The extinction of conditioned fear: structural and molecular basis and therapeutic use

A extinção do medo condicionado: bases estruturais e moleculares e utilização terapêutica

Abstract

Objective: Through association, a large variety of stimuli acquire the property of signaling pleasant or aversive events. Pictures of a wedding or of a plane disaster may serve as cues to recall these events and/or others of a similar nature or emotional tone. Presentation of the cues unassociated with the events, particularly if repeated, reduces the tendency to retrieve the original learning based on that association. This attenuation of the expression of a learned response was discovered by Pavlov 100 years ago, who called it extinction. In this article we review some of the most recent findings about the behavioral and biochemical properties of extinction. Results and Discussion: It has been shown that extinction is a new learning based on a new link formed by the cues and the absence of the original event(s) which originated the first association. Extinction does not consist of the erasure of the original memory, but of an inhibition of its retrieval: the original response reappears readily if the former association is reiterated, or if enough time is allowed to pass (spontaneous recovery). Extinction requires neural activity, signaling pathways, gene expression and protein synthesis in the ventromedial prefrontal cortex and/or basolateral amygdala, hippocampus, entorhinal cortex and eventually other areas. The site or sites of extinction vary with the task. Conclusions: Extinction was advocated by Freud in the 1920’s for the treatment of phobias, and is used in cognitive therapy to treat diseases that rely on conditioned fear (phobias, panic, and particularly posttraumatic stress disorder). The treatment of learned fear disorders with medications is still unsatisfactory although some have been shown useful when used as adjuncts to behavioral therapy.

Descriptors: Fear; Extinction (Psychology); Memory; Learning; Forgetting

Resumo

Objetivo: Muitos estímulos podem adquirir características prazerosas ou aversivas por meio da formação de associações. Fotografias de um casamento ou de um acidente aeronáutico podem servir como dicas para lembrar esses eventos e outros de natureza ou caráter emocional semelhante. Porém, sabe-se que a apresentação repetida de uma dica na ausência do estímulo ao qual está associada reduz a probabilidade de expressão da memória em questão. Este fenômeno de atenuação foi descoberto por Pavlov há quase 100 anos, recebendo o nome de extinção. Neste artigo de revisão, comentamos alguns dos achados mais recentes a respeito das propriedades comportamentais e bioquímicas do processo de extinção de memórias. Resultados e Discussão: Tem sido demonstrado que a extinção não envolve esquecimento, mas a inibição da expressão da memória original juntamente com um novo aprendizado, que inclui a formação de uma relação entre a dica e a ausência do estímulo que originou a primeira associação. De fato, a memória original reaparece rapidamente após a re-exposição ao estímulo adequado ou, simplesmente, com o passar do tempo (recuperação espontânea). A extinção requer atividade neural, diferentes vias de sinalização neuronal, incluindo a expressão de genes e a síntese de proteínas, em diferentes áreas do cérebro. Estas variam com a tarefa, mas distintos estudos sugerem que tanto o córtex pré-frontal medial como o córtex entorinal, a amígdala basolateral, hipocampo entre outras áreas desempenham um papel fundamental neste processo. Conclusões: Nos anos 20 do século XX, Freud recomendou a utilização de terapias baseadas na extinção para o tratamento de fobias. Hoje, a extinção é utilizada na terapia cognitiva de distintas desordens, incluindo o pânico e o estresse pós-traumático. Ainda que alguns medicamentos tenham demonstrado sua eficácia como coadjuvantes na terapia comportamental do medo aprendido, a resposta destes pacientes ao tratamento farmacológico ainda não é satisfatória.

Descritores: Medo; Extinção (Psicologia); Memória; Aprendizagem; Esquecimento

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Introduction

Learning results in the storage of information as a consequence of practice, experience, introspection or insight, resulting in a relatively permanent alteration of real or potential behavior. The information generated by learning is called memory, and its expression is called retrieval.\(^1^-^3\) The long-lasting establishment of a more or less definitive memory trace results from a long phase of consolidation which lasts several hours,\(^7\) throughout which the acquired information becomes progressively stabilized becoming resistant to interference by other memories,\(^4^-^6\) by endogenous or injected substances,\(^7\) or by molecular aggressions to the underlying mechanisms.\(^1^-^2\)

Memory consolidation depends on a series of neurochemical events that have been identified. In the hippocampus it is initiated by the activation of glutamatergic NMDA (N-methyl-D-aspartate) receptors and the entry of Ca\(^{2+}\) into pyramidal cells, followed by the activation of several signaling pathways and culminating in gene expression, protein synthesis and synaptic modifications.\(^1^-^6\) The process lasts for 5-12 h.\(^1^-^2\) Some psychologists believe that consolidation is a process that lasts for days, months or years (see \(^1^-^7\)).

