Can anxiety damage the brain?

Linda Mah*a,b, Claudia Szabuniewiczb, and Alexandra J. Fiocco*c

Purpose of review
Stress exacerbates mental illnesses such as depression but also appears to increase risk of dementia, suggesting a common mechanism for development of stress-induced affective and cognitive impairment. The purpose of this review is to address the question of whether anxiety ‘damages’ the brain, and to identify potential mechanisms for the link between stress and neuropsychiatric illness.

Recent findings
Anxiety disorders are associated with alterations in fear neurocircuitry such that ‘bottom-up’ processes in the amygdala which respond to threat are exaggerated, and regulation of these processes by the prefrontal cortex (PFC) and hippocampus is impaired. Chronic stress exposure similarly alters fear neurocircuitry by enhancing amygdalar functioning while causing structural degeneration in the PFC and hippocampus thereby inhibiting PFC/hippocampus control over the stress response. Pharmacological (e.g., antidepressant medications) and nonpharmacological interventions (cognitive-behavioral therapy, exercise) may reverse stress-induced damage in the brain.

Summary
Pathological anxiety and chronic stress lead to structural degeneration and impaired functioning of the hippocampus and the PFC, which may account for the increased risk of developing neuropsychiatric disorders, including depression and dementia. Longitudinal studies are needed to determine whether reversal of stress-induced brain changes by interventions such as cognitive-behavioral therapy can reduce risk of neuropsychiatric illness.

Keywords
anxiety, cognition, emotion regulation, hippocampal neurogenesis, stress

INTRODUCTION
Anxiety is a feeling of unease, nervousness, or worry about an event with an uncertain outcome [1]. These subjective symptoms are often accompanied by physiological signs of arousal, such as sweating, trembling, dizziness, or a rapid heartbeat. Anxiety is a normal part of life when it is occasional and temporary, but can become pathological or a disorder when it is frequent or chronic and begins to interfere with daily activities such as work, school, and relationships. The terms anxiety, fear, and stress are often used interchangeably, with the main differences arising in the ‘nature of the event’ that elicits the emotional response and arguably, the extent to which the response is appropriate or ‘normal’. Because anxiety is a feeling associated with an imminent event or a hypothetical situation that may or may not happen [2], it is often conceptualized as being a negative or maladaptive state. In contrast, fear is typically defined as an emotional reaction when confronted with immediate or perceived threat, and is considered to be vital to survival. But fear can also be pathological, as in the phobic disorders. Stress is typically conceptualized as an adaptive response to a specific challenge or demand, and its definitions emphasize physiological, in addition to emotional changes. Chronic stress, however, is a pathological state that is caused by prolonged activation of the normal acute physiological stress response, which can wreak havoc on immune, metabolic, and cardiovascular systems. Thus anxiety, fear, and stress are not distinct but rather are inter-related, by virtue of common neuroendocrine and arousal mechanisms and an extensively overlapping neurocircuitry [3*]. When

*aDepartment of Geriatric Psychiatry, University of Toronto, bRotman Research Institute, Baycrest Centre for Geriatric Care and cDepartment of Psychology, Institute for Stress and Wellbeing Research, Ryerson University, Toronto, Ontario, Canada

Correspondence to Linda Mah, MD, MHS, Rotman Research Institute, Baycrest Health Sciences, 3960 Bathurst Street, BHC 738, Toronto, ON, M6A 2E1, Canada. Tel: +1 416 785 2500 x3365; e-mail: lmah@research.baycrest.org

Curr Opin Psychiatry 2016, 29:56–63
DOI:10.1097/YCO.0000000000000223
functioning optimally, these systems serve to direct attentional resources toward salient information in the environment and mobilize appropriate behaviors in response. Thus, this review addresses the question of whether anxiety ‘damages’ the brain and identifies potential mechanisms for this putative causal relationship by integrating findings from animal models of stress and fear conditioning and from neuroimaging studies of stress and anxiety in healthy individuals and in clinical populations. We begin by reviewing the neurocircuitry of fear and anxiety and provide an overview of how this neurocircuitry is altered in clinical anxiety disorders. We then review the neurocircuitry of the stress response, discuss the impact of chronic stress on the brain, and conclude by reviewing some recent findings on the effect of antianxiety interventions on the brain.

