocorticoid receptors, which favor LTP, in such animals might be expected to exhibit the opposite. Furthermore, comparative molecular techniques may be able to resolve polymorphic alleles that show evidence of a selective sweep, balanced polymorphism or other distinctive signatures of positive selection. Detailed knowledge of this type of natural variation could help inspire effective pharmacological or gene therapy treatments for humans.

The evolutionary and comparative perspectives delineated here could potentially provide structure for empirical investigations in behavioral ecology or psychiatric research. Molecular phylogenetic analyses should be able to determine if the analogues of the stress cascade in other mammals are actually homologous to those in humans, and trace the evolution of the relevant genes. Better knowledge of the shared molecular pathways and neural circuits involved will provide a framework for therapies aimed at ameliorating neuropsychiatric symptoms as well as the more subtle, everyday effects of stress on human cognition.

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