We feel, however, that innumerable new learning experiences may impinge on memories over longer periods. Mood oscillation, development, and aging may affect short and long-term memory, and its expression is called retrieval.

Mechanisms involved in learning

These involve the parallel and sequential participation of several biochemical cascades, most of which are initiated by N-methyl-D-aspartate (NMDA) glutamate receptors in the hippocampus and in anatomically-related structures.\(^1^-^2\) Some of these cascades, in hippocampus, entorhinal cortex and posterior parietal cortex, result in the formation of short-term memory lasting up to 3 h.\(^11^-^12\) Other parallel cascades in hippocampus, entorhinal cortex, basolateral amygdala and several areas of the cingulated cortex\(^1^-^2,12\) result in the consolidation of long-term memory. These are similar to those that have been described for long-term potentiation in the CA1 region of the hippocampus\(^3^-^5,11^-^13\) but not in the other regions mentioned (e.g., \(^14^-^15\)).

Most, but not all, learning, result from associative processes: one or several stimuli are linked to other stimuli and/or responses. For example, a “cue” from the external or internal environment (a sound, a scene, a flavor) associated with a “biologically significant” stimulus (pain, food, fear) generates a new response to the cue (i.e., to run). Pavlov called this “conditioned reflexes”; the cue being the conditioned stimulus (CS), the “biologically significant” stimulus being the unconditioned stimulus (US), and the new response to the cue (e.g., running) being the conditioned response (CR).\(^16\)

It was fashionable in physiologically-minded circles of the ‘30s up to the ‘70s to translate all terms related to learning or memory into Pavlovian language (CSs, USs, CRs, etc.). This was then very much opposed by American and British psychologists or psychiatrists. Although feasible, the translation was soon found not to be practical. Learning by insight or memories formed through thinking is difficult to translate into Pavlovian terms.

However, it is difficult to explain extinction without referring to Pavlovian terminology, particularly once it became clear that it consists of the change of the connection of a cue (i.e., a CS) to a given significant stimulus (i.e., a U.S.),\(^17\) and that is why most authors\(^17^-^22\) use it. On his days, Freud,\(^28\) who disliked Pavlov, chose the term “habituation” to call the phenomenon of extinction; for Pavlov, who discovered both, habituation is a different form of learning.\(^15\) Superficially similar but non-associative,\(^29\) Diehard anti-Pavlovians prefer the word “exposure”\(^30^-^31\) or other words. There is nothing to be gained by the use of synonyms.

Extinction

Once animals have acquired a CR, repetition of the CS alone without the US causes an attenuation of the performance of the CR. This usually gradual inhibition of retrieval is called extinction.\(^16^-^27\) It is generally viewed not as a loss of the CR but as a new learning based on the new association of the CS with the lack of the US.\(^17,20\) Thus, an animal that originally learned to develop fear to a given CS (say, a light) and to respond by running as a CR, once the light is presented alone will tend to associate it now with the lack of fear and abstain from running (new CR).\(^17\) This tendency is of course enhanced by repetition of the unassociated CS.\(^16^-^17,20^-^27,29\)

In this account, the term CS can be substituted by “cue”, the term US can be substituted by aversive or pleasant stimuli, and the term CR by learned response.

Is the persistence of conditioned fear the result of a syndrome of extinction deficit?

Some animals, particularly humans, are devastated by experiences that cause fear; others, exposed to the same experiences in a similar environment, suffer less. Some develop psychiatric disorders such as phobias, panic or, worst of all, post-traumatic stress disorder.\(^30^-^34\) Others recover quickly, often on their own, and show no outward signs of psychological damage. In the syndromes that are based on conditioned fear, symptoms are, as it is known, usually persistent and recurrent, which makes the life of their bearers very difficult. They are literally haunted by bad and often terrorizing memories that spring to their minds under circumstances of stress, or often for no apparent reason (“flashbacks”).

The distinction between those who do and those who do not develop serious symptoms after fearsome experiences, and the fact that fear disorders are treated with therapy based on extinction procedures (see next section), has led many psychiatrists around the world to consider fear disorders as resulting from a syndrome of a deficit of extinction. It is difficult to establish who was the first to use such concept or terminology. The idea that a deficit of the capacity to extinguish memories of fear is at the root of such disorders is currently used and has been adopted by a very large number of mental health professionals. Thickness of the ventromedial prefrontal cortex\(^35\) and orbitofrontal cortex\(^36\) has been reported to correlate to the capacity to extinguish in humans. The opposite (a peculiar thinness of any of those regions in humans with fear disorders) has not been reported.