**NEUROCIRCUITRY OF FEAR AND ANXIETY**

Detection of threat or other salient information in the environment and generation of autonomic arousal and emotions such as fear and anxiety in response to threat are mediated by a ‘bottom-up’ or ventral neural system. This system includes the amygdala, insula, ventral striatum, hypothalamus, periaqueductal grey, and ventral regions of the anterior cingulate cortex (ACC) and of the prefrontal cortex (PFC), specifically ventromedial PFC (vmPFC) and orbitofrontal cortex [4]. The amygdala plays a central role in this circuit. The amygdala selectively attends to threat and is essential for expression of fear. It also plays an essential role in fear conditioning by learning cues that predict adverse events [5]. This ventral network has been delineated based on animal models of fear conditioning and extinction [5,6], lesion studies [7,8,9], and human neuroimaging studies of fear and anxiety (Fig. 1) [10,11].

‘Top-down’ cognitive processes, or a dorsal neural system, regulate these emotional responses through cognitive appraisal of the potential threat and inhibition of autonomic and emotional processes when they are no longer appropriate for the situation [12,13]. Both the PFC and the hippocampus play important roles in downregulation of bottom-up processing of threat. Regulation of emotional responses such as fear and anxiety may be achieved through voluntary or involuntary subprocesses. Voluntary or conscious subprocesses include extinction of previously conditioned fear responses, inhibition of autonomic responses and physiological arousal, automatic redirection of attention, and automatic cognitive appraisal and reappraisal. These voluntary processes are supported by dorsal and lateral regions of the PFC and ACC [dorsolateral PFC (dlPFC), ventrolateral PFC (vLPFC), dorsal ACC, dorsomedial PFC (dmPFC)] [14–16]. Involuntary, automatic, or ‘unconscious’ processes include extinction of previously conditioned fear responses, inhibition of autonomic responses and physiological arousal, automatic redirection of attention, and automatic cognitive appraisal and reappraisal. The processes of extinction and inhibition of autonomic responses are mediated primarily through interactions between the amygdala and vmPFC [17,18]. Functional neuroimaging studies in healthy individuals also demonstrate that the ability to decrease negative affect is subserved by amygdala-vmPFC coupling [19]. In contrast, automatic redirection of attention away...
from threat appears to depend on activation of the rostral ACC [20].

Although the hippocampus plays an important role in memory formation, it also serves to regulate emotions through contextual extinction during fear conditioning. In contrast to the amygdala which processes cues predicting a threatening or aversive stimulus during fear conditioning, the dorsal hippocampus relays contextual information about the specific threat cue through interactions with the amygdala and the vmPFC [21,22]. The dorsal hippocampus encodes contextual information or cues relevant to the threat which is then retrieved when subsequently presented with the stimulus [23]. This allows the organism to discriminate threat from safety cues and appraise the relative threat level of the stimulus [24*]. In animal models of fear conditioning, for example, when rats are presented with a tone predicting a shock, they learn to fear the tone cue as well as the place (context) where the tone-shock pairings occurred. This ability to discriminate between features that signal threat versus those that indicate safety may contribute to automatic cognitive appraisal and reappraisal as a means to regulate emotions. In humans, there appear to be dissociable contextual effects of the hippocampus on medial prefrontal cortex (mPFC) pathways with the dmPFC mediating the effect of hippocampus on amygdala activity during fear renewal (reinstatement of conditioned fear following extinction) and the vmPFC partially mediating the effect of hippocampus on the amygdala during extinction recall [25**].

