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EDITORIAL

Editorial: the psychopharmacology of extinction—from theory to therapy

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Extinction—defined as the gradual disappearance of a learned response following the withdrawal of reinforcement—was first described by Pavlov (1927), and has been a subject of great psychological and neurobiological interest for a number of decades. Extinction is a fundamental learning process that has also formed the basis of prolonged exposure treatments for mental health disorders, including post-traumatic stress disorder and phobia, but potentially also for addictions. However, prolonged exposure therapy is not effective for all patients. Advances in understanding the psychopharmacology of extinction, at the whole-organism and circuit levels, are directing us to novel ways for optimising therapy-based around extinction. It is increasingly providing us with novel insights into the basic process itself. Preclinical research is also helping to address the underlying mechanisms and clinical feasibility of interventions such as exploiting memory updating mechanisms by extinguishing a memory within a critical window of reconsolidation.

This special issue on 'The Psychopharmacology of Extinction' aims to provide a comprehensive set of reviews and empirical papers that address these questions and others from many of the leading scientist currently working in this area. The issue developed out of a symposium held at the 2017 biennial European Behavioural Pharmacology Society meeting in Crete. This symposium, like the current collection of articles, highlighted some of the exciting developments in understanding the extinction of both appetitive and aversive memories that have emerged in the 90 years since Pavlov published his foundational ideas. We hope you find the collection of interest and value to your own work as we look ahead to the next era of extinction research.

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Models, procedures and individual differences influencing the psychopharmacology of extinction

This issue begins by considering the animal models and procedures used to study the psychopharmacology of extinction, with a particular emphasis on sex- and individual-differences in extinction learning. Bouton (2019) extends his previous seminal work (Bouton 1994, 2002, 2004) on the influence of both spatial and temporal contexts on the expression of Pavlovian extinction, to consider how instrumental extinction can be understood more generally as a form of retroactive interference. In particular, Bouton argues that contexts can directly influence the expression of an instrumental response, revealing further subtleties in the way in which the internal and external environment can influence ongoing behaviour.

Inside and outside of the laboratory, learning occurs against the background of prior experiences. Previous experiences in which the environment is perceived as controllable or uncontrollable can influence the perceived controllability and learning that occurs in a new situation (for review, see Moscarello and Hartley 2017). Here, Hartley et al. (2019) compare the effects of control (proactive instrumental avoidance) of a fear-relevant cue to passive Pavlovian extinction of that cue, in terms of subsequent fear reduction. The capacity to actively avoid a fearful stimulus leads to greater reductions in fear, with a correlation between fear reduction and individual differences in dopaminergic function.

By contrast, a previous history of chronic, uncontrollable stress is known to impair subsequent safety learning. The review by Wellman and Moench (2019) relates the effect of acute and chronic stress to microstructural and functional

changes in key regions of the prefrontal cortex, with a call for a mechanistic understanding of impairments in extinction learning at the neurochemical, circuit-level and psychological levels. Providing another perspective on the effects of chronic stress, Chakraborty and Chattarji (2019) investigate the critical importance of the timing of stress in inducing changes in fear learning and extinction. Despite chronic stress inducing similar microstructural changes in key regions such as the basolateral amygdala and infralimbic cortex irrespective of when it is experienced, the authors show that only prior chronic stress leads to deficits in fear extinction.

As already mentioned, the process of extinction is essentially the basis for prolonged exposure therapy, but this therapy remains lacking in term of its efficacy and applicability across all patients. Singewald and Holmes (2019) make the case for the value of rodent models of *impaired* extinction to improve the efficacy and longevity of exposure therapy. They discuss how disruptions at the circuit, genetic and environmental levels interact to disrupt fear extinction; providing critical mechanistic insight and a springboard for the development of new therapeutic approaches. A complementary approach is proposed by Monfils et al. (2019), who report on their development of a prescreening tool to determine whether what is learned during extinction will be retained by specific individuals. The identification of individual differences in the efficacy of fear extinction could provide a means for streamlining treatment approaches, focusing resources for prolonged exposure therapy on those who would most benefit from it.

Not all patients are responsive to prolonged exposure therapy. Consequently, there has been great interest in targeting the reconsolidation of the original fear memory to provide a novel method to reduce fear in this patient group. Here, Kida (2019) reviews what is known about the mechanisms underlying fear memory extinction and reconsolidation, and how these might be facilitated or disrupted respectively for the treatment of mental health disorders based upon maladaptive fear memories. Finally, this section concludes with a valuable perspective, together with a reasonable set of recommendations, laid out by Wotjak (2019), on how the field can better enhance the comparability of fear conditioning and fear extinction studies going forward.

New mechanistic insights into the psychopharmacology of extinction

From the perspective of facilitating treatment development, understanding the mechanisms underlying extinction is critical. Furthermore, it provides vital insight into fundamental learning processes involved. This is the theme of the issue's next section, which begins with the exciting area of epigenetic regulation of fear extinction in a review by Marshall and Bredy (2019). They discuss how epigenetic mechanisms exert a powerful influence over fear extinction, an influence that might be harnessed for therapeutic benefit. de Quervain and Roozendaal (2019) then discuss how one system that has been found to be under epigenetic regulation, namely glucocorticoid signalling, provide a key link in the intracellular communication that occurs between the nucleus and at the synapse to lay down extinction memories.

