# Potential Mechanisms Underlying the Facilitation of Fear Memory Extinction by Cotinine

**Valentina Echeverria[1,2,3*] and Alex Iarkov[1]**

[1]*Research and Development Service, Department of Veterans Affairs, Bay Pines VA Healthcare System, Bay Pines Florida 33744, USA.*
[2]*Research Service, Department of Veterans Affairs, Tampa, Florida 33612, USA.*
[3]*Department of Molecular Medicine, University of South Florida, Tampa, Florida 33647, USA.*

*Authors' contributions*

*This work was carried out in collaboration between both authors. Author VE wrote the manuscript, performed literature searches and participated of the scientific discussion of the ideas presented. Author AI performed literature searches and participated of the scientific discussion of the ideas presented. Both authors read and approved the final manuscript.*

**Review Article**

## ABSTRACT

Posttraumatic stress disorder is a type of anxiety disorder that manifests after exposure to a traumatic event that was perceived as life threatening. Individuals with posttraumatic stress disorder have a deficiency in the extinction of fear memory. Moreover, environmental cues similar to the ones present during the trauma induced abnormal symptoms of fear and anxiety. Current therapies only help a small percentage of patients with this condition, thus pharmacological interventions to reduce the conditioned fear response are needed. Nicotine and its main metabolite, cotinine, have been shown to help in the extinction of fear memories in animal models. In this article we will discuss potential mechanisms and brain regions that may be underlying the effect of cotinine in enhancing the extinction of fear response after fear conditioning. The relevance of these mechanisms in posttraumatic stress disorder is discussed.

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*\*Corresponding author: Email: echeverria.valentina@gmail.com;*

## 1. INTRODUCTION

Posttraumatic stress disorder (PTSD) is a devastating condition that imposes a big burden for the individual and society, affecting millions of people around the world [1,2]. According to guidance of the American Psychiatric Association, PTSD symptoms include intrusive symptoms (flashbacks, nightmares, and intrusive thoughts), avoidance of trauma-related stimuli, persistent negative alterations in cognition and mood, numbing of general responsiveness, and hyperarousal (hypervigilance, irritability, exaggerated startle response, aggressive behavior, and reckless or self-destructive behavior) [3-6]. The failure to extinguish traumatic memories is one of the most devastating symptoms of PTSD that forces the patient to continue re-experiencing the trauma, sometimes for the rest of their lives. These memories, triggered by trauma-associated environmental cues, provoke fear and anxiety in patients with PTSD. Behaviors during dissociative flashbacks are unintended and can be abrupt. Sometimes a traumatic event that is reenacted while the person is under a dissociated state leads to aggressive behavior with enormous personal consequences. Individuals with PTSD have augmented psychophysiological and negative affect responses to trauma-related stimuli, display more attention to negative emotional stimuli [7], have more electrocortical responses to sad faces [8], and show altered startle responses [9-12].

PTSD is also characterized by functional and structural changes in the brain [13], including the neuronal fear circuitry involving brain regions such as the amygdala (AMY), hippocampus, medial prefrontal cortex (mPFC), dorsal anterior cingulate cortex, hypothalamus, and insular cortex [14-17]. These alterations are thought to underlie many of the PTSD symptoms and the impairment of FE. Abnormal morphological and functional changes of the hippocampus have been reported to be present in individuals experiencing PTSD. In addition, local hippocampal lesions diminish the context-dependence of extinction in rodents [18,19]. This and other research evidence suggests that the hippocampus is involved in FE [20-25]. Numerous functional imaging studies have shown an altered pattern of neuronal activity in several of these regions among people with PTSD [13,26-30]. For example, a functional magnetic resonance (fMRI) study showed that PTSD patients have an augmented AMY reactivity to fearful faces and coincident decreased mPFC reactivity as compared to non-PTSD controls [31]. In addition, LeDoux *et al* observed that lesions of the ventral mPFC (vmPFC) impaired extinction, and were the first to propose that prefrontal inputs to the amygdala might modulate the expression of conditioned fear [32,33]. PTSD symptoms and the failure in FE correlate with hormonal changes such as the over-activation of the hypothalamus-pituitary-adrenal axis, and pathological changes of several neurotransmitter systems such as the sympathetic, dopaminergic, and serotoninergic systems [34].

