Published in final edited form as:

Biochem Pharmacol. 2015 October 15; 97(4): 498–511. doi:10.1016/j.bcp.2015.07.029.

Nicotine Modulation of Fear Memories and Anxiety: Implications for Learning and Anxiety Disorders

Munir Gunes Kutlu, Ph.D. and Thomas J. Gould, Ph.D.

Temple University, Weiss Hall, Philadelphia, PA 19122, USA

Abstract

Anxiety disorders are a group of crippling mental diseases affecting millions of Americans with a 30% lifetime prevalence and costs associated with healthcare of \$42.3 billion. While anxiety disorders show high levels of co-morbidity with smoking (45.3% vs. 22.5% in healthy individuals), anxiety disorders are also more common among the smoking population (22% vs. 11.1% in the non-smoking population). Moreover, there is clear evidence that smoking modulates symptom severity in patients with anxiety disorders. In order to better understand this relationship, several animal paradigms are used to model several key symptoms of anxiety disorders; these include fear conditioning and measures of anxiety. Studies clearly demonstrate that nicotine mediates acquisition and extinction of fear as well as anxiety through the modulation of specific subtypes of nicotinic acetylcholine receptors (nAChRs) in brain regions involved in emotion processing such as the hippocampus. However, the direction of nicotine's effects on these behaviors is determined by several factors that include the length of administration, hippocampus-dependency of the fear learning task, and source of anxiety (novelty-driven vs. social anxiety). Overall, the studies reviewed here suggest that nicotine alters behaviors related to fear and anxiety and that nicotine contributes to the development, maintenance, and reoccurrence of anxiety disorders.

Keywords

Nicotine; Anxiety Disorders; Fear Conditioning; Anxiety; Extinction

1) Introduction

Anxiety disorders, such as panic disorders, phobias, generalized anxiety disorder, and post-traumatic stress disorder (PTSD), are a group of crippling mental disorders affecting 40 million Americans with an 18% 12-month prevalence and a 30% lifetime prevalence [1, 2]. These statistics suggest that anxiety disorders are one of the most common mental disorders [3]. This group of disorders is associated with an estimated \$42.3 billion in psychiatric and non-psychiatric treatment costs, indirect workplace costs, mortality-related costs, and

Correspondence: Thomas J. Gould, Ph.D., 1701 N. 13th St, Weiss Hall, Philadelphia, PA 19122, tgould@temple.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

prescription costs; this comprises approximately one third of the total mental health budget of the U.S. [4]. Moreover, anxiety disorders are associated with impaired workplace performance [4] and increased risk of morbidity and mortality related to cardiovascular problems [5–7]. Therefore, in addition to the devastating personal and social costs, anxiety disorders are responsible for a significant burden to the U.S. economy and taxpayers.

Anxiety disorders can develop following a single traumatic event or a highly stressful period [8]. Although different disorders under the anxiety disorder umbrella are defined by different symptoms, they are often characterized by an exaggerated fear response to cues and contexts that are not dangerous [9]. Common symptoms that most anxiety disorders share include re-experiencing (intrusive memories and nightmares), avoidance (avoidance of trauma-associated stimuli and memories), emotional numbing (loss of interest and interpersonal detachment), and hyperarousal (irritability, difficulty concentrating, hypervigilance, insomnia; [10]). For example, patients with PTSD usually re-experience the traumatic event through intrusive fearful memories, nightmares, and flashbacks, which evoke physiological distress, arousal and fear responses. Similarly, individuals with panic disorder usually experience episodes of intense fear even in situations where real danger is absent. Finally, patients with specific phobias experience similar exaggerated fear-related physiological responses to specific objects or situations [11].

Given the central role of fear response in anxiety disorders, many etiological accounts of anxiety disorders proposed that malfunctioning Pavlovian conditioning mechanisms are responsible for the development of anxiety disorders. One of the first accounts was offered by Watson and Rayner in 1920 as an explanation for phobias [12]. In their seminal “Little Albert” study, a baby was presented a white rat, which initially did not elicit a fear response, together with a fear-eliciting loud noise. These white rat-loud noise pairings resulted in a conditioned fear response to the white rat that eventually generalized to other furry objects. This early attempt to explain phobias suggested that the fear elicited by a loud noise was associated with another neutral stimulus present at the time (e.g., a white rat) and therefore, the fear of the rat developed based on this Pavlovian association.

Although anxiety is a different behavioral output than fear, based on the same principles, Pavlovian associations may result in “learned anxiety” to a conditioned cue or context. This “learned anxiety” may be generalized to other similar objects or settings causing anxiety [13]. The Pavlovian conditioning explanation has also been adopted for other anxiety disorders (see [14] for a review). For instance, later theories of PTSD argue that uncontrollable stress during severe trauma leads to re-experiencing symptoms triggered by the reminders of the traumatic event (e.g., [8, 15, 16]). According to these accounts, the elicited unconditioned fear response becomes associated with a variety of neutral cues and contexts during trauma and after the traumatic event these previously neutral stimuli trigger negative emotional responses, such as fear and anxiety, by reminding the person of the trauma. In support of these theories, evidence from animal research suggests that animals exposed to uncontrollable and unpredictable electric shock or a socially superior conspecific develop PTSD-like symptoms such as heightened fear and anxiety responses to stimuli associated with these experiences (e.g., [17–19]).

One of the most commonly used animal models of learned fear is fear conditioning, a Pavlovian conditioning paradigm involving an aversive unconditioned stimulus (US, e.g., mild foot shock) and a neutral cue or context akin to the design used by Watson and Rayner [12]. In fear conditioning, the neutral stimulus is paired with an aversive US that elicits a fear response. After the pairings, the previously neutral stimulus will elicit a fear response. Therefore, fear conditioning models the encoding and stimulus-based retrieval of the traumatic memories [14]. Similarly, there are several animal models of innate anxiety-related symptoms. The elevated plus maze (EPM), developed by Handley and Mithani [20], is the most utilized animal model of anxiety-related symptoms associated with anxiety disorders. The EPM, and variations such as the elevated zero maze [21] and elevated T-maze [22], take advantage of the innate exploratory behavior of rodents and their tendency to avoid bright open areas. Animals are placed in an apparatus that has open and closed arms and are allowed to explore the apparatus freely. The amount of time spent in the closed arms is an indicator of anxiety-like behavior and the time spent exploring the open arms indicates reduced anxiety. Evidence showing that classical anxiolytic drugs, such as benzodiazepines, reduce the time spent in the closed arms in rodents [23] suggest that these tasks are assessing anxiety. Other rodent models of anxiety also use innate behaviors indicative of anxiety such as marble burying (increased duration of burying an object; e.g., glass marbles) and social anxiety (social interaction test; decreased time spent by pairs of male rats in social interaction; [24]). However, it is important to note that the anxiety paradigms described above measure the innate anxiety response to a novel context or a conspecific as opposed to “learned anxiety” [13]. Nevertheless, animal models of anxiety are commonly utilized to understand the mechanisms responsible for the anxiety response independent from the learning component and therefore, provide invaluable information about anxiety-related symptoms in psychological disorders.

While the animal paradigms described above model the development and maintenance of anxiety disorder symptoms, fear extinction, a safety learning paradigm, is a model for exposure-based therapies of anxiety disorders. Mechanisms of extinction of conditioned responses were first proposed by Ivan Pavlov in his seminal work in 1920's [25]. Following Pavlov, both animal and human studies have shown that repeated presentations of fear eliciting cues and contexts without the fear eliciting stimuli lead to extinction of negative emotional response in fear conditioning paradigms [26, 27]. Importantly, there are several studies suggesting that fear extinction is impaired in individuals with anxiety disorders [28–31]. Therefore, to promote extinction learning, the patient in exposure therapy is repeatedly given actual (in vivo exposure) or imaginary exposure to the trauma-associated cues or contexts followed by relaxation in order to reduce the negative emotional response elicited by these stimuli [32–34]. Exposure therapies have been successfully used to treat anxiety disorders since the work of Wolpe and his colleagues in 1960's ([35, 36]; see [37] for a historical perspective) and they continue to be the most effective treatment method for a variety of anxiety disorders. The critical premise of the exposure therapies is that trauma-related memories should be reactivated during the process for successful extinction. In line with the importance of memory reactivation in exposure therapies, evidence from animal studies suggests that fear memories become labile and can be modified during memory retrieval, a process known as reconsolidation [38], which leads to a reduction of fear

response in the absence of aversive stimulus. While extinction is different from the reconsolidation process [39], modification of memories during reconsolidation can also contribute to the success of exposure therapy. Although exposure therapies are relatively successful for treatment of anxiety disorder, relapse of the symptoms after a successful exposure therapy is common (19%–62%; [40, 41]). The relapse of symptoms may occur because extinction is an active inhibitory learning process that does not erase original fear memories and therefore, fear response resurfaces in the contexts other than the extinction context (renewal) or simply after a period of time (spontaneous recovery; see [42] for a review).

Overall, there are multiple parallels between anxiety disorder symptoms and fear learning, suggesting that some symptoms of anxiety disorders arise from malfunctioning learning and memory processes. The mechanisms responsible for formation, consolidation, and retrieval of fear memories as well as anxiety-like behavior have been shown to be affected by many factors ranging from neurobiological mechanisms, such as protein synthesis (e.g., [38]), to outside factors such as stress (e.g., [17]). Numerous studies suggest that fear and anxiety-related learning and consequently, anxiety disorders, are especially vulnerable to the effects of drugs of abuse such as nicotine (e.g., [43]). In line with this idea, nicotine dependence has been shown to be critically involved in the symptom severity of anxiety disorders [44]. Therefore, this review focuses on the relationship between smoking and anxiety disorders based on the evidence from human studies as well as the studies reporting the effects of nicotine exposure on fear and anxiety-related behavior in animal models of anxiety disorders.

2) Co-morbidity of Nicotine and Anxiety Disorders

Patients with anxiety disorders are susceptible to unhealthy behaviors such as drug abuse [45, 46], which results in increased health costs [4], decreased quality of life [47], and poor health behaviors [48]. Patients with anxiety disorder show a particularly high rate of comorbidity with nicotine dependence [3, 49–52]. Specifically, the rates of nicotine dependence have been shown to be significantly higher in the population with anxiety disorders (45.3%) in comparison to healthy individuals (22.5%; [53, 54]), in addition anxiety disorders are more prevalent among the individuals who smoke (22%) than in the non-smoking population (11.1%, [55, 56]). In line with the high co-morbidity observed between smoking and anxiety disorders, prior smoking history has been found to be a predictor of a increased vulnerability to developing PTSD [52] and panic disorder [57] following a traumatic experience. Moreover, both smoking initiation and daily smoking rates have been shown to increase after a trauma [3, 49] and in patients with social phobia [58]. Patients with PTSD show lower rates of successful quitting [53, 59] and higher rates of relapse to smoking behavior [60] than the non-clinical population, which might be related to the more severe withdrawal symptoms they experience [44]. These results suggest a strong bi-directional relationship between anxiety disorders and nicotine dependence.

In line with the link between anxiety disorders and smoking, numerous studies have identified a significant association between smoking and anxiety disorder symptoms such as re-experiencing, avoidance, emotional numbing, and hyperarousal [48, 50, 61–63]. These

results suggest that smoking behavior may be a modulator of the anxiety disorder symptoms. For example, several studies showed that heavy smoking behavior in PTSD patients was positively correlated with PTSD symptom severity [4, 48, 63, 64]. Importantly, while smoking is positively correlated with PTSD symptoms, there is also evidence showing that PTSD patients who smoke experience more severe nicotine withdrawal symptoms when they encounter trauma-related stimuli than non-PTSD smokers [65]. In addition, PTSD patients who smoke experience craving symptoms when presented with anxiety-triggering stimuli [66]. These studies suggest that although smoking increases the chances of developing PTSD and PTSD patients that smoke experience increased intensity of PTSD symptoms compared to non-smoking PTSD patients, smoking may serve as a means of alleviating some PTSD symptoms. The “self-medication” hypothesis of drug abuse is a well-supported theory that can explain high levels of smoking-anxiety disorder co-morbidity [67–72]. According to the self-medication hypothesis, a patient with an anxiety disorder acquires a substance abuse disorder to alleviate the anxiety symptoms. In support, specific PTSD symptoms are also linked to self-medication via smoking. For example, emotional numbing has been shown to be significantly associated with smoking, which is in line with the data showing that positive mood induction is more successful following nicotine administration in smokers who experience anhedonia, lack of pleasure towards natural reinforcers [73]. Similarly, hyperarousal symptom also strongly correlated with nicotine dependence, which may be because nicotine can reduce anxiety-like symptoms in humans [74–78] and nicotine withdrawal can aggregate PTSD symptoms [44]. These results suggest that nicotine mediates specific symptoms associated with anxiety disorders as nicotine provides short-term reduction of these symptoms but leads to increased baseline severity of anxiety disorder symptoms.

