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Review

The learning of fear extinction

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ABSTRACT

Recent work on the extinction of fear-motivated learning places emphasis on its putative circuitry and on its modulation. Extinction is the learned inhibition of retrieval of previously acquired responses. Fear extinction is used as a major component of exposure therapy in the treatment of fear memories such as those of the posttraumatic stress disorder (PTSD). It is initiated and maintained by interactions between the hippocampus, basolateral amygdala and ventromedial prefrontal cortex, which involve feedback regulation of the latter by the other two areas. Fear extinction depends on NMDA receptor activation. It is positively modulated by D-serine acting on the glycine site of NMDA receptors and blocked by AP5 (2-amino-5-phosphono propionate) in the three structures. In addition, histamine acting on H2 receptors and endocannabinoids acting on CB1 receptors in the three brain areas mentioned, and muscarinic cholinergic fibers from the medial septum to hippocampal CA1 positively modulate fear extinction. Importantly, fear extinction can be made state-dependent on circulating epinephrine, which may play a role in situations of stress. Exposure to a novel experience can strongly enhance the consolidation of fear extinction through a synaptic tagging and capture mechanism; this may be useful in the therapy of states caused by fear memory like PTSD.

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1. Introduction

1.1. Definitions and terminology

Extinction consists of the learned inhibition of retrieval of previously acquired memories. It was first described by Pavlov and Anrep (1927) in the early 1900s by systematically omitting the unconditioned stimulus (US, also called "reinforcement") in test trials of a previously acquired conditioned reflex (CR). He studied this first in **alimentary conditioning**, where the conditioned stimulus (CS) was a sound and the US was a piece of meat, and then in what he called "defence conditioned reflexes", one in which the US was the ingestion of acid, and another one in which the US was a shock to a hind leg. Defence conditioned reflexes are nowadays known by most neuroscientists as forms of "learned fear". Pavlov and his original followers did not use the term "fear" because it implies assuming that the observed behavior of animals is equal to the complex phenomenon that humans call 'fear", which englobes subjective components, some of which are conscious and others constitute a particular unconscious state. There is no way of knowing whether animals experience a similar state and a conscious realization of threats as humans do. This can only be inferred from interpretations of animal behaviors in human terms, by analogy. One of the most influential workers in the field, Joseph LeDoux, suggests that the terms "threat" and "defense responses" should be used instead of "fear memory" or "fear responses" (LeDoux, 2014; Schiller et al., 2013). He realizes, like Pavlov, that the mechanisms through which the brain responds to threats are "distinct from those that make possible the conscious feeling of fear that can occur when one is in danger" (LeDoux, 2014). We can infer from the behavior of animals that they do perceive and recognize threats in "defence conditioned reflex situations": to begin with, they tend to escape. But we cannot deduce that they experience or "feel" exactly what humans call "fear".

In spite of agreeing with the point of view of Pavlov or LeDoux, we will refer throughout this article to "fear conditioning", "fear memory" and "fear extinction", just because it is more familiar to a majority of workers in the field and thus easily understandable by all of them; but we will not refer to "fear mechanisms" because these may be different in humans and in laboratory animals. There are many metaphorical terms in Biology and especially in the health sciences, which are customarily used despite their real or original meaning, like "anemia". This word has been used for centuries to express a low level of oxygenated hemoglobin, although the word comes from the Greek *a haima*, which means, "lack of blood" or "no blood". The term "fear" as applied to animals other than humans is also a metaphor coming from what we humans experience in threat situations. There is no way of knowing if animals exposed to a threat "feel" the peculiar combination of states that humans call "fear". In particular, aside from the conscious feeling of fear that varies from species to species, the accompanying unconscious state of fear is difficult to define, and persists during and in spite of extinction (Costanzi et al., 2011). It may be different in humans and in laboratory animals (LeDoux, 2014). In rats, it has been called "drive" and defined as a nonassociative entity responsible for pseudoconditioned responses that "contaminate" real learned responding (Izquierdo and Cavalheiro, 1976a; see Wyrwicka, 1999). This unconscious state is probably at the root of the known fact that sudden unexpected stimuli may recover the original task long after it has been completely extinguished (Maren, 2014).