According to current hypotheses, a hyporesponsive mPFC (a region involved in cognitive control of emotional responses) fails to inhibit AMY (a region involve in emotional memory and fear responses) resulting in a failure of FE and an exaggerated fear response [13,14,16]. The environment has a major role in regulating the acquisition, extinction, and reinstatement of fear responses [35]. FE can be stimulated by psychotherapy treatments, and studies on molecular and cellular mechanisms of FE have shown that targeting specific signaling targets can be useful in facilitating FE during psychotherapy. For example, behavioral therapy of phobias and PTSD showed to be more effective when facilitated by the partial N-methyl-D-aspartate receptor agonist, D-cycloserine [36,37]. Also, ligands stimulating the endogenous cannabinoid system and glucocorticosteroids have been used as augmentation therapies for exposure procedures during cognitive behavioral therapy for anxiety disorders [38]. Nonetheless, the occurrence of reinstatement and the fact that a large

percentage of individuals are not responsive to current therapies, new pharmacological approaches, or adjunctive interventions manifests the need for a treatment to reduce the impact of conditioned cues in eliciting these maladaptive responses.

Fear conditioning (FC) in rodents is an experimental model of associative learning that mimics the behavioral, anatomical, and functional changes in the brain induced by high levels of stress. FC has been extensively used to investigate the pathological mechanisms underlying PTSD [39] and the associated failure in FE [39-41]. Furthermore, because this paradigm can be tested across species, FC is an ideal translational tool to discover new therapies directed to enhance FE [42-44]. To induce FC, the experimental animals are exposed to a conditioned stimulus (CS) that is paired with a reinforcing unconditioned stimulus (US, foot shock). The CS consists of a sound in the cued FC and the conditioning chamber (the context) in the contextual FC. To investigate contextual FC, twenty-four hours following FC, the animals are subjected to a retrieval session that consists of a one-time exposure to the chamber to assess the acquisition of fear memories. After this initial testing, to induce contextual memory extinction, the experimental animals are repeatedly exposed to the training chamber (Context, US) in absence of the US, and the fear response (freezing behavior) is measured. Contextual FE is defined as the decrease in fear response after repeated exposure to the CS (Context), which no longer predicts the aversive US and is expressed as an almost total disappearance of the fear response to the CS. In patients with PTSD, FE is the therapeutic goal of clinical interventions such as exposure therapy aimed to change symptoms such as abnormal arousal and avoidance occurring in response to certain environmental cues. However, fear can reappear due to different mechanisms, including reinstatement (RI), renewal, and spontaneous recovery[13]. For example, contextual associations with the original conditioning event can trigger the RI of trauma-associated fear responses after FE is achieved. RI is usually triggered by the presentation of the US. Also, a renewal of fear can happen after FE by exposure to a non-extinguished CS that reinstates the conditioned fear responses to an extinguished CS [45]. Reinstatement and renewal are big problems in the treatment of PTSD [46].

People with PTSD show elevated rates of cigarette smoking (40%–63%) when compared to population averages (20%–30%) [47-49]. This evidence has permitted researchers to speculate that people with PTSD smoke to alleviate their symptoms [50,51]. Recently, an association between PTSD symptoms clusters and cigarette smoking has been found [52,53]. Studies on the effect of nicotine over PTSD pathology in humans and rodents have shown a positive effect of nicotine on FE [51]. In the search for therapies to enhance FE, and considering that most of nicotine is transformed to cotinine, its more stable metabolite [50]; we studied and characterized the effect of the main metabolite of nicotine, cotinine, on anxiety and FE in mice subjected to FC [54]. We studied cotinine to understand whether nicotine effects are in part mediated by cotinine actions, and have been motivated by studies showing a strong association between PTSD and tobacco dependence [2,48,49,55]. In this overview, we discuss the similarities and differences of the effect of cotinine compared to nicotine on FE as well as the potential mechanism(s) involved in the enhancement of FE by cotinine.