The therapeutic use of extinction

The adaptive importance of extinction learning with its clear emotional content that overrides pre-existing emotional components is obviously high. It enables subjects to keep information both on previous association(s) and to incorporate a new association. Thus, depending on the circumstances
subjects will preferentially perform adequate responses to one or to the other. Subjects must learn that a stimulus or situation that was once dangerous may become less dangerous or cease to be so, but they also have to keep a trace of the signaled danger in order to avoid it if necessary.

Extinction was established as a tool to treat conditioned fear by Freud in the 1920’s. Various forms of fear conditioning have accordingly been used to study the molecular mechanisms of extinction. This has led to the reincorporation of Pavlovian terms and techniques to modern psychiatry and psychology in relation to the treatment of learned fear (see above, and reference17).

For the experimental study of extinction of acquired fear it is, thus, necessary to establish a conditioned fear response (say, by pairing a sensory cue with a footshock, a strong noise, a puff of air) to an adequate level of consolidation, and then proceed to present the cue alone a number of times, which varies with the nature of the CS and the US under study. Real life presents us with a wide variety of forms and types of conditioned fear. Daily activities, traffic, travel, and/or disease offer numerous examples. Many of these instances induce long-lasting memory disturbances, including panic attacks, phobias and posttraumatic stress disorder (PTSD). As it has been said, these conditions, particularly PTSD, are now viewed as persist. This has been termed reconsolidation, and counterintuitive as it may be to Pavlov’s appraisal of extinction and to its well-documented use in clinical psychiatry or psychology, evidence in favor of its existence has steadily increased in the past few years9,37. The present article will ignore the issue of reconsolidation, which has been reviewed extensively and repeatedly in recent years (see 9) and concentrate on the more practical subject of extinction, which, in the end and over repetition of an unassociated CS, always predominates16-27,29,37. The reason why it is so much used in the psychotherapy of learned fear disorders. If anything, conceptually, reconsolidation poses a hindrance to extinction therapy.21

The basis of extinction at the system and molecular levels
What happens during extinction? At the end of an extinction procedure, a superficial analysis of the subject’s behavior will suggest that the subject has lost a memory and in a sense has become again what it had been before the original training. But as Pavlov16 and Rescorla17 have shown, extinction is not equal to forgetting. It consists of the downgrading of a response by an inhibitory process directed against the probability of giving that response, which is caused by its substitution by another response (or by the specific lack of a response). In short, it is a form of learning.17 Much evidence shows that extinction is not equal to forgetting: given an appropriate interval between one session of extinction and the next, the response thought to be extinguished may reappear (spontaneous recovery). Very often, related memories may bring back retrieval of the one thought to be extinguished: fear is mindful of fear, sex is mindful of sex, etc.21 There may also be context-dependency in extinction: a response may appear as extinct in one given environmental context but not in others.17,23 Systematic studies on the brain areas involved in extinction learning and on its molecular substrates have been carried out by several groups.18-21,23-27,35-36,38-42 The evidence has shown that extinction is processed at various specific brain areas by different sets of neurochemical events, depending on the task. As happens with memory consolidation and retrieval,1-2 the extinction of one-trial inhibitory avoidance in rats has been the most widely studied. This is due to the fast acquisition of the task (it is learned in seconds, in one trial), and to the reproducibility of the results obtained with it1-2. In this task, animals learn to refrain from performing a given behavior because that performance results in punishment: a rat refrains from stepping down from a platform because this results in a footshock; humans learn to avoid placing their fingers into electric sockets, people learn to look to the left when crossing a street in Brazil, and to the right in England. The extinction of one-trial inhibitory avoidance in rats requires intact glutamate N-methyl-D-aspartate (NMDA) receptors and cAMP-dependent protein kinase (PKA) in hippocampus, amygdala25-27 and entorhinal cortex;41 the extracellularly regulated protein kinases (ERKs) 1/271 and Src-tyrosine kinases44 in the hippocampus, and the calcium-calmodulin dependent protein kinase II in hippocampus27 and entorhinal cortex.43

The extinction of fear-potentiated startle, which is a task much dependent on the basolateral amygdala, also requires NMDA receptors, ERKs and protein synthesis in that region.7,41,45-46