Nevertheless, the extent of nicotine’s effects on anxiety disorder symptoms varies between specific anxiety disorder subtypes. For example, while panic disorder has the highest prevalence of smoking among anxiety disorders and smoking is shown to increase the risk of initiation and maintenance of panic attacks [49, 79], OCD patients show the lowest rates of smoking and prospective studies could not find any predictive power of smoking on the development of OCD (e.g., [80]). Thus, different neural pathways may be involved in the different subtypes of anxiety disorders and nicotine’s effect on these pathways may vary. The next section reviews neural underpinnings of fear, anxiety, and other symptoms specific to anxiety disorder subtypes.

3) Neurobiology of anxiety disorders

The neurobiological mechanisms underlying the symptomatology of anxiety disorders are complex as they involve several distinct systems including pathways responsible for emotional processing as well as different neuroendocrine and neurotransmitter signaling pathways (see [81] for an extended review). A central hypothesis explaining the general problems with emotional processing observed in patients with anxiety disorders is that following a traumatic event or a highly stressful period, the balance between the cognitive and emotional control over behavior shifts towards emotional control [81]. The limbic cortex, which is the primary pathway responsible for emotional processing, and the prefrontal cortex (PFC), which controls higher level cognition (e.g. decision making,

executive control), are interconnected and compete for functional control of behavioral ([82–84]; see [85] for a review). On the one hand, the limbic cortical regions, including the amygdala and hippocampus, process and integrate sensory and emotional information to control internal bodily responses through the modulation of the hypothalamic–pituitary–adrenal (HPA) axis, a neuroendocrine system responsible for stress response ([86]; Figure 1). Specifically, the hippocampus assumes control over the HPA axis by forming a negative feedback loop and regulating the sensitivity of the HPA system to corticosteroids [87]. On the other hand, the ventromedial PFC is responsible for modulating visceral emotional responses [88]. For example, the medial PFC has been shown to reduce fear response to previously fear-eliciting stimulus during extinction by inhibiting activity in the amygdala [82, 84]. Similarly, while the prelimbic subregion of the medial PFC reduces its spontaneous firing rate in the presence of a fear eliciting stimulus in parallel to the increased neuronal activity in the amygdala [89], lesions of the infralimbic subregion of the medial PFC have been shown to prevent recall of fear extinction [84]. In addition, lesions to the anterior cingulate cortex (ACC) have been shown to increase fear response to a conditioned stimulus [82]. Together, these results indicate that the interplay between prefrontal regions and the limbic cortex determines the behavioral outcome of the previously learned emotional associations.

In line with the hypothesis suggesting that the balance between the limbic and prefrontal regions is disturbed in patients with anxiety disorders, there is evidence suggesting that activation patterns of several prefrontal and limbic structures are altered in patients with anxiety disorders. For example, the amygdala, a limbic region central for fear learning and regulation, is hyperactive in patients with PTSD, which results in further difficulties in successful treatment [90]. Also, amygdala activation has been shown to correlate with the severity of PTSD symptoms [91]. While there is evidence for increased activity in fear learning-related structures, Bryant et al. [90] showed that rostral ACC volume in PTSD patients predict the success of the exposure therapies. Therefore, decreased prefrontal cortical function may be associated with impaired extinction learning observed in PTSD patients [28–31, 81]. Furthermore, Morey et al. [92] showed that ventromedial PFC activation was positively correlated with symptom severity in Iraq war veterans with PTSD and that PTSD patients exhibited exaggerated ventromedial PFC activity to combat-related stimuli. The increased PFC activity may be a direct response to the hyperactive limbic cortex activity triggered by trauma-related stimuli. While imaging studies of PTSD patients usually utilize a fear-related task, anxiety-related tasks are used with generalized anxiety disorder (GAD) patients. As in PTSD, GAD patients showed increased activity in the limbic circuitry, especially in the amygdala and insula [93, 94]. Also similar to PTSD patients, patients with GAD showed increased right amygdala activity when viewing angry faces; this activity was negatively correlated with ventrolateral PFC activity [95]. Finally, changes in prefrontal-limbic activity may modulate symptoms of panic disorder. Compared to healthy individuals, patients with panic disorder showed decreased PFC and increased cingulate gyrus and amygdala activity after administration of the respiratory stimulant doxapram, which induces panic attacks [96]. These results clearly suggest that the PFC-amygdala relationship determines anxiety disorder symptoms.

As a modulator of the HPA axis and with its strong connections with both the PFC and the amygdala, the hippocampus appears to have an especially important role in modulating anxiety disorder symptoms (Figure 1). Studies suggest that in patients with PTSD, hippocampal activity is increased [97–102] and this activity is positively correlated with PTSD symptoms [103, 104]. Moreover, hippocampal volume has been found to be decreased in PTSD patients [105–117] and the size of the hippocampus was negatively correlated with symptom severity [107, 108, 114]. These results suggest that hippocampal dysfunction contributes to PTSD symptomatology. Hippocampal abnormalities have also been linked to panic disorder [118, 119]. Thus, the hippocampus may modulate prefrontal cortical-amygdala interactions and changes in the connectivity between and the function of these areas may determine the symptomatology of anxiety disorders. Therefore, it is possible that the action of nicotine on these brain regions significantly contributes to smoking-related changes in anxiety disorders.

4) Neurobiology of nicotine and nicotinic receptors

Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels with seventeen known subunit combinations expressed in central and peripheral nervous systems [120–123]. Nicotinic receptors either contain only α subunits ($\alpha 7$ – $\alpha 10$) or a combination of α ($\alpha 2$ – $\alpha 6$) and β ($\beta 2$ – $\beta 4$) subunits ([124–126]; see [127] for a review). In the central nervous system, $\alpha 7$ and $\alpha 4\beta 2^*$ nAChRs (* designates potential additional subunit) are the most commonly expressed nAChRs [128–133]. Importantly, in terms of their affinity, functional changes, and localization, $\alpha 7$ and $\alpha 4\beta 2^*$ nAChRs manifest different characteristics. For example, $\alpha 4\beta 2^*$ nAChRs show higher affinity for nicotine, desensitize relatively slowly but upregulation of these receptors is long lasting, whereas $\alpha 7$ nAChRs show lower affinity to nicotine but desensitize rapidly [134, 135]. In addition, $\alpha 7$ and $\alpha 4\beta 2^*$ nAChRs show differential cellular localization. While $\alpha 7$ nAChRs are mainly expressed in the granule and pyramidal cells of the hippocampus as well as other limbic system regions such as the amygdala and hypothalamus [136–138], $\alpha 4\beta 2^*$ nAChRs are located in the dentate gyrus and CA1 sub-regions of the hippocampus [132]. Therefore, because of their different characteristics, $\alpha 7$ and $\alpha 4\beta 2^*$ nAChRs may play different roles in the modulation of behavior.

While nAChRs gate sodium and/or calcium (Ca^{2+} , [132, 139, 140]), they can also stimulate the release of neurotransmitters including acetylcholine, serotonin, GABA, dopamine, norepinephrine, and glutamate [141–148]. The pre- and post-synaptic locations on neurons increase the functional diversity of nAChR effects. For example, while nAChRs located on glutamatergic neurons modulate excitatory circuitries, those located on GABAergic neurons mediate inhibitory processes [137, 143]. Similarly, nAChRs expressed in pre-synaptic neurons trigger neurotransmitter release [137, 143, 149–153] whereas nAChRs in post-synaptic neurons contribute to depolarization and activation of secondary messenger systems [137, 153, 154]. By activating secondary messenger systems and cell-signaling cascades, nAChRs can be critically involved in the processes underlying synaptic plasticity and formation of long-term memory ([132, 139, 140, 155–159]; see [160] for a review). For example, nAChR activation can directly induce long-term potentiation (LTP; [161–163]), a form of synaptic plasticity thought to underlie formation of long-term memories [164]. LTP

occurs through simultaneous activation of pre- and post-synaptic N-methyl-D-aspartic acid (NMDA) receptors. In support of the role of NMDA-dependent synaptic plasticity in fear learning, there are numerous studies showing that inhibition of NMDA receptors prevents formation of long-term fear memories (e.g. [165–169]; see [170] for a review). As a result of NMDA receptor activation, Ca^{2+} flows into the cell [171, 172], which triggers depolarization as well as changes in protein activation, mRNA synthesis, and protein translation [173–179]. Specifically, Ca^{2+} activates a variety of different cell-signaling cascades. One of the primary cascades activated during the LTP process is the CREB-dependent gene transcription pathway, which is initiated by the conversion of intracellular adenosine diphosphate (ADP) to cyclic adenosine monophosphate (cAMP, [180]). In turn, cAMP phosphorylates protein kinase A (PKA) can activate cAMP-response element binding protein (CREB) either directly or indirectly through activation of the mitogen activated protein kinases (MAPKs; e.g., extracellular-regulated kinase 1/2; ERK1/2). CREB activation leads to protein synthesis, which plays a crucial role in the induction of LTP and long-term memory formation [181–183].

As described above, nAChR activation can also lead to Ca^{2+} influx into the cell [184], which can modulate PKA and ERK1/2 activation [185]. Thus, nAChRs have the ability to trigger CREB-dependent gene transcription pathway and modulate synaptic plasticity (Figure 2). Several studies reported that the activation of nAChRs via nicotine and other agonists can enhance [186–188] or directly induce hippocampal LTP [161–163]. Specifically, Matsuyama and Matsumoto [162] showed that both nicotine and the $\alpha 4\beta 2^*$ nAChR agonist epibatidine induced LTP in the mouse dentate gyrus whereas $\alpha 7$ nAChR activation was required for the epibatidine-induced LTP to reach the size of the nicotine-induced LTP. Also, both acute and chronic nicotine have been shown to enhance LTP induction while acute nicotine administration in hippocampal slices chronically treated with nicotine resulted in further enhancement of LTP [189]. Withdrawal from chronic nicotine abolished the nicotine-induced reduction of LTP threshold [190]. Also, Mann & Greenfield [186] showed that nicotine application in hippocampal slices decreased the threshold for LTP induction and this effect was reversed by the $\alpha 7$ nAChR-specific antagonist α -bungarotoxin, but not by the $\alpha 4\beta 2^*$ nAChR antagonist dihydro- β -erythroidine (DH β E) or the non-specific nicotinic antagonist mecamylamine. In contrast, Fujii et al. [191] showed that inhibition of $\alpha 7$ nAChRs facilitated LTP-induction in the hippocampal slices not treated with nicotine, which suggests that $\alpha 7$ and non- $\alpha 7$ nAChRs may have opposing roles in the nicotine-induced enhancement of LTP. Specifically, while $\alpha 4\beta 2^*$ nAChR activation enhanced LTP, activation of $\alpha 7$ nAChRs downregulated LTP induction. In addition, nAChRs seem to modulate LTP process through NMDA receptors (NMDARs), as there is evidence showing that cholinergic lesions impaired LTP and nicotine rescued LTP impairment by facilitating NMDAR activity [192]. There is also evidence showing that nAChR agonists nicotine and epibatidine can reverse the GABAergic inhibition of LTP in the hippocampal CA1 sub-region [191]. Similarly, activation of $\alpha 4\beta 2^*$ nAChRs through epibatidine can also reverse amyloid β -protein induced suppression of hippocampal LTP [193]. Interestingly, nicotine may destabilize already consolidated LTP [194], which indicates differential effects of nicotine when administered before or after memory

consolidation. These results clearly show that nicotine has a modulatory effect on LTP and several nAChR subtypes may be involved in the process.

5) Involvement of nicotine and nAChRs in modulation of fear and safety learning: Evidence from animal studies

By modulating neurotransmitter release and cell signaling cascade activation, nAChRs may have direct effects on behavior such as learning and memory (see [195] for a review). There are several animal models used to investigate the effects of nicotine and other nAChR agonists/antagonists on fear-related symptoms observed in anxiety disorders. Specifically, fear conditioning has been widely utilized as a translational model to study traumatic experience, and safety learning paradigms such as fear extinction have been used to model exposure therapies [196]. Research on the neurobiology of fear conditioning has identified different types of fear memories mediated by different brain regions; i.e., hippocampus-dependent contextual and trace fear conditioning and hippocampus-independent cued fear conditioning [197–201]. Utilizing these animal paradigms, the effects of nicotine on fear conditioning have been extensively studied (see [127] for a review). These studies repeatedly showed that in mice, acute nicotine administration enhanced hippocampus-dependent contextual [43, 202–206] and trace [204, 207] fear conditioning but had no effect on hippocampus-independent fear conditioning or on general freezing behavior (e.g., [43, 205]). While these results show that nAChR activation is required for enhancement of hippocampus-dependent fear conditioning, Gould and Higgins [43] also showed that the non-specific nAChR antagonist mecamylamine had no effect on contextual fear conditioning. This indicates that nAChR activation is not critical for normal contextual fear learning. These studies suggest that acute nicotine administration, which models the initial effects of smoking, may enhance fear memories and potentially aggravate fear-related anxiety disorder symptoms such as intrusive memories. There is also evidence from multiple studies showing that the enhancing effects of acute nicotine on hippocampus-dependent memory are mediated by $\beta 2$ -containing nAChRs. Specifically, studies show that systemic administration of an $\alpha 4\beta 2^*$ nAChR antagonist, Dh β E, reversed the acute nicotine-induced enhancement of contextual fear conditioning, while a low-affinity $\alpha 7$ nAChR antagonist, methyllycaconitine (MLA), had no effect [208]. In line with this study, studies also showed that acute nicotine had no effect on contextual and trace [207] fear conditioning in knock-out (KO) mice that lack $\beta 2$ -containing nAChRs. These results strongly suggest that $\beta 2$ -containing nAChRs are necessary for the enhancing effects of acute nicotine on hippocampus-dependent learning.