## 2.1 Effects of Cotinine and Nicotine on Fear Extinction: Similarities and Differences

### 2.1.1 Nicotine and fear extinction

The study of the effect of nicotine on FC in animal models showed that nicotine enhanced contextual learning [56-58]. Later studies investigated the effect of cotinine over conditional reinstatement of conditioned fear. In the first approach, the FC and contextual FE trials were conducted in the same context. In the second approach, the FC and FE trials were conducted in different contexts. Using these approaches, it was found that nicotine administered before training did not alter extinction, but when administered prior to the extinction sessions it enhanced extinction [51]. However, nicotine administered before conditioning and during extinction, decreased extinction. During the analysis of fear renewal, it was found that when the extinction sessions were conducted in the training context, nicotine administered before extinction blocked context-induced renewal of conditioned fear, but when it was administered during training and extinction, nicotine enhanced the context renewal of conditioned fear [51]. The authors hypothesized that nicotine, when administered at both training and extinction would interfere with extinction by strengthening contextual fear associations. Since nicotine has pro-cognitive effects [59], it is thought that nicotine enhances contextual learning by promoting learning and memory [60].

Clinical studies have shown that nicotine can modulate fear-related behaviors, and that the final effect correlates with functional changes in the brain fear network. One of these studies showed that in smoker participants, nicotine reduced the disruptive effects caused by negative stimuli and the anxiety when negative pictures were presented in combination with neutral pictures. Also, nicotine reduced the depressive effect when the participant had an attentional choice between positive and negative stimuli [61]. These beneficial effects can be associated with nicotine-induced changes in brain regions involved in fear responses. In this regard, neuroimaging studies showed that nicotine changes the activity of the limbic regions that mediate emotional information processing such as the amygdala and PFC [62,63]. In a separate 12-hour nicotine deprivation study, Feldner et al. examined the involvement of nicotine in mediating the association between PTSD and the responses to bodily arousal in 52 participants [64]. The authors found that when compared to control participants, persons with PTSD responded to a 3-min voluntary hyperventilation procedure with greater increases in anxiety and more intense cognitive and physical panic symptoms, despite no group differences in physiological arousal. Nicotine withdrawal intensified this effect. These results strongly suggest that nicotine also modulates the anxious and fearful reactivity to bodily arousal in smokers with PTSD [64]. In a more recent pilot clinical study, McClernon et al. [31] evaluated the effect of nicotine on emotional reactivity in PTSD and non-PTSD smokers using fMRI scanning 2 hours after application of a 21 mg transdermal nicotine or placebo patch. During scanning, participants viewed emotional or neutral face stimuli. A significant effect of nicotine was observed in brain regions involved in emotional and facial feature processing. As in previous studies, PTSD was associated with larger brain responses to emotional face stimuli in the amygdala and PFC regions. The results suggest a greater reactivity to emotional cues in the sulcus frontal gyrus, a region of the PFC, when smokers with PTSD were in a nicotine-deprived state. Across groups, nicotine increased brain activation in response to fearful/angry faces (compared to neutral faces) in ventral caudate. These findings suggest that nicotine differentially modulates negative information processing in PTSD and non-PTSD smokers [31].