Appropriately, the section continues by considering the synaptic basis of fear extinction, beginning with a review by Luchkina and Bolshakov (2019), who make the case that synaptic plasticity is both necessary and sufficient for the learning of the original fear memory and the memory underlying extinction. The importance of the NMDA receptor (NMDAR) in synaptic plasticity and memory is well-established, but subtleties in the contributions of NMDARs with different subunit compositions presents challenges for the exploitation of NMDAR-mediated signalling as a therapeutic target, argue Radulovic et al. (2019). The exploitation of NMDARs may be further complicated not only by sex differences in the mechanisms underlying extinction, but also by the interaction between female reproductive history and the requirement for NMDARs in extinction reported by Tang and Graham (2019). Thus, a complex constellation of factors may contribute to individual differences in receptor expression, such as those described by O'Connor et al. (2019) for metabotropic glutamate receptors, and consequent differences in fear extinction.

The interactions between stress, anxiety and fear have generated a robust body of research demonstrating the enhancement of fear memory consolidation produced by activation of the noradrenergic system. This has led to the development of pharmacological adjuncts to prolonged exposure therapy for PTSD based upon targeting the adrenergic system—in particular, antagonising the α_1 subtype of adrenergic receptor (α_1-AR). However, despite the success of α_1-AR antagonists such as prazosin in reducing cognitive symptoms of PTSD, little is known about the mechanism through which α_1-ARs contribute to fear memory regulation. This question is taken up by Lucas et al. (2019), who report that α_1-AR activity during fear conditioning determines subsequent capacity for extinction learning. Modulation of activity within the bed nucleus of the stria terminalis (BNST), particularly of NPY neurons, may also represent a viable therapeutic target, as illustrated in an intriguing empirical paper focussing on the NPY-Y2 receptor subtype, by Pape and colleagues (Verma et al. 2019). Indeed, another mechanism that might regulate the impact of the BNST on fear extinction is endocannabinoid signalling. As reviewed by Lisboa and Guimãraes (2019), the endocannabinoid system continues to receive significant interest as a potential pharmacotherapy for PTSD.

Despite a wealth of potential pharmacological targets for the augmentation of prolonged exposure therapy, there has been relatively little translation to new treatments in the clinic. Richardson and colleagues (King et al. 2019) propose that this mismatch between robust effects in the laboratory and weaker effects in the clinic is attributable to a number of factors that vary in patients, but not in laboratory animals. The promise of this approach, focused on interindividual variability, is highlighted by a companion data paper from Graham and Richardson (2019), in which the enhancement of extinction recall produced by treatment with fibroblast growth factor-2 (FGF2) is related to individual differences in the efficacy of within-session extinction learning.

Extinction, and prolonged exposure therapy for anxiety disorders, depends upon repeated non-reinforced presentations of a previously fearful cue. However, shorter non-reinforced re-exposure sessions can recruit an alternative mnemonic process, that of memory reconsolidation (Nader et al. 2000). It is important in this regard to be open to the possibility, and then to test for, that pharmacological agents may be targeting either reconsolidation or extinction mechanisms. In an illustration of this, Schiller and colleagues (Hu et al. 2019) report how oxytocin administered following re-exposure to a fear-associated cue enhanced subsequent extinction learning but without disrupting reconsolidation of the original fear memory.

As reconsolidation-based interventions might require administration of amnestic drugs, there have been attempts to develop behavioural interference strategies to disrupt the fear reconsolidation. However, as noted by Cahill and Milton (2019), studies exploiting the updating function of memory reconsolidation to overwrite the original cue-fear memory with an extinction (cue-no fear) memory have not been universally replicated. They argue that a better understanding of the neurochemical and molecular mechanisms required for the persistent reduction in fear expression following 'extinction within the reconsolidation window' is needed to clarity this issue and determine whether the effect is one of disrupted reconsolidation or facilitated extinction.

Neural circuits underlying the psychopharmacology of extinction

The issue's next section moves from a focus on extinction at the intracellular and neurochemical level, to work tackling questions at the level of neural circuits and networks. The importance of the amygdala, hippocampus and prefrontal cortical regions in fear memory extinction is well-established. However, technological and theoretical advances have broadened this understanding to include functional and microstructural changes, changes in circuitry at extended time points, and differences between Pavlovian and instrumental extinction.

Sah and colleagues (Marek et al. 2019) open this section with a state-of-the-science review of the neural circuits implicated in fear memory extinction, emphasising how the development of chemogenetic and optogenetic approaches has led to unprecedented understanding of the contribution of microcircuits to the expression (or not) of fearful behaviour. In light of the fact that patients undergoing prolonged exposure therapy for disorders such as PTSD do not seek treatment immediately, Gräff and colleagues (Silva et al. 2019) report on intriguing findings indicating that the attenuation of remote fear memories through extinction training recruits circuitry that overlaps with that engaged by the extinction of recent fear memories. This overlap is evident despite, as shown by the data reported by Johnson and colleagues (Jacques et al. 2019), the differences in which neurons are activated by recent and remote fear memory recall.