Although acute nicotine seems to have profound effects on fear memory, many of the anxiety disorder patients that smoke are heavy smokers with established nicotine dependence [209]. The chronic effects of nicotine can be modeled in mice with continuous subcutaneous (s.c.) administration of nicotine via osmotic mini-pumps (e.g. [208, 210]). Using this model, several studies have investigated the effects of both chronic nicotine and withdrawal from chronic nicotine on fear conditioning in mice [210–214]. These studies showed that while chronic nicotine had no effect on fear conditioning, withdrawal from chronic nicotine resulted in deficits in contextual and trace fear conditioning. There are

several changes occurring in the brain during chronic nicotine administration and withdrawal that may be responsible for these effects. First, during chronic nicotine administration hippocampal nAChRs desensitize and upregulate [215–218]. Therefore, it is suggested that in the absence of nicotine during withdrawal, upregulated nAChRs resensitize, which results in a hypersensitive cholinergic system and deficits in hippocampus-dependent learning [215]. This hypothesis was supported by Gould et al.'s [216] findings that the duration of withdrawal deficits in fear conditioning paralleled the duration of nAChR upregulation in the hippocampus. Moreover, in support of a hypersensitive cholinergic system during withdrawal, Wilkinson and Gould [218] found that acute nicotine administration during nicotine withdrawal resulted in an even greater enhancement of contextual fear conditioning compared to acute nicotine administration in nicotine naïve mice. Finally, Gould et al. [219] showed that tolerance to the effect of nicotine on contextual fear conditioning takes a shorter duration of chronic nicotine exposure to develop than nicotine withdrawal effects and that during tolerance nAChRs are not significantly upregulated. Thus, it is possible that nAChR desensitization, which occurs faster than receptor upregulation, underlies tolerance whereas slowly developing nAChR upregulation is necessary for withdrawal.

In sum, studies investigating the effects of acute, chronic, and withdrawal from chronic nicotine demonstrate that while acute nicotine enhances hippocampus-dependent fear learning, withdrawal results in impaired fear learning and chronic nicotine has no effect. Therefore, although nicotine withdrawal seemingly results in reduced fear learning it does not mean it is beneficial in terms of anxiety disorder symptoms. This is because nicotine withdrawal is also associated with many other psychological symptoms such as irritability, depression, restlessness, insomnia, anxiety, hunger, and poor concentration [220] and anxiety disorder patients that smoke experience more severe nicotine withdrawal symptoms when they encounter trauma-related stimuli than smokers without anxiety disorders [65]. Consequently, as discussed previously, patients with anxiety disorders show lower rates of successful quitting [53, 59] and an increased level of relapse to smoking [60] than non-anxiety disorder smokers. Although re-initiation of smoking may help patients with anxiety disorders reduce the withdrawal symptoms, Wilkinson and Gould's [218] results suggest that an increased sensitivity of the cholinergic system during withdrawal may enhance fear learning during relapse of nicotine use, which could worsen the condition of the patient.

Similar to their role in acute nicotine's effects on hippocampus-dependent learning, $\beta 2$ -containing nAChRs have also been shown to be necessary for withdrawal effects. For example, Portugal et al. [221] demonstrated that KO animals that lack the $\beta 2$ subtype of nAChRs did not show withdrawal deficits in contextual fear conditioning. Furthermore, there is evidence showing that infusions of the $\alpha 4 \beta 2$ nAChR antagonist Dh β E into the dorsal hippocampus precipitated deficits in contextual [222] and trace [214] fear conditioning in mice treated chronically with nicotine. Importantly, the involvement of the $\beta 2$ -containing nAChRs may also add translational value to the animal studies of fear conditioning. This is because the $\beta 2$ -containing nAChRs have been implicated to play a critical role in anxiety disorder symptomatology in humans. Specifically, using the radiotracer [123 I]5-IA-85380 and single-photon emission computed tomography (SPECT), Czermak et al. [223] investigated the relationship between nAChRs and PTSD and found that compared to non-

Biochem Pharmacol. Author manuscript; available in PMC 2016 October 15.

retrieval in a “safe” context. In contrast to the results suggesting that PTSD patients show normal extinction learning performance, there are studies showing impaired cued and contextual fear extinction learning in PTSD patients [28, 234]. Also, Michael et al. [29] demonstrated that individuals with panic disorder showed resistance to fear extinction. Furthermore, in a series of experiments, Jovanovic and colleagues demonstrated that PTSD patients also exhibited diminished safety discrimination learning, where fear-potentiated startle response in individuals with PTSD was enhanced during a safety signal ([235–237]; for a review, see [238]). Therefore, our results showing impaired contextual fear extinction and safety discrimination as a result of acute nicotine administration [227, 228] suggest that smoking may further disrupt already impaired safety learning in patients with anxiety disorders and potentially prolong the course of the disorder. In support, there is evidence from human studies showing that PTSD patients showed altered contextual information processing during extinction [239]. Furthermore, Calhoun et al. [240] showed that the exaggerated fear response to the trauma context observed in PTSD patients was aggravated with smoking. Although the underlying neurobiological mechanisms of nicotine’s effects on safety learning are unknown, further investigation of these mechanisms will aid in understanding the effects of smoking on the exposure therapy processes used in anxiety disorder treatment.

Overall, in line with the human studies suggesting that smoking and withdrawal have substantial effects on anxiety disorder symptomatology, the evidence from animal studies also suggest that acute, chronic, and withdrawal from chronic nicotine have differential effects on hippocampus-dependent and hippocampus-independent fear learning as well as on extinction and safety discrimination. In addition, human and animal studies converge on the potential involvement of hippocampal $\beta 2$ -containing nAChRs in the effects of nicotine on PTSD symptoms. Furthermore, there is translational evidence suggesting that nicotine may impair anxiety disorder treatment processes by blocking safety learning. Therefore, translational research investigating the neurobiological mechanisms involved in the nicotinic modulation of fear learning will inform on potential treatment mechanisms to alleviate nicotine’s negative effects on anxiety disorders.

6) Involvement of nicotine and nAChRs in modulation of anxiety: Evidence from animal studies

While animal fear conditioning paradigms inform on learned fear symptoms of anxiety disorders, rodent models of anxiety-like behaviors have been widely utilized for the neurobiological and pharmacological investigations of innate anxiety symptoms [241]. As mentioned, these behavioral models usually take advantage of the innate anxiety-like behaviors of rodents such as avoidance of open spaces and model anxiety disorder symptoms such as hyperarousal. Therefore, the rodent models of anxiety have long been utilized to understand the effects of nicotine on anxiety as well as involvement of specific nAChRs in these behaviors. However, the effects of nicotine and other nicotinic agonists/antagonists on anxiety-like behavior in rodents are less clear than the effects of nicotine on fear conditioning (Table 1). For instance, there is evidence showing that subcutaneous injections of acute nicotine (0.1 mg/kg) 30 minutes prior to EPM increased anxiety-like

behavior [242]. Also, there is evidence for acute nicotine's anxiogenic effects with higher doses (0.5 and 1 mg/kg) when injected intraperitoneally (i.p.; [243]). Interestingly, Irvine et al. [242] also showed that repeated s.c. injections of nicotine, similar to chronic administration, 5 mins prior to EPM testing had anxiolytic effects after 7 days of administration, whereas the same repeated administration regimen resulted in increased anxiety when testing occurred during withdrawal 24 hrs after the last injection. This anxiogenic effect of nicotine withdrawal has been shown to be reversed by nicotine challenge [244]. In addition, Irvine et al. [245] previously showed that acute nicotine injections 5 mins before the behavioral test decreased social interaction, an anxiogenic effect. However, the same study also showed that nicotine injections 30 min before the task increased social interaction, an anxiolytic effect. Moreover, employing a social interaction task, File et al. [246] found that while the lower doses of acute nicotine (0.01, and 0.1 mg/kg) decreased anxiety, higher doses (0.5 and 1.0 mg/kg) increased anxiety. Thus, acute nicotine has differential effects on anxiety-like behavior, which may be due to the involvement of different neurobiological substrates depending on the task and the nicotine delivery method. In support, File et al. [247] found that while local nicotine infusion into both the dorsal hippocampus and lateral septum resulted in anxiogenic effects in the social interaction test, in EPM nicotine had anxiogenic effects only when infused in the lateral septum but not when injected into the dorsal hippocampus.

Because lower doses decrease anxiety-like behavior in the social interaction task but not in EPM, it is possible that these paradigms have different sensitivities to nicotine's effects and/or measure different aspects of anxiety. In line with increased sensitivity of EPM to the anxiogenic effects of acute nicotine, Elliot et al. [248] found that s.c. injections of both low and high doses of nicotine (0.1, 0.5, and 1.0 mg/kg) resulted in reduced open arm duration, an anxiogenic effect, in EPM. Interestingly, there is also evidence from studies using EPM that both i.p. and s.c. acute nicotine injections decreased anxiety [244, 249]. Nevertheless, the contradictory results showing different effects of acute nicotine on EPM may be explained by different species and rat strains used in the studies. Specifically, Irvine et al. [242] and Ouagazzal et al. [243] showed the anxiogenic effects of acute nicotine using Hooded Lister rats, whereas studies showing anxiolytic effects nicotine used Wistar rats and CD1 mice [244, 249]. This suggests strain/genetic differences contribute to the effects of nicotine on anxiety. In support, differences in anxiety-like behavior between Wistar and Hooded Lister rats have been documented [250]. These studies suggest that although nicotine may be used as a mean to self-medicate anxiety-related symptoms in anxiety disorders, its effects on anxiety may be dependent on a variety of factors including the source or type of anxiety the patient experiences and genetic background. Therefore, it is possible that nicotine-based self-medication may be effective only for some individuals with specific types of anxiety and/or specific genotypes. In support there is evidence showing that the prevalence of self-medication with alcohol and other drugs among different subtypes of anxiety disorders vary from 3.3% in specific phobias and panic disorder to 18.3% in generalized anxiety disorder [72].

Specific nAChRs seem to have different roles in the effects of nicotine on anxiety (Table 2). Similar to the role of the high-affinity $\alpha 4\beta 2$ nAChRs in nicotine's effects on hippocampus-dependent fear conditioning, these nAChR subtypes also play a modulatory role in anxiety-

like behavior. For example, ABT-418, an $\alpha 4\beta 2$ nAChR agonist, has been shown to have anxiolytic effects in EPM while both ABT-418 and an $\alpha 4\beta 2$ nAChR partial agonist, ABT-089, have been shown to reverse the anxiogenic effects observed during nicotine withdrawal [124, 251, 252]. Also, Brioni et al. [251] showed that the anxiolytic effects of ABT-418 can be reversed by the injections of non-specific nAChR antagonist mecamylamine. In addition to studies using $\alpha 4\beta 2$ nAChR agonists, McGranahan and colleagues [253] showed that selective deletion of $\alpha 4\beta 2$ nAChRs located on dopaminergic neurons also reversed nicotine's anxiolytic effects. However, studies showed that KO mice lacking the $\beta 2$ subtype of nAChRs showed normal levels of anxiety in EPM as well as the light/dark box and mirrored chamber tasks [254], which suggests that $\beta 2$ -containing nAChRs may be required for the effects of nicotine on anxiety but may not be directly involved in anxiety. In contrast, there is evidence showing that $\alpha 4$ KO and heterozygous mice showed increased anxiety in the EPM paradigm [255, 256]. This shows that $\alpha 4$ -containing nAChRs may modulate anxiety.