### 2.1.2 Cotinine effect on fear extinction

Cotinine is an alkaloid present in tobacco leaves and is the main metabolite of nicotine [50]. Because most nicotine is rapidly metabolized to cotinine in the body, we hypothesized that the underlying effects of cotinine in the brain could explain some of its effects on extinction. Several cellular and animal studies have shown that cotinine is neuroprotective and a memory enhancer [65-69]. The cotinine-induced neuroprotective and memory enhancing effects in Alzheimer's disease (AD) mice was accompanied by stimulation of Akt and inhibition of its downstream target, the glycogen synthase kinase 3β (GSK3β) in the hippocampus and neocortex. Interestingly, previous reports have shown that GSK3β inhibition significantly stimulated axonal growth and promoted behavioral recovery after CNS injury in adult female rats [70] as well as elicited similar neuroprotective and cognitive effects in several neurological and psychiatric disorders [71-74]. Moreover, memory enhancers and activators of PI3K, the main activator of the Akt/GSK3β pathway in the brain, are thought to be useful in promoting FE [75-77]. Since cotinine is a memory enhancer and also stimulates the Akt/GSK3β pathway, we speculated that cotinine would facilitate FE. To investigate the effect of cotinine on FC and FE, adult male mice were treated before and during or after FC with cotinine *via* gavage and then subjected to daily extinction trials (days 3-6) [54]. The analysis of freezing behavior after FC showed that in contrast with nicotine, cotinine did not enhance FC, nor did it diminish the acquisition or initial consolidation of contextual fear memory in mice. However, cotinine enhanced FE and decreased anxiety in the mice after FC, as tested in the elevated plus maze and open field tests [54] (Fig.1). Cotinine-treated mice showed a faster decrease in freezing behavior than vehicle-treated mice during the extinction trials (repeated and sequential daily exposure to the conditioning chamber). This evidence suggests that cotinine has a different effect on fear memory than nicotine and has potential to be used before exposure to stressful events without exacerbating the post-trauma and fear-associated behavior.
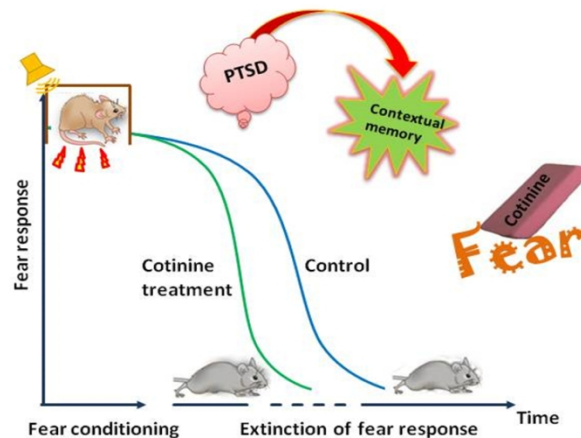


**Fig. 1. Cotinine enhanced fear extinction in mice** *The figure represents the facilitation of contextual fear extinction by cotinine.*

Furthermore, in absence of daily extinction trials, when cotinine was administered immediately after the retention trial and continuously throughout the experiment, it decreased the fear response (78% reduction) in mice re-exposed to the conditioning chamber eight days after the retention test [54]. At the molecular level, we found that

cotinine increased the expression of the activated form of the extracellular signal-regulated kinases 1/2(ERKs) in the hippocampus. The activation of ERKs in the hippocampus is a molecular event previously observed during FE and has been shown that this activation is required for extinction [77,78].

### 2.1.3. Brain regions involved in fear extinction

Numerous investigations have defined several regions involved in the consolidation and extinction of fear memories. Evidence suggests that the AMY, mPFC, and hippocampus modulate FE [79-82]. From these studies, we have learned that the mPFC facilitates extinction by reducing AMY output. Subjects with PTSD have reduced mPFC activity during trauma recall and a hyperresponsive AMY. According to current hypotheses about PTSD, a hyporesponsive PFC fails to inhibit amygdalar activity, and this failure results in a deficit in FE and emotional balance [83]. The AMY is considered the keystone of the FE process. Although firing of AMY neurons is important for the retrieval of conditioned fear memories after the extinction of conditioned fear, their activity is inhibited by the mPFC [84]. Several studies suggest that FE is facilitated by projections from the infralimbic region (IL) of the mPFC to the intercalated nuclei (ICNs) of the AMY [79,80]. The ICNs are clusters of small GABAergic neurons that are found around the periphery of the amygdalar basolateral nuclear complex [85]. The ICNs send GABAergic projections to the central nucleus that can inhibit AMY outputs to both hypothalamic and brainstem regions and consequently diminish the expression of fear, [79,85-87] thus the inhibitory control of the mPFC over AMY is a possible mechanism of FE [80]. Also, the hippocampus mediates spatial and contextual memory [88], and *in vivo* studies indicate that the hippocampus processes contextual information during FC and FE. Concurrent with this function, the hippocampus substantially innervates both the AMY [89] and mPFC [90]. Using neuroimaging techniques, several psychological processes that are relevant to PTSD, including fear conditioning, habituation, extinction, cognitive-emotional interactions, and self-related and social emotional processing have been investigated. These studies have revealed that the mPFC is involved in the "contextualization" of stimuli, which its alteration may underline the appearance of PTSD symptoms [13].