In summary, a simplification of fear and anxiety neurocircuitry is that the amygdala (bottom-up/ventral neural system) functions to detect threat and generate emotions such as fear and anxiety, whereas the mPFC and hippocampus (top-down/dorsal ventral system) function to downregulate the amygdala. Emotion regulation is achieved when activity of the amygdala is balanced with the activity of the mPFC and hippocampus.

FUNCTIONAL NEUROANATOMY OF ANXIETY DISORDERS

The hallmark of anxiety disorders is impaired ability to regulate emotional responses to perceived threat. This may occur because of a reduction in threshold for activation of the amygdala and other limbic/subcortical regions in the ventral neural system, exaggerated activity within these regions, or failure of top-down processes to downregulate the ventral neural system. In other words, the ventral neural system (amygdala) responding to threat is hyperactive, whereas the dorsal neural system (PFC and hippocampus) is hypoactive. A wealth of evidence indicates that anxiety disorders are associated with increased sensitivity to threat or negative information in the external environment, such that attention is selective for threat, and exposure to threat is associated with enhanced amygdala activity. This has been demonstrated in panic disorder [26,27], social anxiety disorder (SAD) [28,29], simple phobias [30–32], generalized anxiety disorder (GAD) [33–35], and posttraumatic stress disorder (PTSD) [36–38]. There is also evidence of impaired extinction learning [39], reduction of mPFC activity [28,29,34,40–42], and decoupling of the amygdala and mPFC in these disorders [43,44*,45*], suggesting decreased PFC control over the amygdala and other regions in the ventral neural system. Anxiety disorders are also associated with the tendency to overgeneralize or generalize fear across stimuli, events or contexts because of impaired ability to discriminate between threats versus safety cues, that is, impaired discriminative conditioning. Deficits in discriminative conditioning have been demonstrated in GAD [46*], panic disorder [47], PTSD [39,48*] and social phobia [49]. In PTSD, impaired discriminative conditioning is associated with reduced hippocampus volume [50,51]. Reduced contextual control of extinction by the hippocampus, leading to reinstatement of conditioned fear that was previously extinguished, or ‘fear renewal’ is suggested as a mechanism for development of anxiety disorders [52].

NEUROCIRCUITRY OF STRESS RESPONSE

Exposure to acute stress results in catecholamine release peripherally through the sympathetic-adreno-medullary system and an increase in the stress hormone cortisol through the central hypothalamic-pituitary-adrenal (HPA) system [53]. The hypothalamus stimulates the adrenal medulla to release the catecholamines epinephrine and norepinephrine into the blood stream, which leads to autonomic changes, such as increased heart rate, blood pressure, respiratory rate, and skin conductance. These changes constitute a ‘fight-or-flight response’ that facilitates and directs attention and arousal to the immediate threat while inhibiting functions that are nonadaptive in the current situation, such as digestion and sexual behavior. Closely following sympathetic-adreno-medullary activation is activation of the HPA axis, which begins with the secretion of corticotropin-releasing hormone from the hypothalamus. Corticotropin-releasing hormone activates release of adrenocorticotropic hormone from the pituitary into the blood portal, which then stimulates the adrenal cortex to secrete
glucocorticoids, or cortisol in humans. Circulating glucocorticoids facilitates a cascade of physiological changes, including increased metabolism, cardiovascular output, and glucogenesis, all of which facilitate the fight-or-flight response. Glucocorticoids further play a key role in regulating the stress response by providing inhibitory feedback at various levels of the HPA axis, which terminates the stress response once the stressor has subsided. All aforementioned events are orchestrated to allow the individual to adapt to the demands of their changing environment, enabling a homeostatic balance of physiological parameters within a dynamic environment, a process that has been termed allostasis [54].