Paylor et al. found that in contrast to $\alpha 4$ KO mice, $\alpha 7$ KO mice showed decreased anxiety in EPM [257]. In line with the Paylor et al. [257] results, Pandya and Yakel [258] demonstrated that an $\alpha 7$ -selective agonist, PNU-282987 increased anxiety-like behavior in the open field paradigm. Finally, Yohn et al. [252] found that a partial $\alpha 7$ nAChR agonist, ABT-107, which desensitizes and effectively inhibits further activation of $\alpha 7$ nAChRs, reversed the anxiogenic effects of nicotine withdrawal in a novelty-induced hypophagia paradigm, an anxiety paradigm measuring the novelty-induced reduction of feeding behavior. Also in this task, Yohn et al. [252] found that a partial agonist of $\alpha 4\beta 2$ nAChR, ABT-089, resulted in the reversal of withdrawal-related anxiety but produced anxiogenic effects in nicotine naïve animals. Therefore, these results show that $\alpha 4\beta 2$ and $\alpha 7$ nAChRs differentially mediate both anxiety and nicotine's effects on anxiety. In sum, while elimination or inhibition of $\alpha 4\beta 2$ nAChRs reverses the anxiolytic effects of nicotine, agonists at these receptors results in a decrease in anxiety-like behavior. In contrast, activation of $\alpha 7$ nAChRs results in an anxiogenic effect while inhibiting $\alpha 7$ activation reverses anxiogenic effects of nicotine withdrawal. Given that nicotine differentially binds to these two classes of nAChRs, pharmacological differences between $\alpha 7$ and $\alpha 4\beta 2$ nAChRs may determine the outcome of nicotine administration in terms of its anxiolytic and anxiogenic effects.

7) Conclusion: Towards understanding the relationship between nicotine and anxiety disorders

In summary, the studies reviewed here suggest a strong relationship between nicotine and anxiety and fear learning, which underlie some of the most common symptoms of anxiety disorders. Human studies suggest that although smoking may be an attempt to self-medicate, it is also correlated with symptom severity. In line with these results, animal studies suggest that acute nicotine enhances hippocampus-dependent fear-learning in animals that are nicotine-naïve and this effect is greater in animals withdrawn from chronic nicotine. There is evidence from multiple studies that the enhancing effects of nicotine on hippocampus-dependent fear learning are modulated by the $\beta 2$ -containing nAChRs in the hippocampus.

Moreover, these studies also suggest that nicotine impairs contextual fear extinction and contextual safety learning, which suggests that nicotine may reduce the effectiveness of exposure therapy and prolong the course of the disorder. Together with the human studies suggesting a positive correlation between smoking and anxiety disorder symptom severity and data showing that contextual fear is enhanced with smoking, these results clearly indicate that nicotine may worsen fear-related symptoms of anxiety disorders. This effect may be mainly mediated by the high-affinity nAChRs in the hippocampus. Although the effects of nicotine on learned fear are relatively clear, nicotine's effects on other anxiety symptoms are variable. These effects are dependent on both $\alpha 7$ and $\alpha 4$ subtypes of nAChRs. The animal studies employing models of anxiety suggest that acute nicotine may have both anxiolytic and anxiogenic effects at different doses based on the type of anxiety (novelty-driven or social anxiety) and potentially genetic background. This may explain the different rates of self-medication prevalence observed in the subtypes of anxiety disorders. Further work in this area may aid in the development of behavioral and pharmacological interventions for anxiety disorders and nicotine addiction.

Acknowledgments

Funding

This work was funded with grant support from the National Institute on Drug Abuse (T.J.G., DA017949).

References

1. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Jama*. 2003; 289(23):3095–3105. [PubMed: 12813115]
2. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry*. 2005; 62(6):617–627. [PubMed: 15939839]
3. Breslau N, Novak SP, Kessler RC. Psychiatric disorders and stages of smoking. *Biological psychiatry*. 2004; 55(1):69–76. [PubMed: 14706427]
4. Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, et al. The economic burden of anxiety disorders in the 1990s. *Journal of Clinical Psychiatry*. 1999; 60(7):427–435. [PubMed: 10453795]
5. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation*. 2005; 111(4):480–487. [PubMed: 15687137]
6. Kawachi I, Colditz GA, Ascherio A, Rimm EB, Giovannucci E, Stampfer MJ, et al. Prospective study of phobic anxiety and risk of coronary heart disease in men. *Circulation*. 1994; 89(5):1992–1997. [PubMed: 8181122]
7. Smoller JW, Pollack MH, Wassertheil-Smoller S, Jackson RD, Oberman A, Wong ND, et al. Panic attacks and risk of incident cardiovascular events among postmenopausal women in the Women's Health Initiative Observational Study. *Archives of general psychiatry*. 2007; 64(10):1153–1160. [PubMed: 17909127]
8. Mineka S, Zinbarg R. A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. *American psychologist*. 2006; 61(1):10. [PubMed: 16435973]
9. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*. 2010; 35(1):169–191. [PubMed: 19625997]

10. Gualtieri CT, Morgan DW. The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *The Journal of clinical psychiatry*. 2008; 69(7):1122–1130. [PubMed: 18572982]
11. Association, D-AP. *Diagnostic and statistical manual of mental disorders*. Arlington: American Psychiatric Publishing; 2013.
12. Watson JB, Rayner R. Conditioned emotional reactions. *Journal of experimental psychology*. 1920; 3(1):1.
13. Wolpe J. The dichotomy between classical conditioned and cognitively learned anxiety. *Journal of behavior therapy and experimental psychiatry*. 1981; 12(1):35–42. [PubMed: 7251880]
14. Mineka S, Oehlberg K. The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. *Acta psychologica*. 2008; 127(3):567–580. [PubMed: 18226795]
15. Foa EB, Zinbarg R, Rothbaum BO. Uncontrollability and unpredictability in post-traumatic stress disorder: an animal model. *Psychological bulletin*. 1992; 112(2):218. [PubMed: 1454893]
16. Wolpe J, Rowan VC. Panic disorder: A product of classical conditioning. *Behaviour research and therapy*. 1988; 26(6):441–450. [PubMed: 3071352]
17. Rau V, DeCola JP, Fanselow MS. Stress-induced enhancement of fear learning: an animal model of posttraumatic stress disorder. *Neuroscience & biobehavioral reviews*. 2005; 29(8):1207–1223. [PubMed: 16095698]
18. Rodgers R, Cole J. Anxiety enhancement in the murine elevated plus maze by immediate prior exposure to social stressors. *Physiology & behavior*. 1993; 53(2):383–388. [PubMed: 8446702]
19. Van Dijken HH, Van Der Heyden JA, Mos J, Tilders FJ. Inescapable footshocks induce progressive and long-lasting behavioural changes in male rats. *Physiology & behavior*. 1992; 51(4):787–794. [PubMed: 1594677]
20. Handley SL, Mithani S. Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of ‘fear’-motivated behaviour. *Naunyn-Schmiedeberg's archives of pharmacology*. 1984; 327(1):1–5.
21. Shepherd JK, Grewal SS, Fletcher A, Bill DJ, Dourish CT. Behavioural and pharmacological characterisation of the elevated “zero-maze” as an animal model of anxiety. *Psychopharmacology*. 1994; 116(1):56–64. [PubMed: 7862931]
22. Viana M, Tomaz C, Graeff F. The elevated T-maze: a new animal model of anxiety and memory. *Pharmacology biochemistry and behavior*. 1994; 49(3):549–554.
23. Pellow S, File SE. Anxiolytic and anxiogenic drug effects on exploratory activity in an elevated plus-maze: a novel test of anxiety in the rat. *Pharmacology biochemistry and behavior*. 1986; 24(3):525–529.
24. Lister RG. Ethologically-based animal models of anxiety disorders. *Pharmacology & therapeutics*. 1990; 46(3):321–340. [PubMed: 2188266]
25. Pavlov IP. *Conditioned reflexes. An Investigation of the physiological activity of the cerebral cortex*. 1927
26. Myers KM, Davis M. Behavioral and neural analysis of extinction. *Neuron*. 2002; 36(4):567–584. [PubMed: 12441048]
27. Phelps EA, Delgado MR, Nearing KI, LeDoux JE. Extinction learning in humans: role of the amygdala and vmPFC. *Neuron*. 2004; 43(6):897–905. [PubMed: 15363399]
28. Blechert J, Michael T, Vriends N, Margraf J, Wilhelm FH. Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomic, experiential, and behavioural responses. *Behaviour research and therapy*. 2007; 45(9):2019–2033. [PubMed: 17442266]
29. Michael T, Blechert J, Vriends N, Margraf J, Wilhelm FH. Fear conditioning in panic disorder: Enhanced resistance to extinction. *Journal of abnormal psychology*. 2007; 116(3):612. [PubMed: 17696717]
30. Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, et al. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. *Biological psychiatry*. 2009; 66(12):1075–1082. [PubMed: 19748076]

31. Waters AM, Henry J, Neumann DL. Aversive Pavlovian conditioning in childhood anxiety disorders: impaired response inhibition and resistance to extinction. *Journal of abnormal psychology*. 2009; 118(2):311. [PubMed: 19413406]
32. Cukor J, Olden M, Lee F, Difede J. Evidence-based treatments for PTSD, new directions, and special challenges. *Annals of the New York Academy of Sciences*. 2010; 1208(1):82–89. [PubMed: 20955329]
33. Foa EB. Psychosocial therapy for posttraumatic stress disorder. *J Clin Psychiatry*. 2006; 67(Suppl 2):40–45. [PubMed: 16602814]
34. Foa EB, Kozak MJ. Emotional processing of fear: exposure to corrective information. *Psychological bulletin*. 1986; 99(1):20. [PubMed: 2871574]
35. Wolpe J. The systematic desensitization treatment of neuroses. *The Journal of nervous and mental disease*. 1961; 132(3):189–203. [PubMed: 13786444]
36. Wolpe J. Psychotherapy by reciprocal inhibition. *Conditional reflex: a Pavlovian journal of research & therapy*. 1968; 3(4):234–240. [PubMed: 5712667]
37. Moscovitch DA, Antony MM, Swinson RP. Exposure-based treatments for anxiety disorders: Theory and process. *Oxford handbook of anxiety and related disorders*. 2009:461–475.
38. Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*. 2000; 406(6797):722–726. [PubMed: 10963596]
39. Merlo E, Milton AL, Goozee ZY, Theobald DE, Everitt BJ. Reconsolidation and extinction are dissociable and mutually exclusive processes: behavioral and molecular evidence. *The journal of neuroscience*. 2014; 34(7):2422–2431.
40. Craske MG. *Anxiety disorders: Psychological approaches to theory and treatment: Basic Books*. 1999
41. Vervliet B, Craske MG, Hermans D. Fear extinction and relapse: state of the art. *Annual review of clinical psychology*. 2013; 9:215–248.
42. Rosenthal MZ, Kutlu MG. Translation of associative learning models into extinction reminders delivered via mobile phones during cue exposure interventions for substance use. *Psychology of addictive behaviors*. 2014; 28(3):863. [PubMed: 25134055]
43. Gould TJ, Higgins JS. Nicotine enhances contextual fear conditioning in C57BL/6J mice at 1 and 7 days post-training. *Neurobiology of learning and memory*. 2003; 80(2):147–157. [PubMed: 12932430]
44. Dedert EA, Calhoun PS, Harper LA, Dutton CE, McClernon FJ, Beckham JC. Smoking withdrawal in smokers with and without posttraumatic stress disorder. *Nicotine & tobacco research*. 2011:ntr142.
45. Hidalgo RB, Davidson JR. Posttraumatic stress disorder: epidemiology and health-related considerations. *Journal of Clinical Psychiatry*. 2000; 61:5–13. [PubMed: 10795604]
46. Leeies M, Pagura J, Sareen J, Bolton JM. The use of alcohol and drugs to self-medicate symptoms of posttraumatic stress disorder. *Depression and anxiety*. 2010; 27(8):731–736. [PubMed: 20186981]
47. Hoffman DL, Dukes EM, Wittchen HU. Human and economic burden of generalized anxiety disorder. *Depression and anxiety*. 2008; 25(1):72–90. [PubMed: 17146763]
48. Beckham JC, Kirby AC, Feldman ME, Hertzberg MA, Moore SD, Crawford AL, et al. Prevalence and correlates of heavy smoking in Vietnam veterans with chronic posttraumatic stress disorder. *Addictive behaviors*. 1997; 22(5):637–647. [PubMed: 9347066]
49. Breslau N, Davis GC, Schultz LR. Posttraumatic stress disorder and the incidence of nicotine, alcohol, and other drug disorders in persons who have experienced trauma. *Archives of general psychiatry*. 2003; 60(3):289–294. [PubMed: 12622662]
50. Feldner MT, Babson KA, Zvolensky MJ. Smoking, traumatic event exposure, and post-traumatic stress: A critical review of the empirical literature. *Clinical psychology review*. 2007; 27(1):14–45. [PubMed: 17034916]
51. Fu SS, McFall M, Saxon AJ, Beckham JC, Carmody TP, Baker DG, et al. Post-traumatic stress disorder and smoking: a systematic review. *Nicotine & tobacco research*. 2007; 9(11):1071–1084. [PubMed: 17978982]