New imaging techniques have permitted researchers to assess structural and functional changes in the neural circuit of fear in PTSD patients [91-95]. Recent studies using fMRI have shown that patients with PTSD show changes in this circuit. For example, patients with PTSD resulting from exposure to motor vehicle accidents showed higher activation in the AMY, precuneus, and fusiform gyrus but lower activation in the inferior frontal cortex insula and left supramarginal gyrus than non-PTSD controls [91]. Another study, performed on forty African-American women with civilian trauma with and without PTSD, found that relative to non-PTSD controls, women with PTSD showed an enhanced AMY response to fearful stimuli. Right amygdala activation correlated positively with the severity of hyperarousal symptoms in the PTSD group. Also, patients with PTSD exhibited diminished functional connectivity between the right AMY and left vmPFC [92].

Also, new evidence, obtained using MRI, showed that veterans with PTSD had smaller hippocampal, caudal anterior cingulate, insula, and corpus callosum volumes than non-PTSD controls. In addition, it has been found that veterans with PTSD had a reduced volume of several brain structures (hippocampus, caudal anterior cingulate, insula, and corpus callosum) than veterans with remitted PTSD as well as smaller hippocampal and caudal anterior cingulate volumes than veterans without PTSD. Interestingly, there was no significant volume differences between veterans with remitted PTSD compared to non-PTSD

controls [96]. Furthermore, changes in the amygdalar volume are considered a susceptibility factor for PTSD [92,96-98] and other psychiatric disorders [99,100].

Brain imaging techniques have permitted researchers not only to be able to assess structural and functional changes in the brain associated with PTSD, but also the reversion of these structural and functional changes with treatment [91,101,102]. One of these studies, using single photon emission computed tomography (SPECT) imaging, found significant changes in the anterior cingulate cortex (ACC) and hippocampus after 12 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs) [103]. Another study, using magnetic resonance imaging (MRI) to study changes in brain structure in PTSD patients before and after treatment with paroxetine, indicated that improvement of PTSD symptoms such as verbal declarative memory deficits, positively correlated with an increase in the main hippocampal volume [101]. We speculate that cotinine may help promote the inhibition of the AMY by projections from the mPFC by means of stimulation of the presynaptic $\alpha$7nAChRs, as discussed below in the following section.