This state may be reconstructed or rekindled by retrieval, and we think it might be related to the phenomenon or process of reconsolidation described in recent years (Nader et al., 2000; Nader, 2003), which has changed our outlook on memory processes quite a lot.

Reconsolidation develops following retrieval in parallel to extinction and also necessitates ribosomal (Nader et al., 2000; Duvarci et al., 2008) and nonribosomal (Myskiw et al., 2008) protein synthesis in the hippocampus (Nader et al., 2000; Duvarci et al., 2008) and, as described initially (Nader et al., 2000), in the amygdala (Duvarci et al., 2008). It is a process whose probable main *raison-d'être* is to update (add information to, or change the meaning of) memories (Sara, 2000a,b; Schiller et al., 2010; Forcato et al., 2010, 2013). As time passes, and the interval between training and the first session of retrieval becomes longer, the probability of extinction predominates over that of reconsolidation, which typically can be seen only at relatively short training-retrieval intervals (a few days at the most; see Milekic and Alberini, 2002; Inda et al., 2011). The reconsolidation of memories motivated by alimentary or other reinforcers unrelated to fear has been much less studied than that of fear memories, even less than the extinction of alimentary conditioning. There have been, however, some exceptions, like the reconsolidation of object recognition in rats (Myskiw et al., 2008) and declarative verbal learning in humans (Forcato et al., 2010, 2013).

In the first 30 years after its discovery, the study of extinction was restricted to **classical conditioning,** in which there is a pairing of the CS and the US regardless of the performance of CRs. **Instrumental conditioning** in which the CR is used by the animals as an instrument to either get or avoid the US was discovered in Pavlov's laboratory only in 1937 (Konorski and Miller, 1937). In the same year, its mechanical version called operant conditioning was first described independently in Minnesota by Skinner (1937); see Wyrwicka (1994). We prefer the term "instrumental" to "operant" because except in specially designed apparatuses the responses of the animals do not directly "operate" any gadget: freezing, flexing a leg, crossing a hurdle, omitting a response, salivating, etc. are the most commonly studied instrumental responses in fear motivated tasks. The animals use the response as an instrument to either obtain the US (food, water) in alimentary tasks or to prevent delivery of the US (usually a footshock) in fear-motivated tasks. The term "operant" is still widely used in the U.S.A. to denote instrumental conditioning because of the Skinnerian tradition.

As said, in classical conditioning the development of CRs depends on the pairing of an initially neutral stimulus with the US (Izquierdo and Cavalheiro, 1976a); through this pairing the neutral stimulus then becomes a conditioned stimulus (CS). Classical fear conditioning still is the most widely used animal model to study fear-motivated learning (or defensive responses to threats). It is acquired quickly, lasts very long, and is amenable to physiological, pharmacological and behavioral observations. Most of what we know today about the brain's fear system and its modulation comes from research using Pavlovian fear conditioning.

The development of CRs in instrumental conditioning depends not on the CS–US pairing but rather on the contingency between the CR and the US (Izquierdo and Cavalheiro, 1976a,b). The performance of a given CR (e.g., leg flexion) determines whether the animals will receive the following US (e.g., a footshock). In fear-motivated tasks, which have been by far the most used forms of instrumental conditioning in the last 50 years (Gold, 1986; Izquierdo and Medina, 1997; Izquierdo et al., 2006; LeDoux, 2014; De Quervain and McGaugh, 2014), the contingency may rely on the performance of a given CR or in the inhibition of a response in order to avoid a US; for example, animals may be taught to cross a line or to jump or not to cross a line or to refrain from jumping in order to avoid a footshock; i.e., they may learn to emit or to omit a response. Fear- or displeasure-motivated instrumental learning is also called "avoidance" learning: the CR is used to effectively avoid the US.

The study of extinction in instrumental (avoidance) conditioning started with Konorski and Miller (1937) and its analysis in forms of learning other than conditioned reflexes began years later. It was clear from the beginning that fear extinction in instrumental conditioning is slower than in classical conditioning, probably because