Acute stress also increases release of the catecholamine dopamine in the PFC, a process that is controlled by the amygdala [55–57]. Dopamine release occurs even with mild levels of stress in the primate dlPFC [58]. Acute stress also increases noradrenergic levels in the PFC [59], through amygdalar activation of corticotrophin-release factor receptors which, in turn, activate noradrenergic neurons on the locus coeruleus [60]. In experimental studies with animals using dopamine or NE agonists to elicit, and antagonists to block stress-induced PFC function, increased catecholamine release in the PFC results in impaired function, particularly in the domain of working memory [61–64]. Catecholamine levels are further increased by glucocorticoid through blockage of transporters on glia which normally remove extracellular catecholamines [65] and through its actions on the hypothalamus and on suprahypothalamic regions that contain glucocorticoid receptors, including the PFC, amygdala, and hippocampus [66]. Glucocorticoid-sensitive hippocampal neurons provide negative feedback to the HPA axis to terminate the stress response when it is no longer adaptive [67]. Regulation of HPA activity is also achieved through the mPFC which plays a top-down role by modulating hippocampal and amygdala activity via glucocorticoid negative feedback mechanisms [68].

Thus, the hippocampus and mPFC regions of the dorsal neural system in fear neurocircuity serve to regulate emotions through functional connectivity with the amygdala, and these regions additionally regulate the stress response through glucocorticoid-mediated feedback mechanisms.

**IMPACT OF PATHOLOGICAL ANXIETY AND CHRONIC STRESS EXPOSURE ON THE BRAIN**

Although adaptive in the short run, frequent, or chronic activation of stress-sensitive systems can lead to an eventual ‘wear and tear’ of the neuroendocrine system, which over time infringes upon the function of other interconnected physiological systems, including immune, metabolic, and cardiovascular systems. This breakdown in the physiological milieu of the organism is referred to as allostatic load and is associated with increased risk of diseases, including cardiovascular disease, diabetes, metabolic syndrome, and neuropsychiatric disorders [69–71]. It has long been appreciated that the experience of stress exacerbates mental illness, contributing to risk of depression [72], and triggering the onset of disorders such as schizophrenia [73] or bipolar disorder [74] and development of PTSD [75]. It was recently reported that women who experienced significant psychosocial stress in middle age were at increased risk for developing Alzheimer’s disease 20 years later [76,77]. Anxiety symptoms also increase the risk of Alzheimer’s disease in cognitively normal elderly and in amnestic mild cognitive impairment (aMCI), a prodrome of Alzheimer’s disease, by as much as 2.5-fold [78–81] (but see [82–88]). Further, anxiety in MCI is associated with Alzheimer’s disease biomarkers including abnormal concentrations of Ab42 and t-tau in cerebrospinal fluid [89]. Stress-level glucocorticoid administration in animal models of Alzheimer’s disease results in increased amyloid formation and tau accumulation [90]. Although previous studies which included depression as a covariate have found an inverse or no association between anxiety and Alzheimer’s disease [82–84,88], we recently reported using data from the Alzheimer’s disease neuroimaging initiative, that anxiety severity in aMCI, as measured by the Neuropsychiatric Inventory, increased the rate of conversion to Alzheimer’s disease, even after controlling for depression and cognitive decline [91]. The hazards ratio for anxiety was 1.33, indicating that risk of Alzheimer’s disease increased by 33, 78, and 135% for mild, moderate, and severe anxiety, respectively. Anxiety severity in aMCI was also associated with increased rate of atrophy within the entorhinal cortex of the medial temporal lobe, an early neuroimaging biomarker of Alzheimer’s disease. To identify potential mechanisms to account for the associations between stress and development of affective and cognitive disorders, we turn to the evidence on the impact of chronic stress on the brain structure and function.