### 2.1.4 The role of the $\alpha$7nAChRs in the prefrontal cortex in fear extinction and cotinine

The $\alpha$7nAChRs play a key role in mediating FE. For example, these receptors, located in the presynaptic glutamatergic neurons that project from the mPFC to GABA neurons in the AMY, may facilitate the inhibition of the AMY by the mPFC and consequently FE [13]. Also, the stimulation of nicotinic receptors in the AMY can affect fear responses. For example, it has been shown that scopolamine (a muscarinic antagonist) and mecamylamine (a nicotinic antagonist) induced a dose-dependent impairment of passive avoidance [104]. The effects of the cholinergic antagonists on passive avoidance performance were smaller in amygdala-lesioned rats than in the controls, indicating an involvement of the cholinergic receptors in the AMY on this effect. Nicotine, a nicotinic agonist, and arecoline, a muscarinic agonist, restored passive avoidance performance in nucleus basalis-lesioned rats but not in the nucleus basalis plus amygdala-lesioned rats. These results suggested that the nucleus basalis cholinergic projection may modulate passive avoidance performance via amygdaloid muscarinic and nicotinic receptors [104]. In fact, nicotine induced a dose-dependent increase in neuronal activity in a distributed system of brain regions, including the nucleus accumbens, AMY, cingulate, and frontal lobes [105]. Furthermore, a recent study showed that exposure to nicotine during pre- and early postnatal development induced anxiety on adult rats and blocked extinction learning in a FC paradigm. Analysis of mRNA for the $\alpha$4, $\alpha$7, and $\beta$2 subunits of the nAChRs revealed lower expression of these subunits in the adult hippocampus and mPFC following nicotine exposure [106]. Therefore, this evidence suggests that pro-cholinergic compounds may be useful to stimulate the PFC projections that inhibit the AMY. The use of activators of these receptors to enhance FE is a plausible therapeutic strategy. However, the persistent activation by agonists leads to the desensitization of the receptors and consequently very short-term effects. According to a recent report, cotinine's effects on fear extinction are at least in part mediated by nAChRs in the hippocampus [107]. This idea is coherent with evidence suggesting that cotinine is a positive allosteric modulator (PAM) of the $\alpha$7nAChRs [108]. These PAMs may enhance the activation of the $\alpha$7nAChR by its endogenous and exogenous agonists and at the same time prevent receptor desensitization [109-111]. In agreement with these results, cotinine stimulated the Akt/GSK3$\beta$ pathway, downstream of the $\alpha$7nAChRs, in the hippocampus and PFC of these mice. Cotinine as an allosteric modulator may instead enhance the activation of these receptors by their agonists without inducing their desensitization.

The facilitation of FE, induced by cotinine, was accompanied by the activation of the extracellular regulated kinases 1/2 (ERKs) in the hippocampus of mice. ERKs are signaling factors downstream of the $\alpha$7nAChR that play an important role in both mediating learning and memory processes and are required for FE. Also, the involvement of the activation of the expression of the NR2B subunits of the NMDA receptors has been suggested as a mechanism of action of vorinostat, a histone deacetylase (HDAC) inhibitor [112]. The hippocampus innervates both the AMY [89] and mPFC [113] and processes contextual information during FC and FE [13]. Control of fear extinction by context involves interactions between the dorsal hippocampus and the lateral nucleus of the amygdala [45].

We hypothesized that cotinine may facilitate FE by positively modulating the $\alpha$7nAChRs in the AMY, mPFC, and/or hippocampus. In the mPFC, by modulating this receptor, cotinine can stimulate glutamate release from neurons from the mPFC, innervating gamma-aminobutyric acid, (GABA)-ergic neurons, in the ICN of the AMY. The activation of these GABAergic neurons in turn will facilitate FE by enhancing the inhibitory control on the AMY (Fig.2).
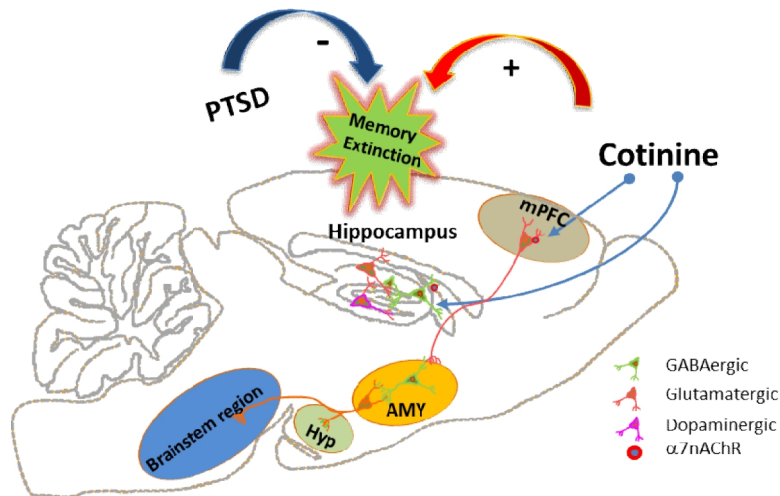


**Fig. 2. Scheme showing the potential effect of cotinine on fear responses by stimulating the inhibition of AMY and the activation of the hippocampus**
*mPFC, medial prefrontal cortex, NAc, nucleus accumbens; VTA,Ventral tegmental area; DDRn, Dorsal raphe nucleus.*