The extinction of conditioned taste aversion involves NMDA receptors, ERK activity and protein synthesis in the insular cortex, and it is modulated by cholinergic muscarinic and β-noradrenergic receptors in that area.18 In addition it requires protein synthesis in the basolateral amygdala.42 Extinction of a conditioned reflex in humans involving a visual cue followed by a shock to the hand is accompanied by increased irrigation in the ventromedial prefrontal cortex and by decreased irrigation in the hippocampus, as seen by functional magnetic resonance.24 The hippocampus is known to be critical for retrieval.47 Even though the areas and, to an extent, the molecular mechanisms involved in extinction vary with the task, two points deserve special notice. First, the ventromedial prefrontal cortex surely plays a key role in extinction of all the tasks in which it has been studied so far (see below). Second, in all cases, extinction requires both gene expression and protein synthesis at its very onset, be it in entorhinal cortex,43 hippocampus,25-27 basolateral amygdala,26 insular cortex48 or ventromedial prefrontal cortex,48 or in all or several of the areas measured, depending on the task (see 24).

This signals the fact that extinction involves a new learning process,17 superimposed upon that of the original task and behaviorally overwhelming it, since the response requirement of extinction is precisely the opposite of it, but not erasing it at all.19 The biochemical variables mentioned are characteristic of the formation of new learned associations.1-2,19

The diversity of areas—and, to a smaller extent, that of molecular processes— responsible for extinction indicate that, like the original learning they stem from, extinction of different tasks involves a family of brain systems. So far, the involvement of the medial temporal structures (hippocampus, amygdala and entorhinal cortex) and the need for gene expression and protein synthesis have been shown to be rather widespread in this type of memory process. The modulation of extinction by treatments given into the basolateral amygdala does not require or otherwise involve the hippocampus.49

The modulation of extinction

Indeed, the study of the modulation of extinction has so far barely begun. In a series of elegant experiments, using mice unable to express the CB1 endocannabinoid receptor or animals treated with the cannabinoid antagonist SR141716, Marsicano et al. have shown that CB1 receptors are important for extinction of fear responses.22 They act probably by stimulating the release of GABA in the amygdala. For further references on endogenous cannabinoid regulation of memory, see.50-51

The modulatory influence of cannabinoids on extinction goes side by side with other findings showing that the GABA agonist muscimol as well as noradrenaline, promote extinction of a conditioned fear task when given into the basolateral amygdala. The two neurotransmitter systems are interrelated and their antagonists block the effects of both.49 Several authors48-51 have commented on the opposite role of glutamate and γ-aminobutyric acid in fear extinction, and Davis and Myers have commented its clinical implications for extinction therapy.7,46

The data on cannabinoid regulation of extinction are so far inductive as to whether the hippocampus, the amygdala or the prefrontal corticomedial cortex are involved.22,50-51 The cannabinoid system does not regulate the extinction of non-aversive behavior.50-51

The ventromedial prefrontal – amygdala pathway suggested by Quirk et al. as important for extinction44 would appear to operate in parallel to an anterolateral prefrontal-amygdala – entorhinal connection proposed by Anderson et al. in fMRI studies as the basis for Freudian repression.52 Repression and extinction are different forms of retrieval inhibition and possibly pertain to related but essentially separate psycho- and physiological processes.21

The “center for extinction”?
As mentioned, a number of studies indicate that the ventromedial prefrontal cortex may be crucial for extinction in several animal species [21,39,54]. The ventromedial prefrontal cortex has connections with areas that participate in this process (hippocampus,20-21,25-27 [59], amygdala7,21,26,47,48,49 and entorhinal cortex).45

The ventromedial prefrontal cortex has functions that go beyond its well-known role in working memory.43,44 Ventromedial units fire in relation to the generation of extinction.38 Protein synthesis in this region is necessary for the generation of extinction of conditioned fear; in addition, there is increased c-Fos production in the ventromedial prefrontal area at the time of extinction.53 Electrical stimulation of ventromedial prefrontal cortex reduces conditioned fear in a temporal-specific manner.55 Lesions of this area impair extinction of fear conditioning in rats.38 As mentioned above, thickness of this region in humans correlates with extinction performance.37

Actually, these findings are perhaps the main bases for the hypothesis that fear disorders may be the expression of a syndrome of deficient extinction (see above).

Extinction and the enhancement of its US (no fear) component

Extinction can be enhanced by increasing exposure to the “no fear” (“no US”) component of the memory to be extinguished. Rats trained in one-trial step-down inhibitory avoidance were tested during 5 consecutive days allowing them to remain in the apparatus and explore it freely without the danger of another footshock for 30 sec after they stepped down in the retention tests.20 This increases extinction to the point where performance of the avoidance response cannot be improved by a variety of retrieval-enhancing drugs, and in order to be reacquired the animals had to be exposed again to the footshock (the US). This retraining was fully blocked by intra-hippocampal administration of either an inhibitor of gene expression or by the protein synthesis blocker, anisomycin;13 these drugs completely block new learnings.1,2

The enhancement of the “no US” component (the no-fear component) in psychotherapeutic extinction sessions, be it by prolonging their time of duration or by expanding its significance, therefore appears as a highly desirable thing to do in the extinction treatment of learned fear syndromes, particularly PTSD.24

Drug enhancement of extinction: is it possible, and, if so, is it effective?
The issue is of interest inasmuch as it is sometimes important to accelerate extinction as much as possible in its therapeutic application.