**HIPPOCAMPAL DAMAGE**

Enhanced receptor binding following chronic HPA activation and subsequent increases in glucocorticoid secretion has been found to inflict detrimental effects on the hippocampus in both animals and...
Chronic stress and excessive glucocorticoid exposure may compromise the integrity of the hippocampus. This is evidenced by hippocampal atrophy, and decreased hippocampus neurogenesis [95]. Damage or atrophy of the hippocampus is associated with a feed-forward impairment on the organism’s ability to inhibit the HPA axis once the stressor has subsided, leading to prolonged HPA activation and further neuronal damage [96]. Notably, chronic stress is found to cause decreases in brain-derived neurotrophic factor, a brain chemical necessary for neurogenesis, which in turn disrupts serotonin activity [97].

It has been suggested that deficits in hippocampus neurogenesis lead to affective and anxiety disorders [98,99] and reinstatement of hippocampus neurogenesis may be one mechanism of antidepressant action [100–102]. Decreased neurogenesis in the hippocampus of rodents results in cognitive deterioration, depressive-like symptoms, and anxiety-like behaviors [103–105]. A similar phenomenon is observed in human studies, which have reported hippocampal atrophy and HPA dysregulation in psychiatric disorders, including major depressive disorder and posttraumatic stress disorder [106]. Chronic fluoxetine exposure led to increased expression of myelination-related genes in the hippocampus, which correlated negatively with anxiety-like behavior in rats exposed to fluoxetine as adults or neonates [107]. In transgenic mice, arrest of hippocampus neurogenesis impaired associative learning, whereas also sensitizing mice to the generalized fear and anxiety caused by fear conditioning. Thus, adult hippocampus neurogenesis may enhance the ability to learn predictive contingencies involving aversive events, whereas attenuating the anxiety experienced during fear conditioning [108*]. This observation may account for the co-occurrence of cognitive deficits in mood and anxiety disorders or the depression and anxiety often observed in dementia and individuals at risk for dementia.

**PREFRONTAL CORTEX DAMAGE**

Chronic stress exposure in the rodent also causes structural and functional degeneration of the PFC [109]. Specifically, loss of dendrites and spines in the pyramidal cells of the PFC occurs after sustained stress exposure in the rat [110–112] which correlated with impaired working memory [113]. Other animal work suggests that chronic stress exposure is circuit specific. In contrast to ‘loss’ of dendrites in the PFC, chronic stress ‘increases’ dendritic growth in the amygdala, which further accentuates the imbalance in amygdalar versus PFC function (i.e., enhanced bottom-up versus impaired top-down processes) [114]. Further, PFC neurons are differentially affected by chronic stress. Although PFC neurons that form cortico-cortical connections show dendritic loss, orbital PFC neurons and the subset of PFC neurons that activate the amygdala do not atrophy during chronic stress [110,112]. In humans, decreased PFC gray matter volume correlates with exposure to adverse events [115]. Chronic stress is also associated with reduced functional connectivity of the PFC [116] and weakened PFC regulation of the amygdala [117]. Depressed adults followed over 3 years who had remitted had less volume decline than nonremitted patients in the hippocampus, anterior cingulate, and the dorsomedial and dorsolateral regions of the PFC [118]. Although the literature suggests that stress-induced PFC degeneration may contribute to development of psychiatric disorders, including depression and PTSD, whether this mechanism also accounts for increase in dementia risk is unknown.