Nicotinic acetylcholine receptors containing the $\alpha$7 receptor gene product are highly expressed in GABAergic interneurons in the hippocampus and other brain regions [114]. GABA is an inhibitory neurotransmitter, controlling excitability in most areas of the brain. During stress, alterations in GABA neurotransmission have been implicated in the pathogenesis of anxiety disorders, including PTSD. Low plasma GABA levels after trauma are predictive of ensuing development of PTSD [115]. SPECT imaging with the benzodiazepine ligand, ($^{123}$I) iomazenil, showed a reduction of the benzodiazepine-GABA (A) receptor in the PFC in combat-related PTSD. A more recent study, using positron emission tomography (PET) and ($^{11}$C) flumazenil to investigate GABA receptors binding in the brain of Norwegian veterans, showed that veterans with PTSD have a reduced GABA receptors binding in the cortex, hippocampus, and thalamus compared to veterans without

PTSD [115]. The importance of the control of GABA-ergic transmission on fear response has been known for many decades. A classical study by Strzelczuk and Romaniuk [116] showed that intrahypothalamic infusions of d-tubocurarine (DT, antagonist for nAChRs) and bicuculline (BM, antagonist of the GABA receptors) in a cat produced a fear reaction with an important increase in the noradrenergic system activity in the emotional brain areas (hypothalamus, midbrain, amygdala) and frontal cortex at the time of the fear drive. Similar behavioral effects, evoked by DT and BM, suggested that the fear responses were derived from the action of these drugs on the GABA receptor [116]. This evidence supports the view that cholinergic drugs must be targeting the pathobiology of PTSD by directly or indirectly stimulating GABA-ergic neurotransmission.

Recently, a comparative study investigating the effect of nicotine, cotinine, mecamylamine (MEC, a general nicotinic receptor antagonist), methyllycaconitine (MLA, $\alpha$7 nicotinic acetylcholine receptor ($\alpha$7nAChR) antagonist), and dihydro-beta-eritroidine (DH$\beta$E, $\alpha$4$\beta$2 nAChR antagonist) on memory extinction in rats has been reported [107]. These results showed that the intrahippocampal infusion of nicotine, cotinine, or DH$\beta$E enhanced FE, diminishing the step-down latencies during the extinction trials. MLA or MEC did not affect extinction. These results are in agreement with the observed effect of cotinine in FE in mice but make it difficult to understand the role of the nAChRs on its effects. However, because the cholinergic modulators were infused immediately after FC, and not immediately after FE, it is possible that these antagonists affected other mechanisms different from extinction such as memory consolidation. In agreement with our results, the authors found an increase in the activity of ERKs in the hippocampus induced by cotinine.

Taken together, these findings support the view that cotinine may be in part responsible for the perceived anxiolytic effects of tobacco and be an underlying form of self-medication in individuals with PTSD [50]. More importantly, this evidence suggests that cotinine has the potential to be useful as an adjuvant to exposure therapy.

## 3. DISCUSSION

People suffering from PTSD have a higher prevalence of tobacco consumption than the general population, and it has been postulated that PTSD patients smoke to alleviate their symptoms [50,52,53,55,117]. Also, new studies have found a strong correlation between the severity of emotional numbing and smoking behavior in individuals with PTSD. Consistent with this view, two components present in tobacco leaves, nicotine and cotinine, both enhance FE in mice models of PTSD [50,51,54,107,118]. The mechanisms underlying these effects are currently under investigation. However, we hypothesize that cotinine may facilitate extinction by stimulating the glutamatergic neurons from the mPFC projecting to the AMY. Moreover, a deficiency in glutamatergic neurotransmission, induced by genetic defects, has been postulated to have a causal role in the smoking behavior of patients with PTSD or other psychiatric conditions.