52. Koenen KC, Hitsman B, Lyons MJ, Niaura R, McCaffery J, Goldberg J, et al. A twin registry study of the relationship between posttraumatic stress disorder and nicotine dependence in men. *Archives of general psychiatry*. 2005; 62(11):1258–1265. [PubMed: 16275813]
53. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *Jama*. 2000; 284(20):2606–2610. [PubMed: 11086367]
54. Ziedonis D, Hitsman B, Beckham JC, Zvolensky M, Adler LE, Audrain-McGovern J, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. *Nicotine & tobacco research*. 2008; 10(12):1691–1715. [PubMed: 19023823]
55. Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the united states: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of general psychiatry*. 2004; 61(11):1107–1115. [PubMed: 15520358]
56. Grant BF, Stinson FS, Dawson DA, Chou S, Dufour M, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. *Alcohol Research & Health*. 2006; 29(2):107–120.
57. Goodwin RD, Lewinsohn PM, Seeley JR. Cigarette smoking and panic attacks among young adults in the community: the role of parental smoking and anxiety disorders. *Biological psychiatry*. 2005; 58(9):686–693. [PubMed: 16018987]
58. Sonntag H, Wittchen H, Höfler M, Kessler R, Stein M. Are social fears and DSM-IV social anxiety disorder associated with smoking and nicotine dependence in adolescents and young adults? *European psychiatry*. 2000; 15(1):67–74. [PubMed: 10713804]
59. Hapke U, Schumann A, Rumpf H-J, John U, Konerding U, Meyer C. Association of smoking and nicotine dependence with trauma and posttraumatic stress disorder in a general population sample. *The Journal of nervous and mental disease*. 2005; 193(12):843–846. [PubMed: 16319709]
60. Beckham JC, Calhoun PS, Dennis MF, Wilson SM, Dedert EA. Predictors of lapse in first week of smoking abstinence in PTSD and non-PTSD smokers. *Nicotine & tobacco research*. 2012; 14(2):252.
61. Beckham JC, Feldman ME, Vrana SR, Mozley SL, Erkanli A, Clancy CP, et al. Immediate antecedents of cigarette smoking in smokers with and without posttraumatic stress disorder: a preliminary study. *Experimental and clinical psychopharmacology*. 2005; 13(3):219. [PubMed: 16173885]
62. Greenberg JB, Ameringer KJ, Trujillo MA, Sun P, Sussman S, Brightman M, et al. Associations between posttraumatic stress disorder symptom clusters and cigarette smoking. *Psychology of addictive behaviors*. 2012; 26(1):89. [PubMed: 21688875]
63. Thorndike FP, Wernicke R, Pearlman MY, Haaga DA. Nicotine dependence, PTSD symptoms, and depression proneness among male and female smokers. *Addictive behaviors*. 2006; 31(2):223–231. [PubMed: 15919158]
64. Baschnagel JS, Coffey SF, Schumacher JA, Drobos DJ, Saladin ME. Relationship between PTSD symptomatology and nicotine dependence severity in crime victims. *Addictive behaviors*. 2008; 33(11):1441–1447. [PubMed: 18442884]
65. Beckham JC, Roodman AA, Shipley RH, Hertzberg MA, Cunha GH, Kudler HS, et al. Smoking in Vietnam combat veterans with post-traumatic stress disorder. *Journal of traumatic stress*. 1995; 8(3):461–472. [PubMed: 7582610]
66. Beckham JC, Lytle BL, Vrana SR, Hertzberg MA, Feldman ME, Shipley RH. Smoking withdrawal symptoms in response to a trauma-related stressor among Vietnam combat veterans with posttraumatic stress disorder. *Addictive behaviors*. 1996; 21(1):93–101. [PubMed: 8729711]
67. Brown PJ, Wolfe J. Substance abuse and post-traumatic stress disorder comorbidity. *Drug and alcohol dependence*. 1994; 35(1):51–59. [PubMed: 8082556]
68. Chilcoat HD, Breslau N. Posttraumatic stress disorder and drug disorders: testing causal pathways. *Archives of general psychiatry*. 1998; 55(10):913–917. [PubMed: 9783562]
69. Keane TM, Lyons JA, Wolfe J, Gerardi RJ. The Interrelationship of Substance Abuse and Posttraumatic Stress Disorder Epidemiological and Clinical Considerations. *Recent developments in alcoholism: Springer*. 1988:27–48.

70. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. *Clinical psychology review*. 2000; 20(2): 149–171. [PubMed: 10721495]
71. Quitkin FM, Rifkin A, Kaplan J, Klein DF. Phobic anxiety syndrome complicated by drug dependence and addiction: a treatable form of drug abuse. *Archives of general psychiatry*. 1972; 27(2):159–162. [PubMed: 5042823]
72. Robinson J, Sareen J, Cox BJ, Bolton J. Self-medication of anxiety disorders with alcohol and drugs: Results from a nationally representative sample. *Journal of anxiety disorders*. 2009; 23(1): 38–45. [PubMed: 18571370]
73. Cook JW, McFall MM, Calhoun PS, Beckham JC. Posttraumatic stress disorder and smoking relapse: A theoretical model. *Journal of traumatic stress*. 2007; 20(6):989–998. [PubMed: 18157879]
74. Buchhalter AR, Acosta MC, Evans SE, Breland AB, Eissenberg T. Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction*. 2005; 100(4):550–559. [PubMed: 15784070]
75. Jarvik ME, Caskey NH, Rose JE, Herskovic JE, Sadehpour M. Anxiolytic effects of smoking associated with four stressors. *Addictive behaviors*. 1989; 14(4):379–386. [PubMed: 2782121]
76. Morissette SB, Tull MT, Gulliver SB, Kamholz BW, Zimering RT. Anxiety, anxiety disorders, tobacco use, nicotine: a critical review of interrelationships. *Psychological bulletin*. 2007; 133(2): 245. [PubMed: 17338599]
77. Pomerleau CS, Pomerleau OF. The effects of a psychological stressor on cigarette smoking and subsequent behavioral and physiological responses. *Psychophysiology*. 1987; 24(3):278–285. [PubMed: 3602283]
78. Pomerleau OF, Turk DC, Fertig JB. The effects of cigarette smoking on pain and anxiety. *Addictive behaviors*. 1984; 9(3):265–271. [PubMed: 6496202]
79. Goodwin R, Hamilton SP. Cigarette smoking and panic: the role of neuroticism. *American journal of psychiatry*. 2002
80. Johnson JG, Cohen P, Pine DS, Klein DF, Kasen S, Brook JS. Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *Jama*. 2000; 284(18): 2348–2351. [PubMed: 11066185]
81. Martin EI, Ressler KJ, Binder E, Nemeroff CB. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. *Psychiatric clinics of North America*. 2009; 32(3):549–575. [PubMed: 19716990]
82. Morgan MA, LeDoux JE. Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behavioral neuroscience*. 1995; 109(4): 681. [PubMed: 7576212]
83. Öngür D, Price J. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral cortex*. 2000; 10(3):206–219. [PubMed: 10731217]
84. Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *The journal of neuroscience*. 2000; 20(16):6225–6231. [PubMed: 10934272]
85. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annual review of neuroscience*. 2001; 24(1):167–202.
86. Tsigos C, Chrousos GP. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of psychosomatic research*. 2002; 53(4):865–871. [PubMed: 12377295]
87. Jacobson L, Sapolsky R. The Role of the Hippocampus in Feedback Regulation of the Hypothalamic-Pituitary-Adrenocortical Axis. *Endocrine reviews*. 1991; 12(2):118–134. [PubMed: 2070776]
88. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current opinion in neurobiology*. 2001; 11(2): 240–249. [PubMed: 11301246]
89. Garcia R, Vouimba R-M, Baudry M, Thompson RF. The amygdala modulates prefrontal cortex activity relative to conditioned fear. *Nature*. 1999; 402(6759):294–296. [PubMed: 10580500]

90. Bryant R, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, et al. Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for posttraumatic stress disorder. *Psychological medicine*. 2008; 38(04):555–561. [PubMed: 18005496]
91. Dickie EW, Brunet A, Akerib V, Armony JL. An fMRI investigation of memory encoding in PTSD: influence of symptom severity. *Neuropsychologia*. 2008; 46(5):1522–1531. [PubMed: 18321537]
92. Morey RA, Petty CM, Cooper DA, LaBar KS, McCarthy G. Neural systems for executive and emotional processing are modulated by symptoms of posttraumatic stress disorder in Iraq War veterans. *Psychiatry research: Neuroimaging*. 2008; 162(1):59–72. [PubMed: 18093809]
93. Anand A, Shekhar A. Brain imaging studies in mood and anxiety disorders. *Annals of the New York Academy of Sciences*. 2003; 985(1):370–388. [PubMed: 12724172]
94. Rauch SL, Shin LM, Wright CI. Neuroimaging studies of amygdala function in anxiety disorders. *Annals of the New York Academy of Sciences*. 2003; 985(1):389–410. [PubMed: 12724173]
95. Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HM, et al. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of general psychiatry*. 2008; 65(5):568–576. [PubMed: 18458208]
96. Engel K, Bandelow B, Gruber O, Wedekind D. Neuroimaging in anxiety disorders. *Journal of neural transmission*. 2009; 116(6):703–716. [PubMed: 18568288]
97. Geuze E, Vermetten E, Ruf M, de Kloet CS, Westenberg HG. Neural correlates of associative learning and memory in veterans with posttraumatic stress disorder. *Journal of psychiatric research*. 2008; 42(8):659–669. [PubMed: 17698081]
98. Geuze E, Westenberg HG, Jochims A, de Kloet CS, Bohus M, Vermetten E, et al. Altered pain processing in veterans with posttraumatic stress disorder. *Archives of general psychiatry*. 2007; 64(1):76–85. [PubMed: 17199057]
99. Sachinvala N. Increased regional cerebral perfusion by (99m) tc hexamethyl propylene amine oxime single photon emission computed tomography in post-traumatic stress disorder. *Military medicine*. 2000; 165(6):473. [PubMed: 10870367]
100. Semple WE, Goyer PF, McCormick R, Donovan B, Muzic RF Jr, Rugle L, et al. Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. *Psychiatry*. 2000; 63(1):65–74. [PubMed: 10855761]
101. Thomaes K, Dorrepaal E, Draijer NP, de Ruiter MB, Elzinga BM, van Balkom AJ, et al. Increased activation of the left hippocampus region in Complex PTSD during encoding and recognition of emotional words: a pilot study. *Psychiatry research: Neuroimaging*. 2009; 171(1):44–53. [PubMed: 19081708]
102. Werner NS, Meindl T, Engel RR, Rosner R, Riedel M, Reiser M, et al. Hippocampal function during associative learning in patients with posttraumatic stress disorder. *Journal of psychiatric research*. 2009; 43(3):309–318. [PubMed: 18490028]
103. Osuch EA, Benson B, Geraci M, Podell D, Herscovitch P, McCann UD, et al. Regional cerebral blood flow correlated with flashback intensity in patients with posttraumatic stress disorder. *Biological psychiatry*. 2001; 50(4):246–253. [PubMed: 11522258]
104. Shin LM, Shin PS, Heckers S, Krangel TS, Macklin ML, Orr SP, et al. Hippocampal function in posttraumatic stress disorder. *Hippocampus*. 2004; 14(3):292–300. [PubMed: 15132428]
105. Bossini L, Tavanti M, Calossi S, Lombardelli A, Polizzotto NR, Galli R, et al. Magnetic resonance imaging volumes of the hippocampus in drug-naïve patients with post-traumatic stress disorder without comorbidity conditions. *Journal of psychiatric research*. 2008; 42(9):752–762. [PubMed: 17892884]
106. Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biological psychiatry*. 1997; 41(1):23–32. [PubMed: 8988792]
107. Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual

- abuse and posttraumatic stress disorder. *American journal of psychiatry*. 2003; 160:924–932. [PubMed: 12727697]
108. Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, et al. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature neuroscience*. 2002; 5(11):1242–1247. [PubMed: 12379862]
109. Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, et al. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biological psychiatry*. 1996; 40(11):1091–1099. [PubMed: 8931911]
110. Karl A, Schaefer M, Malta LS, Dörfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience & biobehavioral reviews*. 2006; 30(7):1004–1031. [PubMed: 16730374]
111. Kitayama N, Vaccarino V, Kutner M, Weiss P, Bremner JD. Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. *Journal of affective disorders*. 2005; 88(1):79–86. [PubMed: 16033700]
112. Smith ME. Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: A meta-analysis of structural MRI studies. *Hippocampus*. 2005; 15(6):798–807. [PubMed: 15988763]
113. Stein MB, Koverola C, Hanna C, Torchia M, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. *Psychological medicine*. 1997; 27(04):951–959. [PubMed: 9234472]
114. Villarreal G, Hamilton DA, Petropoulos H, Driscoll I, Rowland LM, Griego JA, et al. Reduced hippocampal volume and total white matter volume in posttraumatic stress disorder. *Biological psychiatry*. 2002; 52(2):119–125. [PubMed: 12114003]
115. Wignall EL, Dickson JM, Vaughan P, Farrow TF, Wilkinson ID, Hunter MD, et al. Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. *Biological psychiatry*. 2004; 56(11):832–836. [PubMed: 15576059]
116. Winter H, Irle E. Hippocampal Volume in Adult Burn Patients With and Without Posttraumatic Stress Disorder. *American journal of psychiatry*. 2004; 161(12):2194–2200. [PubMed: 15569889]
117. Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: A meta-analysis. *Hippocampus*. 2008; 18(8):729–736. [PubMed: 18446827]
118. Nordahl TE, Semple WE, Gross M, Mellman TA, Stein M, Goyer P, et al. Cerebral glucose metabolic differences in patients with panic disorder. *Neuropsychopharmacology*. 1990; 3(4):261–272. [PubMed: 2400544]
119. Nordahl TE, Stein MB, Benkelfat C, Semple WE, Andreason P, Zametkin A, et al. Regional cerebral metabolic asymmetries replicated in an independent group of patients with panic disorder. *Biological psychiatry*. 1998; 44(10):998–1006. [PubMed: 9821564]
120. Cordero-Erausquin M, Marubio LM, Klink R, Changeux J-P. Nicotinic receptor function: new perspectives from knockout mice. *Trends in pharmacological sciences*. 2000; 21(6):211–217. [PubMed: 10838608]
121. Le Novère N, Grutter T, Changeux J-P. Models of the extracellular domain of the nicotinic receptors and of agonist- and Ca²⁺-binding sites. *Proceedings of the National Academy of Sciences*. 2002; 99(5):3210–3215.
122. Léna C, Changeux J-P. Allosteric nicotinic receptors, human pathologies. *Journal of physiology-Paris*. 1998; 92(2):63–74.
123. Rush R, Kuryatov A, Nelson ME, Lindstrom J. First and second transmembrane segments of $\alpha 3$, $\alpha 4$, $\beta 2$, and $\beta 4$ nicotinic acetylcholine receptor subunits influence the efficacy and potency of nicotine. *Molecular pharmacology*. 2002; 61(6):1416–1422. [PubMed: 12021403]
124. Decker MW, Brioni JD, Sullivan JP, Buckley MJ, Radek RJ, Raszkiewicz JL, et al. (S)-3-methyl-5-(1-methyl-2-pyrrolidinyl) isoxazole (ABT 418): a novel cholinergic ligand with cognition-enhancing and anxiolytic activities: II. In vivo characterization. *Journal of pharmacology and experimental therapeutics*. 1994; 270(1):319–328. [PubMed: 7913497]

125. Jones S, Sudweeks S, Yakel JL. Nicotinic receptors in the brain: correlating physiology with function. *Trends in neurosciences*. 1999; 22(12):555–561. [PubMed: 10542436]
126. McGehee D. Molecular diversity of neuronal nicotinic acetylcholine receptors. *Annals of the New York Academy of Sciences*. 1999; 868:565. [PubMed: 10414338]
127. Gould TJ, Leach PT. Cellular, molecular, and genetic substrates underlying the impact of nicotine on learning. *Neurobiology of learning and memory*. 2014; 107:108–132. [PubMed: 23973448]
128. Marks MJ, Collins AC. Characterization of nicotine binding in mouse brain and comparison with the binding of alpha-bungarotoxin and quinuclidinyl benzilate. *Molecular pharmacology*. 1982; 22(3):554–564. [PubMed: 7155123]
129. Marks MJ, Stitzel JA, Romm E, Wehner JM, Collins AC. Nicotinic binding sites in rat and mouse brain: comparison of acetylcholine, nicotine, and alpha-bungarotoxin. *Molecular pharmacology*. 1986; 30(5):427–436. [PubMed: 3534542]
130. Orr-Urtreger A, Göldner FM, Saeki M, Lorenzo I, Goldberg L, De Biasi M, et al. Mice deficient in the $\alpha 7$ neuronal nicotinic acetylcholine receptor lack α -bungarotoxin binding sites and hippocampal fast nicotinic currents. *The journal of neuroscience*. 1997; 17(23):9165–9171. [PubMed: 9364063]
131. Orr-Urtreger A, Seldin MF, Baldini A, Beaudet AL. Cloning and mapping of the mouse $\alpha 7$ -neuronal nicotinic acetylcholine receptor. *Genomics*. 1995; 26(2):399–402. [PubMed: 7601470]
132. Perry DC, Xiao Y, Nguyen HN, Musachio JL, Dávila-García MI, Kellar KJ. Measuring nicotinic receptors with characteristics of $\alpha 4\beta 2$, $\alpha 3\beta 2$ and $\alpha 3\beta 4$ subtypes in rat tissues by autoradiography. *Journal of neurochemistry*. 2002; 82(3):468–481. [PubMed: 12153472]
133. Wonnacott S. α -Bungarotoxin Binds to Low-Affinity Nicotine Binding Sites in Rat Brain. *Journal of neurochemistry*. 1986; 47(6):1706–1712. [PubMed: 3772372]
134. Marks MJ, Stitzel JA, Collins AC. Time course study of the effects of chronic nicotine infusion on drug response and brain receptors. *Journal of pharmacology and experimental therapeutics*. 1985; 235(3):619–628. [PubMed: 4078726]
135. Olale F, Gerzanich V, Kuryatov A, Wang F, Lindstrom J. Chronic nicotine exposure differentially affects the function of human $\alpha 3$, $\alpha 4$, and $\alpha 7$ neuronal nicotinic receptor subtypes. *Journal of pharmacology and experimental therapeutics*. 1997; 283(2):675–683. [PubMed: 9353385]
136. del Toro ED, Juiz JM, Peng X, Lindstrom J, Criado M. Immunocytochemical localization of the $\alpha 7$ subunit of the nicotinic acetylcholine receptor in the rat central nervous system. *Journal of comparative Neurology*. 1994; 349(3):325–342. [PubMed: 7852628]
137. Fabian-Fine R, Skehel P, Errington ML, Davies HA, Sher E, Stewart MG, et al. Ultrastructural distribution of the $\alpha 7$ nicotinic acetylcholine receptor subunit in rat hippocampus. *The journal of neuroscience*. 2001; 21(20):7993–8003. [PubMed: 11588172]
138. Seguela P, Wadiche J, Dineley-Miller K, Dani JA, Patrick JW. Molecular cloning, functional properties, and distribution of rat brain alpha 7: a nicotinic cation channel highly permeable to calcium. *The journal of neuroscience*. 1993; 13(2):596–604. [PubMed: 7678857]
139. Broide RS, Leslie FM. The $\alpha 7$ nicotinic acetylcholine receptor in neuronal plasticity. *Molecular neurobiology*. 1999; 20(1):1–16. [PubMed: 10595869]
140. Wonnacott S. Presynaptic nicotinic ACh receptors. *Trends in neurosciences*. 1997; 20(2):92–98. [PubMed: 9023878]
141. Freun RK, Jungschaffer DA, Collins AC, Wehner JM. Evidence for modulation of GABAergic neurotransmission by nicotine. *Brain research*. 1988; 453(1):215–220. [PubMed: 2841012]
142. Fu Y, Matta SG, James TJ, Sharp BM. Nicotine-induced norepinephrine release in the rat amygdala and hippocampus is mediated through brainstem nicotinic cholinergic receptors. *Journal of pharmacology and experimental therapeutics*. 1998; 284(3):1188–1196. [PubMed: 9495882]
143. Radcliffe KA, Fisher JL, Gray R, Dani JA. Nicotinic modulation of glutamate and GABA synaptic transmission in hippocampal neurons. *Annals of the New York Academy of Sciences*. 1999; 868(1):591–610. [PubMed: 10414340]
144. Rapier C, Lunt GG, Wonnacott S. Nicotinic modulation of [3H] dopamine release from striatal synaptosomes: pharmacological characterisation. *Journal of neurochemistry*. 1990; 54(3):937–945. [PubMed: 2303820]

145. Ribeiro EB, Bettiker RL, Bogdanov M, Wurtman RJ. Effects of systemic nicotine on serotonin release in rat brain. *Brain research*. 1993; 621(2):311–318. [PubMed: 8242344]
146. Rowell PP, Winkler DL. Nicotinic stimulation of [3H] acetylcholine release from mouse cerebral cortical synaptosomes. *Journal of neurochemistry*. 1984; 43(6):1593–1598. [PubMed: 6149266]
147. Westfall TC, Grant H, Perry H. Release of dopamine and 5-hydroxytryptamine from rat striatal slices following activation of nicotinic cholinergic receptors. *General Pharmacology: The vascular system*. 1983; 14(3):321–325. [PubMed: 6135645]
148. Grady S, Marks MJ, Wonnacott S, Collins AC. Characterization of nicotinic receptor-mediated [3H]dopamine release from synaptosomes prepared from mouse striatum. *Journal of Neurochemistry*. 1992; 59(3):848–856. [PubMed: 1494911]
149. Araujo D, Lapchak P, Collier B, Quirion R. Characterization of N-[3H] Methylcarbamylocholine Binding Sites and Effect of N-Methylcarbamylocholine on Acetylcholine Release in Rat Brain. *Journal of neurochemistry*. 1988; 51(1):292–299. [PubMed: 3379410]
150. Clarke P, Reuben M. Release of [3H]-noradrenaline from rat hippocampal synaptosomes by nicotine: mediation by different nicotinic receptor subtypes from striatal [3H]-dopamine release. *British journal of pharmacology*. 1996; 117(4):595–606. [PubMed: 8646402]
151. Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA. Hippocampal synaptic transmission enhanced by low concentrations of nicotine. *Nature*. 1996; 383(6602):713–716. [PubMed: 8878480]
152. Wilkie G, Hutson P, Sullivan J, Wonnacott S. Pharmacological characterization of a nicotinic autoreceptor in rat hippocampal synaptosomes. *Neurochemical research*. 1996; 21(9):1141–1148. [PubMed: 8897478]
153. Zarei M, Radcliffe K, Chen D, Patrick J, Dani J. Distributions of nicotinic acetylcholine receptor $\alpha 7$ and $\beta 2$ subunits on cultured hippocampal neurons. *Neuroscience*. 1999; 88(3):755–764. [PubMed: 10363815]
154. Alkondon M, Pereira E, Albuquerque EX. Mapping the location of functional nicotinic and gamma-aminobutyric acidA receptors on hippocampal neurons. *Journal of pharmacology and experimental therapeutics*. 1996; 279(3):1491–1506. [PubMed: 8968375]
155. Barrantes G, Murphy C, Westwick J, Wonnacott S. Nicotine increases intracellular calcium in rat hippocampal neurons via voltage-gated calcium channels. *Neuroscience letters*. 1995; 196(1):101–104. [PubMed: 7501232]
156. Barrantes G, Westwick J, Wonnacott S. Nicotinic acetylcholine receptors in primary cultures of hippocampal neurons: pharmacology and Ca permeability. *Biochemical society transactions*. 1994; 22(3):294S. [PubMed: 7821553]
157. Berg DK, Conroy WG. Nicotinic $\alpha 7$ receptors: synaptic options and downstream signaling in neurons. *Journal of neurobiology*. 2002; 53(4):512–523. [PubMed: 12436416]
158. Porter JT, Cauli B, Tsuzuki K, Lambolez B, Rossier J, Audinat E. Selective excitation of subtypes of neocortical interneurons by nicotinic receptors. *The Journal of Neuroscience*. 1999; 19(13):5228–5235. [PubMed: 10377334]
159. Sorenson E, Shiroyama T, Kitai S. Postsynaptic nicotinic receptors on dopaminergic neurons in the substantia nigra pars compacta of the rat. *Neuroscience*. 1998; 87(3):659–673. [PubMed: 9758232]
160. Kenney JW, Gould TJ. Modulation of hippocampus-dependent learning and synaptic plasticity by nicotine. *Molecular neurobiology*. 2008; 38(1):101–121. [PubMed: 18690555]
161. He J, Deng C-Y, Chen R-Z, Zhu X-N, Yu J-P. Long-term potentiation induced by nicotine in CA1 region hippocampal slice is Ca^{2+} -dependent. *Acta Pharmacologica Sinica*. 2000; 21:429–432. [PubMed: 11324441]
162. Matsuyama S, Matsumoto A. Epibatidine Induces Long-Term Potentiation (LTP) via Activation of. ALPHA. 4. BETA. 2 Nicotinic Acetylcholine Receptors (nAChRs) In Vivo in the Intact Mouse Dentate Gyrus: Both. ALPHA. 7 And. ALPHA. 4. BETA. 2 nAChRs Essential to Nicotinic LTP. *Journal of pharmacological sciences*. 2003; 93(2):180–187. [PubMed: 14578586]
163. Matsuyama S, Matsumoto A, Enomoto T, Nishizaki T. Activation of nicotinic acetylcholine receptors induces long-term potentiation in vivo in the intact mouse dentate gyrus. *European journal of neuroscience*. 2000; 12(10):3741–3747. [PubMed: 11029644]

164. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*. 1993; 361(6407):31–39. [PubMed: 8421494]
165. Decola J, Kim J, Fanselow M. NMDA antagonist MK-801 blocks associative fear conditioning but not nonassociative sensitization of conditional fear. *Society for neuroscience Abstracts*. 1991
166. Helmstetter FJ, Bellgowan PS. Effects of muscimol applied to the basolateral amygdala on acquisition and expression of contextual fear conditioning in rats. *Behavioral neuroscience*. 1994; 108(5):1005. [PubMed: 7826507]
167. Kim J, Landeira-Fernandez J, Decola J, Fanselow M. NMDA receptors mediate acquisition but not expression of Pavlovian fear conditioning. *Society for neuroscience Abstracts*. 1990
168. Kim JJ, DeCola JP, Landeira-Fernandez J, Fanselow MS. N-methyl-D-aspartate receptor antagonist APV blocks acquisition but not expression of fear conditioning. *Behavioral neuroscience*. 1991; 105(1):126. [PubMed: 1673846]
169. Kim JJ, Fanselow MS, DeCola JP, Landeira-Fernandez J. Selective impairment of long-term but not short-term conditional fear by the N-methyl-D-aspartate antagonist APV. *Behavioral neuroscience*. 1992; 106(4):591. [PubMed: 1354443]
170. Davis M, Rainnie D, Cassell M. Neurotransmission in the rat amygdala related to fear and anxiety. *Trends in neurosciences*. 1994; 17(5):208–214. [PubMed: 7520203]
171. Lynch G, Kessler M, Arai A, Larson J. Chapter The nature and causes of hippocampal long-term potentiation. *Progress in brain research*. 1990; 83:233–250. [PubMed: 2168058]
172. Nicoll R, Malenka R. Expression Mechanisms Underlying NMDA Receptor-Dependent Long-Term Potentiation. *Annals of the New York Academy of Sciences*. 1999; 868(1):515–525. [PubMed: 10414328]
173. Akers RF, Lovinger DM, Colley PA, Linden DJ, Routtenberg A. Translocation of protein kinase C activity may mediate hippocampal long-term potentiation. *Science*. 1986; 231(4738):587–589. [PubMed: 3003904]
174. Frey U, Frey S, Schollmeier F, Krug M. Influence of actinomycin D, a RNA synthesis inhibitor, on long-term potentiation in rat hippocampal neurons in vivo and in vitro. *The journal of physiology*. 1996; 490(3):703–711. [PubMed: 8683469]
175. Frey U, Krug M, Reymann KG, Matthies H. Anisomycin, an inhibitor of protein synthesis, blocks late phases of LTP phenomena in the hippocampal CA1 region in vitro. *Brain research*. 1988; 452(1):57–65. [PubMed: 3401749]
176. Klann E, Chen S-J, Sweatt JD. Persistent protein kinase activation in the maintenance phase of long-term potentiation. *Journal of biological chemistry*. 1991; 266(36):24253–24256. [PubMed: 1684790]
177. Krug M, Lössner B, Ott T. Anisomycin blocks the late phase of long-term potentiation in the dentate gyrus of freely moving rats. *Brain research bulletin*. 1984; 13(1):39–42. [PubMed: 6089972]
178. Nguyen PV, Abel T, Kandel ER. Requirement of a critical period of transcription for induction of a late phase of LTP. *Science*. 1994; 265(5175):1104–1107. [PubMed: 8066450]
179. Otani S, Marshall C, Tate W, Goddard G, Abraham W. Maintenance of long-term potentiation in rat dentate gyrus requires protein synthesis but not messenger RNA synthesis immediately post-tetani. *Neuroscience*. 1989; 28(3):519–526. [PubMed: 2710327]
180. Poser S, Storm DR. Role of Ca²⁺-stimulated adenylyl cyclases in LTP and memory formation. *International Journal of developmental neuroscience*. 2001; 19(4):387–394. [PubMed: 11378299]
181. Abel T, Nguyen PV. Regulation of hippocampus-dependent memory by cyclic AMP-dependent protein kinase. *Progress in brain research*. 2008; 169:97–115. [PubMed: 18394470]
182. Impey S, Smith DM, Obrietan K, Donahue R, Wade C, Storm DR. Stimulation of cAMP response element (CRE)-mediated transcription during contextual learning. *Nature neuroscience*. 1998; 1(7):595–601. [PubMed: 10196567]
183. Silva AJ, Kogan JH, Frankland PW, Kida S. CREB and memory. *Annual review of neuroscience*. 1998; 21(1):127–148.
184. Karadsheh MS, Shah MS, Tang X, Macdonald RL, Stitzel JA. Functional characterization of mouse $\alpha 4\beta 2$ nicotinic acetylcholine receptors stably expressed in HEK293T cells. *Journal of neurochemistry*. 2004; 91(5):1138–1150. [PubMed: 15569257]

185. Dajas-Bailador F, Soliakov L, Wonnacott S. Nicotine activates the extracellular signal-regulated kinase 1/2 via the $\alpha 7$ nicotinic acetylcholine receptor and protein kinase A, in SH-SY5Y cells and hippocampal neurones. *Journal of neurochemistry*. 2002; 80(3):520–530. [PubMed: 11905997]
186. Mann EO, Greenfield SA. Novel modulatory mechanisms revealed by the sustained application of nicotine in the guinea-pig hippocampus in vitro. *The journal of physiology*. 2003; 551(2):539–550. [PubMed: 12815181]
187. Welsby P, Rowan M, Anwyl R. Nicotinic receptor-mediated enhancement of long-term potentiation involves activation of metabotropic glutamate receptors and ryanodine-sensitive calcium stores in the dentate gyrus. *European journal of neuroscience*. 2006; 24(11):3109–3118. [PubMed: 17156372]
188. Welsby PJ, Rowan MJ, Anwyl R. Beta-amyloid blocks high frequency stimulation induced LTP but not nicotine enhanced LTP. *Neuropharmacology*. 2007; 53(1):188–195. [PubMed: 17610911]
189. Fujii S, Ji Z, Morita N, Sumikawa K. Acute and chronic nicotine exposure differentially facilitate the induction of LTP. *Brain research*. 1999; 846(1):137–143. [PubMed: 10536221]
190. Yamazaki Y, Fujii S, Jia Y, Sumikawa K. Nicotine withdrawal suppresses nicotinic modulation of long-term potentiation induction in the hippocampal CA1 region. *European journal of neuroscience*. 2006; 24(10):2903–2916. [PubMed: 17156213]
191. Fujii S, Ji Z, Sumikawa K. Inactivation of $\alpha 7$ ACh receptors and activation of non- $\alpha 7$ ACh receptors both contribute to long term potentiation induction in the hippocampal CA1 region. *Neuroscience letters*. 2000; 286(2):134–138. [PubMed: 10825655]
192. Yamazaki Y, Hamaue N, Sumikawa K. Nicotine compensates for the loss of cholinergic function to enhance long-term potentiation induction. *Brain research*. 2002; 946(1):148–152. [PubMed: 12133604]
193. Wu M, He Y, Guo F, Qi J. $\alpha 4\beta 2$ nicotinic acetylcholine receptors are required for the amyloid β protein-induced suppression of long-term potentiation in rat hippocampal CA1 region in vivo. *Brain research bulletin*. 2008; 77(2):84–90. [PubMed: 18602971]
194. Guan X, Nakauchi S, Sumikawa K. Nicotine reverses consolidated long-term potentiation in the hippocampal CA1 region. *Brain research*. 2006; 1078(1):80–91. [PubMed: 16564510]
195. Kutlu MG, Gould TJ. Nicotinic Receptors, Memory, and Hippocampus. *The Neurobiology and Genetics of Nicotine and Tobacco*: Springer. 2015:137–163.
196. Briscione MA, Jovanovic T, Norrholm SD. Conditioned fear associated phenotypes as robust, translational indices of trauma-, stressor-, and anxiety-related behaviors. *Frontiers in psychiatry*. 2014; 5
197. Clark RE, Squire LR. Classical conditioning and brain systems: the role of awareness. *Science*. 1998; 280(5360):77–81. [PubMed: 9525860]
198. Logue SF, Paylor R, Wehner JM. Hippocampal lesions cause learning deficits in inbred mice in the Morris water maze and conditioned-fear task. *Behavioral neuroscience*. 1997; 111(1):104. [PubMed: 9109628]
199. McEchron MD, Bouwmeester H, Tseng W, Weiss C, Disterhoft JF. Hippocampectomy disrupts auditory trace fear conditioning and contextual fear conditioning in the rat. *Hippocampus*. 1998; 8(6):638–646. [PubMed: 9882021]
200. Phillips R, LeDoux J. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behavioral neuroscience*. 1992; 106(2):274. [PubMed: 1590953]
201. Solomon PR, Vander Schaaf ER, Thompson RF, Weisz DJ. Hippocampus and trace conditioning of the rabbit's classically conditioned nictitating membrane response. *Behavioral neuroscience*. 1986; 100(5):729. [PubMed: 3778636]
202. Davis JA, Porter J, Gould TJ. Nicotine enhances both foreground and background contextual fear conditioning. *Neuroscience letters*. 2006; 394(3):202–205. [PubMed: 16260086]
203. Gould TJ. Nicotine produces a within-subject enhancement of contextual fear conditioning in C57BL/6 mice independent of sex. *Integrative physiological & behavioral science*. 2003; 38(2): 124–132. [PubMed: 14527181]

204. Gould TJ, Feiro O, Moore D. Nicotine enhances trace cued fear conditioning but not delay cued fear conditioning in C57BL/6 mice. *Behavioural brain research*. 2004; 155(1):167–173. [PubMed: 15325790]
205. Gould TJ, Wehner JM. Nicotine enhancement of contextual fear conditioning. *Behavioural brain research*. 1999; 102(1):31–39. [PubMed: 10403013]
206. Wehner J, Keller J, Keller A, Picciotto M, Paylor R, Booker T, et al. Role of neuronal nicotinic receptors in the effects of nicotine and ethanol on contextual fear conditioning. *Neuroscience*. 2004; 129(1):11–24. [PubMed: 15489024]
207. Davis JA, Gould TJ. $\beta 2$ subunit-containing nicotinic receptors mediate the enhancing effect of nicotine on trace cued fear conditioning in C57BL/6 mice. *Psychopharmacology*. 2007; 190(3):343–352. [PubMed: 17136517]
208. Davis JA, Kenney JW, Gould TJ. Hippocampal $\alpha 4\beta 2$ nicotinic acetylcholine receptor involvement in the enhancing effect of acute nicotine on contextual fear conditioning. *The journal of neuroscience*. 2007; 27(40):10870–10877. [PubMed: 17913920]
209. McCabe RE, Chudzik SM, Antony MM, Young L, Swinson RP, Zolvensky MJ. Smoking behaviors across anxiety disorders. *Journal of anxiety disorders*. 2004; 18(1):7–18. [PubMed: 14725865]
210. Portugal GS, Wilkinson DS, Kenney JW, Sullivan C, Gould TJ. Strain-dependent effects of acute, chronic, and withdrawal from chronic nicotine on fear conditioning. *Behavior genetics*. 2012; 42(1):133–150. [PubMed: 21822688]
211. André JM, Gulick D, Portugal GS, Gould TJ. Nicotine withdrawal disrupts both foreground and background contextual fear conditioning but not pre-pulse inhibition of the acoustic startle response in C57BL/6 mice. *Behavioural brain research*. 2008; 190(2):174–181. [PubMed: 18367257]
212. Davis JA, James JR, Siegel SJ, Gould TJ. Withdrawal from chronic nicotine administration impairs contextual fear conditioning in C57BL/6 mice. *The Journal of Neuroscience*. 2005; 25(38):8708–8713. [PubMed: 16177040]
213. Portugal GS, Gould TJ. Nicotine withdrawal disrupts new contextual learning. *Pharmacology biochemistry and behavior*. 2009; 92(1):117–123.
214. Raybuck J, Gould T. Nicotine withdrawal-induced deficits in trace fear conditioning in C57BL/6 mice—a role for high-affinity $\beta 2$ subunit-containing nicotinic acetylcholine receptors. *European journal of neuroscience*. 2009; 29(2):377–387. [PubMed: 19200240]
215. Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. *Neuron*. 1996; 16(5):905–908. [PubMed: 8630247]
216. Gould TJ, Portugal GS, André JM, Tadman MP, Marks MJ, Kenney JW, et al. The duration of nicotine withdrawal-associated deficits in contextual fear conditioning parallels changes in hippocampal high affinity nicotinic acetylcholine receptor upregulation. *Neuropharmacology*. 2012; 62(5):2118–2125. [PubMed: 22285742]
217. Marks M, Grady S, Collins A. Downregulation of nicotinic receptor function after chronic nicotine infusion. *The journal of pharmacology and experimental therapeutics*. 1993; 266(3):1268–1276. [PubMed: 8371136]
218. Wilkinson DS, Gould TJ. Withdrawal from chronic nicotine and subsequent sensitivity to nicotine challenge on contextual learning. *Behavioural brain research*. 2013; 250:58–61. [PubMed: 23660650]
219. Gould TJ, Wilkinson DS, Yildirim E, Blendy JA, Adoff MD. Dissociation of tolerance and nicotine withdrawal-associated deficits in contextual fear. *Brain research*. 2014; 1559:1–10. [PubMed: 24594018]
220. West R, Ussher M, Evans M, Rashid M. Assessing DSM-IV nicotine withdrawal symptoms: a comparison and evaluation of five different scales. *Psychopharmacology*. 2006; 184(3–4):619–627. [PubMed: 16308727]
221. Portugal GS, Kenney JW, Gould TJ. $\beta 2$ subunit containing acetylcholine receptors mediate nicotine withdrawal deficits in the acquisition of contextual fear conditioning. *Neurobiology of learning and memory*. 2008; 89(2):106–113. [PubMed: 17584502]