We currently know a lot about the molecular pharmacology of extinction, i.e., about the many drugs that can block extinction by actions upon glutamate receptors, at the level of protein kinase A or extracellularly regulated kinases, Src-kinase, GABAergic inhibition, noradrenergic modulation, and also about the role of gene expression and protein synthesis in extinction, as studied in different areas of the brain by the local infusion of inhibitors of RNA polymerase II and transcription (see 26). However, agents that need to be microinjected into specific brain areas are of no therapeutic value.

Only one of the agents studied so far with actions at the molecular level appears to be of potential therapeutic use: the glycine receptor agonist, D-cycloserine. The glycine receptor is an allosteric site at glutamate NMDA receptors that enhances their sensitivity to glutamate or N-methyl-aspartate.46 D-cycloserine is a drug whose pre-clinical and clinical pharmacology has been known for decades, inasmuch as it has been used for the treatment of tuberculosis. The favorable effect of D-cycloserine on extinction has been very well documented in numerous experiments using fear-potentiated startle in rodents both by intra-amygdala and by systemic administration. The same effect has been documented in other learned fear tasks, where it has been additionally found to disrupt the reacquisition of fear and to induce generalized extinction (i.e., extinction to conditioned stimuli that had not been extinguished).7,45-46 It has yet to be submitted to wide clinical testing.

During some time benzodiazepines were used;30,32 but while these drugs do tranquilize the patient when revival of the fearsome experience at the beginning of the extinction treatment which may be very frightening, they also tend to hinder learning. And extinction is, as mentioned, new learning.17,19

A variety of other treatments have been tried. One of themost studied is the β-noradrenergic receptor blocker, propranolol.55-56 This drug and its analogs have long been known to attenuate both consolidation and retrieval.1,2,13 However, the side-effects of propranolol and other β-blockers may include precipitous falls in blood pressure in patients that are sensitive to the drug; this includes millions of people who use β blockers for the treatment of glaucoma, or other purposes. And of course
the attenuation of consolidation and retrieval are unwelcome side effects. After a peak of popularity of propranolol for the treatment of PTSD about two or three years ago, its use for the enhancement of exposure or extinction therapy and/or for allaying social anxiety or PTSD has waned quite a bit. The side effects as well as its lack of therapeutic effect in many patients have been responsible for this.

Practitioners in general have shunned from the use of cannabinoids to facilitate extinction, and their use in patients is believed by many to be unadvisable, due to drug dependence and uncertain results. The fostering of extinction does not stand out as a recommended use of cannabis compounds, which are often employed in other medical circumstances.57

Then, thus far there is a need to develop a pharmacotherapy for the enhancement of extinction; both for the extemporaneous use in the punctiform treatment of instances in which this is desirable in the short-term (single panic attacks, some transient instances of phobia or of social anxiety) and in the often unbearable long-term (posttraumatic stress disorder, chronic phobias, chronic social anxiety). In the latter cases, as pointed above, we might be dealing with a specific syndrome: the deficit of extinction. The nature of the disorder is very debilitating, and the patients feel anguished to the point of suicide. The urgency of the clinical situation thus defined underlines the need of a more efficient pharmacology of extinction enhancement. Perhaps a good starting point could be analogs of D-cycloserine or other systemically effective underlines the need of a more efficient pharmacology of suicide. The urgency of the clinical situation thus defined underlines the need of a more efficient pharmacology of extinction enhancement. Perhaps a good starting point could be analogs of D-cycloserine or other systemically effective.

In extinction, the first and the last places in the ranking of memories-ready-to-be-retrieved, in order to live a life as normal as possible.19

Final comments

In daily life, as well as in clinical practice, the best survivors of fearsome events are those that do not forget, but extinguish better. Forgetting is counterproductive: subjects that forget about fearsome experiences may incur again in those experiences. But extinction is the desideratum: it is healthier to set aside constant or recurrent fear in order to survive better. To extinguish is not to forget:17 it is to set unwanted memories aside from the first places in the ranking of memories-ready-to-be-retrieved, in order to live a life as normal as possible.19

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