Forgetting a trauma memory is considered a new learning process. Therefore, memory enhancers may facilitate fear extinction by helping to "overwrite" the old trauma memories with new memories [75,119], thus another possible mechanism of action of cotinine in helping the extinction of contextual fear memory is the stimulation of brain plasticity in regions involved in both learning and memory such as the hippocampus and mPFC [119]. In fact, in addition to the potential effect of cotinine in the mPFC, a positive modulation by cotinine of GABA neurons can be instrumental in facilitating the activation of glutamatergic

neurons in the hippocampus, which participate in the new learning process during the extinction of fear memory.

New compounds enhancing FE may be promising tools for the treatment of PTSD. Clinical studies investigating the efficacy of new agents for PTSD have mostly been focused in the glucocorticoid corticotropin-releasing factor and norepinephrine signaling modulators for the prevention and treatment of PTSD. These treatment approaches are directed to modulate the effect of stress on fear memory consolidation after trauma [38,120-122]. Another approach that has been investigated includes the modulation of the levels or activity of other neuronal compounds such as dopamine [123], endocannabinoids [38], gamma-amino butyric acid [124], neurokinin/Substance P, neurosteroids, and oxytocin [125,126]. Also, cognitive enhancers targeting mechanisms of conditioned fear extinction and reconsolidation such as modulators of glutamate signaling, including glycine transporter inhibitors, glycine agonists, or positive modulators of glutamate receptors have been investigated [120].

Cognitive behavioral therapy, including exposure and cognitive restructuring, is broadly practiced to treat PTSD. Extinction-based exposure therapy consists of confronting traumatic memories or related cues that trigger fear responses related to the trauma to elicit the extinction of fear [112,127,128]. This exposure therapy is often supplemented with cognitive procedures intended to diminish thoughts of guilt and other cognitive distortions. In spite of some pharmacological and psychotherapy approaches that are successful in managing PTSD symptoms such as the extinction-based exposure therapy, relapse is common and can occur, thus is important to investigate adjunctive or single therapies that can prevent the renewal, reinstatement, or spontaneous recovery of extinguished fear. In this direction and to increase the efficacy of psychotherapy, many research teams are investigating medication-enhanced psychotherapy (MEP) [75,125]. These medications, when provided before or after exposure therapy, may enhance the therapeutic outcomes in PTSD patients by means of both strengthening of learning and new memories, consequently inhibiting the reconsolidation of fear memories. Ideally, these drugs in addition to the enhancement of fear extinction may facilitate engagement of PTSD patients with psychotherapy by reducing the enhancement of anxiety induced by the exposure therapy [125]. The improvement of cognitive functions is regarded as a useful tool to favor the extinction of fear as well as to help patients to manage fear reactions and thought disorders. One of the promising new approaches is the use of D-cycloserine. Unfortunately, clinical studies have given mixed results, and it seems that D-cycloserine can facilitate reconsolidation of fear memory when exposure procedures are unsuccessful [129]. We propose that cotinine is another attractive candidate to be considered as a therapeutic drug for PTSD due to its unique properties, including its safety profile in humans [130,131]. Furthermore, cotinine has the advantage of not only being a memory enhancer, but also has anxiolytic, antipsychotic, and antidepressant properties that further increase its potential to be used to treat PTSD symptoms. For these reasons, cognitive enhancers such as cotinine have a great potential to be useful adjunctive therapies for the treatment of PTSD. Further clinical studies are needed to demonstrate this hypothesis. It is expected that in the years to come, we will have insights into the clinical efficacy of cotinine and other novel pharmacologic agents to prevent or cure PTSD.

## 4. CONCLUSION

From a broader perspective, diminishing the suffering among people with PTSD and other anxiety associated disorders by characterizing new and more effective therapies is an important goal for the scientific community. The emerging development of brain imaging and

other biomarkers to assess the functional and structural effects of trauma offers outstanding opportunities to test new drugs to facilitate trauma memory extinction. We predict that in the years to come, cotinine will be investigated in its potential as a monotherapy or adjunctive therapy to help to both extinguish trauma memories and treat depressive and anxiety behaviors in individuals suffering from PTSD and related disorders.

## CONSENT

Not applicable.

## ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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