222. Davis JA, Gould TJ. Hippocampal nAChRs mediate nicotine withdrawal-related learning deficits. *European neuropsychopharmacology*. 2009; 19(8):551–561. [PubMed: 19278836]
223. Czemak C, Staley JK, Kasserman S, Bois F, Young T, Henry S, et al. $\beta 2$ Nicotinic acetylcholine receptor availability in post-traumatic stress disorder. *International Journal of Neuropsychopharmacology*. 2008; 11(3):419–424. [PubMed: 18190729]
224. Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld R, et al. Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *American journal of psychiatry*. 2001; 158(11):1920–1922. [PubMed: 11691703]
225. Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences*. 2006; 1071(1):67–79. [PubMed: 16891563]
226. Elias GA, Gulick D, Wilkinson DS, Gould TJ. Nicotine and extinction of fear conditioning. *Neuroscience*. 2010; 165(4):1063–1073. [PubMed: 19931599]
227. Kutlu MG, Gould TJ. Acute nicotine delays extinction of contextual fear in mice. *Behavioural brain research*. 2014; 263:133–137. [PubMed: 24487010]
228. Kutlu MG, Oliver C, Gould TJ. The effects of acute nicotine on contextual safety discrimination. *Journal of psychopharmacology*. 2014 0269881114552743.
229. Tian S, Gao J, Han L, Fu J, Li C, Li Z. Prior chronic nicotine impairs cued fear extinction but enhances contextual fear conditioning in rats. *Neuroscience*. 2008; 153(4):935–943. [PubMed: 18440720]
230. Tronson NC, Schrick C, Guzman YF, Huh KH, Srivastava DP, Penzes P, et al. Segregated populations of hippocampal principal CA1 neurons mediating conditioning and extinction of contextual fear. *The journal of neuroscience*. 2009; 29(11):3387–3394. [PubMed: 19295145]
231. Davis M, Falls WA, Gewirtz J. Neural systems involved in fear inhibition: Extinction and conditioned inhibition. *Contemporary issues in modeling psychopathology*: Springer. 2000:113–141.
232. Lissek S, Powers AS, McClure EB, Phelps EA, Woldehawariat G, Grillon C, et al. Classical fear conditioning in the anxiety disorders: a meta-analysis. *Behaviour research and therapy*. 2005; 43(11):391–424. [PubMed: 15680933]
233. Garfinkel SN, Abelson JL, King AP, Sripada RK, Wang X, Gaines LM, et al. Impaired contextual modulation of memories in PTSD: an fMRI and psychophysiological study of extinction retention and fear renewal. *The journal of neuroscience*. 2014; 34(40):13435–13443.
234. Steiger F, Nees F, Wicking M, Lang S, Flor H. Behavioral and central correlates of contextual fear learning and contextual modulation of cued fear in posttraumatic stress disorder. *International journal of psychophysiology*. 2015
235. Jovanovic T, Kazama A, Bachevalier J, Davis M. Impaired safety signal learning may be a biomarker of PTSD. *Neuropharmacology*. 2012; 62(2):695–704. [PubMed: 21377482]
236. Jovanovic T, Norrholm SD, Blanding NQ, Davis M, Duncan E, Bradley B, et al. Impaired fear inhibition is a biomarker of PTSD but not depression. *Depression and anxiety*. 2010; 27(3):244–251. [PubMed: 20143428]
237. Jovanovic T, Norrholm SD, Fennell JE, Keyes M, Fiallos AM, Myers KM, et al. Posttraumatic stress disorder may be associated with impaired fear inhibition: relation to symptom severity. *Psychiatry research*. 2009; 167(1):151–160. [PubMed: 19345420]
238. Christianson JP, Fernando AB, Kazama AM, Jovanovic T, Ostroff LE, Sangha S. Inhibition of fear by learned safety signals: a mini-symposium review. *The journal of neuroscience*. 2012; 32(41):14118–14124. [PubMed: 23055481]
239. Rougemont-Bücking A, Linnman C, Zeffiro TA, Zeidan MA, Lebron-Milad K, Rodriguez-Romaguera J, et al. Altered processing of contextual information during fear extinction in PTSD: an fMRI study. *CNS neuroscience & therapeutics*. 2011; 17(4):227–236. [PubMed: 20406268]
240. Calhoun PS, Wagner HR, McClernon FJ, Lee S, Dennis MF, Vrana SR, et al. The effect of nicotine and trauma context on acoustic startle in smokers with and without posttraumatic stress disorder. *Psychopharmacology*. 2011; 215(2):379–389. [PubMed: 21188354]
241. Rodgers R. Animal models of 'anxiety': where next? *Behavioural pharmacology*. 1997; 8(6–7): 477–496. [PubMed: 9832964]

242. Irvine EE, Cheeta S, File SE. Tolerance to nicotine's effects in the elevated plus-maze and increased anxiety during withdrawal. *Pharmacology biochemistry and behavior*. 2001; 68(2): 319–325.
243. Ouagazzal A-M, Kenny PJ, File SE. Modulation of behaviour on trials 1 and 2 in the elevated plus-maze test of anxiety after systemic and hippocampal administration of nicotine. *Psychopharmacology*. 1999; 144(1):54–60. [PubMed: 10379624]
244. Ericson M, Olausson P, Engel JA, Söderpalm B. Nicotine induces disinhibitory behavior in the rat after subchronic peripheral nicotinic acetylcholine receptor blockade. *European journal of pharmacology*. 2000; 397(1):103–111. [PubMed: 10844104]
245. Irvine E, Cheeta S, File S. Time-course of changes in the social interaction test of anxiety following acute and chronic administration of nicotine. *Behavioural pharmacology*. 1999; 10(6–7):691–697. [PubMed: 10780511]
246. File SE, Kenny PJ, Ouagazzal A-M. Bimodal modulation by nicotine of anxiety in the social interaction test: role of the dorsal hippocampus. *Behavioral neuroscience*. 1998; 112(6):1423. [PubMed: 9926824]
247. File SE, Cheeta S, Kenny PJ. Neurobiological mechanisms by which nicotine mediates different types of anxiety. *European journal of pharmacology*. 2000; 393(1):231–236. [PubMed: 10771018]
248. Elliott BM, Faraday MM, Phillips JM, Grunberg NE. Effects of nicotine on elevated plus maze and locomotor activity in male and female adolescent and adult rats. *Pharmacology biochemistry and behavior*. 2004; 77(1):21–28.
249. O'Neill AB, Brioni JD. Benzodiazepine receptor mediation of the anxiolytic-like effect of (–)-nicotine in mice. *Pharmacology biochemistry and behavior*. 1994; 49(3):755–757.
250. Ennaceur A, Michalikova S, Bradford A, Ahmed S. Detailed analysis of the behavior of Lister and Wistar rats in anxiety, object recognition and object location tasks. *Behavioural brain research*. 2005; 159(2):247–266. [PubMed: 15817188]
251. Brioni JD, O'Neill AB, Kim D, Buckley MJ, Decker MW, Arneric SP. Anxiolytic-like effects of the novel cholinergic channel activator ABT-418. *Journal of pharmacology and experimental therapeutics*. 1994; 271(1):353–361. [PubMed: 7965735]
252. Yohn NL, Turner JR, Blendy JA. Activation of $\alpha 4\beta 2^*/\alpha 6\beta 2^*$ nicotinic receptors alleviates anxiety during nicotine withdrawal without upregulating nicotinic receptors. *Journal of Pharmacology and Experimental Therapeutics*. 2014; 349(2):348–354. [PubMed: 24627467]
253. McGranahan TM, Patzlaff NE, Grady SR, Heinemann SF, Booker T. $\alpha 4\beta 2$ nicotinic acetylcholine receptors on dopaminergic neurons mediate nicotine reward and anxiety relief. *The journal of neuroscience*. 2011; 31(30):10891–10902. [PubMed: 21795541]
254. Picciotto M, Zoli M, Zachariou V, Changeux J-P. Contribution of nicotinic acetylcholine receptors containing the beta 2-subunit to the behavioural effects of nicotine. *Biochemical society transactions*. 1997; 25(3):824–829. [PubMed: 9388554]
255. Labarca C, Schwarz J, Deshpande P, Schwarz S, Nowak MW, Fonck C, et al. Point mutant mice with hypersensitive $\alpha 4$ nicotinic receptors show dopaminergic deficits and increased anxiety. *Proceedings of the National Academy of Sciences*. 2001; 98(5):2786–2791.
256. Ross SA, Wong JY, Clifford JJ, Kinsella A, Massalas JS, Horne MK, et al. Phenotypic characterization of an $\alpha 4$ neuronal nicotinic acetylcholine receptor subunit knock-out mouse. *The journal of neuroscience*. 2000; 20(17):6431–6441. [PubMed: 10964949]
257. Paylor R, Nguyen M, Crawley JN, Patrick J, Beaudet A, Orr-Urtreger A. $\alpha 7$ nicotinic receptor subunits are not necessary for hippocampal-dependent learning or sensorimotor gating: a behavioral characterization of *Acra7*-deficient mice. *Learning & memory*. 1998; 5(4):302–316. [PubMed: 10454356]
258. Pandya AA, Yakel JL. Activation of the $\alpha 7$ nicotinic ACh receptor induces anxiogenic effects in rats which is blocked by a 5-HT 1a receptor antagonist. *Neuropharmacology*. 2013; 70:35–42. [PubMed: 23321689]

Figure 1. Brain regions involved in the anxiety disorders

The hypothalamic–pituitary–adrenal (HPA) axis is directly influenced by the amygdala and hippocampus whereas the prefrontal cortex indirectly modulates HPA axis activity through its inhibitory control over the amygdala.

Figure 2. Nicotinic modulation of the CREB-dependent gene transcription pathway
 Glutamate binds to NMDARs, leading to Ca^{2+} influx and PKA phosphorylation, which in turn, directly and indirectly through ERK1/2, activates CREB. Acetylcholine also triggers a Ca^{2+} influx by binding to the nAChRs, which can modulate this cell signaling cascade.

Table 1

Effects of acute nicotine on anxiety

Irvine et al. (2001)	Hooded Lister rats	EPM	0.1 mg/kg s.c.	30 mins	Anxiogenic
Ouagazzal et al. (1999)	Hooded Lister rats	EPM	0.5 and 1 mg/kg i.p.	5 mins	Anxiogenic
Elliott et al., (2004)	Sprague – Dawley rats	EPM	0.1, 0.5 and 1 mg/kg s.c.	10 mins	Anxiogenic
O'Neill and Brioni (1994)	Wistar rats	EPM	0.3 mg/kg i.p.	30 mins	Anxiolytic
Ericson et al. (2000)	CD1 mice	EPM	0.35 mg/kg s.c.	Immediate	Anxiolytic
Irvine et al. (1999)	Hooded Lister rats	Social Interaction	0.1 mg/kg s.c.	30 mins	Anxiolytic
				5 mins	Anxiogenic
File et al. (1998)	Hooded Lister rats	Social Interaction	0.01 and 0.1 mg/kg i.p.	3 mins	Anxiolytic
			0.5 and 1 mg/kg i.p.		Anxiogenic

Table 2

Involvement of specific nAChRs in anxiety-like behavior

Brioni et al., (1994)	$\alpha 4\beta 2$	$\alpha 4\beta 2$ nAChR agonist, ABT-418	EPM	Anxiolytic
McGranahan et al. (2011)	$\alpha 4\beta 2$	Selective $\alpha 4\beta 2$ nAChR lesions	EPM	Anxiogenic
Picciotto et al. (1997)	$\beta 2$	$\beta 2$ KO mice	EPM / Light/Dark Box / Mirrored Chamber	No Effect
Labarca et al. (2001)	$\alpha 4$	$\alpha 4$ heterozygous mice	EPM	Anxiogenic
Ross et al. (2000)	$\alpha 4$	$\alpha 4$ KO mice	EPM	Anxiogenic
Paylor et al. (1998)	$\alpha 7$	$\alpha 7$ KO mice	Open Field	Anxiolytic
Pandya and Yakel (2013)	$\alpha 7$	$\alpha 7$ -selective agonist, PNU-282987	Open Field	Anxiogenic
Yohn et al. (2014)	$\alpha 7$	Partial $\alpha 7$ nAChR agonist, ABT-107	Novelty-Induced Hypophagia	Anxiolytic
	$\alpha 4\beta 2$	Partial $\alpha 4\beta 2$ nAChR agonist, ABT-089		Anxiogenic