**EFFECT OF ANTIANXIETY TREATMENT ON FEAR AND ANXIETY NEUROCIRCUITRY**

It is important to note that stress-induced damage to the hippocampus and PFC is not completely irreversible. In animals, desipramine, a selective noradrenaline blocker, can restore the cognitive deficits induced by chronic unpredictable stress, possibly by activating alpha 1-adrenergic receptors in the mPFC [119]. The mood stabilizer lithium also increases hippocampal neurogenesis [120], particularly under stress conditions [121]. Chronic lithium treatment in bipolar patients increases HC volume [122] and may stabilize cognitive decline in aMCI [123]. Antidepressant treatment and physical activity have both been found to increase hippocampal neurogenesis [124,125]. Consolidation of amygdalar-PFC functional connectivity may be normalized following antidepressant treatment for depression [126]. Prazosin, an alpha-adrenergic antagonist, used to treat PTSD reduces flashbacks and improves concentration suggesting PFC function may be improved (reviewed in [127*]). A course of treatment with the Selective serotonin reuptake inhibitor citalopram for older adults with GAD lead to increased functional connectivity between dlPFC and vlPFC and parietal areas involved in attention [128]. Cognitive-behavioral therapies for anxiety disorders reduce amygdalar reactivity [129,130,131*], increase activity in PFC regions supporting cognitive appraisal including dlPFC and dmPFC [130,132] and enhance inverse functional connectivity between the amygdala and dmPFC [132].
Mindfulness training in GAD alters amygdala-PFC connectivity [133] and even simple cognitive tutoring for math anxiety in children reduces amygdala reactivity in addition to decreasing anxiety [134].

CONCLUSION

Chronic stress increases risk of major psychiatric disorders such as depression, and more recently has been linked with onset of dementia. Potential mechanisms for these associations are suggested by the experimental observations that stress enhances amygdalar activity but leads to structural degeneration of the PFC and hippocampus, which in turn leads to deficits in emotion regulation and cognitive impairment. It is thus evident that pathological anxiety/stress can damage the brain – but this damage may be reversible using both pharmacological and nonpharmacological interventions. Whether anxiety interventions can reduce risk of developing neuropyschiatric illness needs to be established with longitudinal studies.

Acknowledgements

None.

Financial support and sponsorship

L.M. holds grants from the Alzheimer’s Society of Canada and the Brain Canada MIRI grant. A.F. is supported by the Mind and Life Institute.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest

9. Motkun JC, Philippi CL, Wolf RC, et al. Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. Biol Psychiatry 2015; 77:276–284. The study is the first definitive test and evidence for the critical role of the vmPFC in regulating the activity of the amygdala in humans, offering novel support for the inhibitory influence of the vmPFC, and corroborating rodent lesion and electrophysiological studies modeling affective dysfunction in mental illnesses.
14. Beauregard M, Levesque J, Bourquin P. Neural correlates of conscious self-consciousness in humans, and reveals the dissociable contextual influences of the hippocampus on the vmPFC, and corroborating rodent lesion and electrophysiological studies modeling affective dysfunction in mental illnesses.
22. Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 2010; 65:7–19.
Geriatric psychiatry


The first study to use dynamic causal modeling to reveal an important neurophysiologic dysfunction in the emotion regulation circuitry of SAD patients, suggesting an upregulation of amygdalar activation and corroborating previous reports of reduced connectivity between the orbitofrontal cortex and amygdala in SAD patients.


An important study investigating multiple neural metrics which suggests that multiple parallel aberrations in distributed brain areas together have a significant impact on vmPFC functioning, which has a critical role in fear generalization.


An article that demonstrates overgeneralization of conditioned fear among GAD patients, and provides clues into the symptomology of the disorder.


The study reveals a general diminished capacity to use contextual information to modulate fear extinction across PTSD patients, suggesting that the deficit in fear extinction recall in this disorder may be a result of more general contextual modulation deficits.


Can anxiety damage the brain? Mah et al.


91. Mah L, Blons MA, Steffens DC. Anxiety symptoms in amnestic mild cognitive impairment are associated with medial temporal atrophy and predict conversion to Alzheimer disease. Am J Geriatr Psychiatry 2015; 23:466–478. The study demonstrated that anxiety symptoms in amnestic mild cognitive impairment increased rate of conversion to Alzheimer’s disease, while controlling for depression and cognitive decline. We also demonstrated that anxiety was associated with increased rate of entorhinal cortex atrophy.


106. Sapolisky RM. Glucocorticoids and hippocampal atrophy in neurodegenerative disorders. Arch Gen Psychiatry 2000; 57:925–935.


109. An excellent overview of neurogenesis and the important role of hippocampal-dependent learning and emotional regulation in relation to aversive experience.