As reviewed by Çalışkan and Stork (2019), there are also changes in neuronal oscillations that occur with time, for example between the prefrontal cortex and amygdala. They propose that the nature of such changes in the oscillatory behaviour within fear networks underlie the fear generalisation and impaired extinction often associated with PTSD. Recent studies indicate that some of these same networks also subserve avoidance—a behaviour associated with a number of anxiety disorders that limits the effectiveness of Pavlovian extinction. Using a combination of immunohistochemical and retrograde tracing techniques, Quirk and colleagues (Martínez-Rivera et al. 2019) identify the neural circuits underlying the extinction of active avoidance, highlighting a specific role for prefrontal (prelimbic) cortical projections to the ventral striatum.

How might understanding of the neural circuitry of extinction and avoidance be informative for treatment development? Stoop and colleagues (Triana-Del Río et al. 2019) review the evidence indicating that oxytocin administration may act to influence synaptic plasticity related to fear and extinction memories, in addition to its acute anxiolytic effects. McIntyre and colleagues (Noble et al. 2019) consider a different strategy to facilitate extinction, based on stimulation of the vagus nerve. Building on their data from rodent models of PTSD, they make the case that vagus-nerve stimulation may provide a promising adjunct for prolonged exposure therapy, even long after trauma. Finally, this section considers the important problem of 'relapse' after prolonged exposure therapy. The persistence of the original fear memory—even if initially strongly inhibited by extinction learning—leads to a risk that an individual will show a return of fear in the longer term. But how does relearning extinction differ from extinguishing fear for the first time? Westbrook and colleagues (Lingawi et al. 2019) review key neural and pharmacological differences between extinction and re-extinction that have major implications for repeated rounds of prolonged exposure therapy.

The psychopharmacology of reward and drug extinction

Prolonged exposure therapy is used routinely to treat mental health disorders based upon maladaptive aversive memories, but less so for disorders based upon maladaptive appetitive memories, such as drug addiction. The papers in this final section consider the extinction of appetitive memories, especially as related to drug-associated cues, and the specific challenges posed by the extinction of these memories.

Two complementary reviews highlight the commonalities in fear memory and drug memory extinction, with Goode and Maren (2019) focusing on preclinical rodent models, and Konova and Goldstein (2019) focusing on humans. Both make the case that the neural circuitry supporting fear memory extinction and drug memory extinction overlaps markedly; with both being dependent on the communication between subcortical regions, such as the amygdala, and prefrontal cortical regions. The requirement for prefrontal cortex in appetitive memory extinction is further underscored in an in-depth review from Xue and colleagues (Zhang et al. 2019). Pertinently, a report from Müller Ewald et al. (2019) shows, using an optogenetic approach, that the contribution of the (infralimbic) prefrontal cortex to the reduction of cocaine-seeking depends upon the subjects' prior extinction training.

Considering the comorbidity between anxiety disorders and alcohol addiction, the interaction of pharmacological processes associated with addiction—such as alcohol withdrawal—and prolonged exposure therapy is potentially of great clinical impact. This relationship is addressed by Williams and Lattal (2019), with their data highlighting the complex relationship between fear learning and drug withdrawal. However, there are commonalities between fear and drug memory extinction, particularly with respect to the impact of individual differences on long-term behavioural outcomes. Lee and colleagues (Hilz et al. 2019) report how individual differences in the tendency to attribute incentive salience to cues associated with drugs also increases resistance to the extinction of drug-associated memories. It is possible that other approaches—such as punishment of drug-seeking behaviour—may be more effective in reducing drug-seeking behaviour in these individuals. Punishment of drug-seeking, whilst also sharing with prolonged exposure therapy the aim of reducing drug intake in the long term, depends upon psychological and neurobiological mechanisms that are partially distinct from the extinction of drug-seeking, as reviewed by Marchant et al. (2019). However, the partial overlap in these circuitries highlights the fact that fear and drug learning are not so different.

Indeed, there are similarities between fear memory and drug memory extinction at the molecular level. Lattal and colleagues (Hitchcock et al. 2019) investigate the requirement for epigenetic modifications in the extinction and reinstatement of cocaine self-administration, allowing parallels to be drawn to fear memory extinction (as reviewed earlier in the issue by Marshall and Bredy 2019). Similarly, differences in the molecular mechanisms underlying fear extinction and fear memory reconsolidation can also be observed in the reconsolidation and extinction of drug-associated memories, as reviewed by Taylor and colleagues (Torregrossa et al. 2019). Thus, despite a number of differences in the psychological processes and neurobiological circuits recruited in aversive and appetitive learning, there are key areas of overlap that allow these different fields of research to inform one another.

We complete the issue with a different perspective on extinction, with a review from Phillips et al. (2019) considering how deficits in extinction learning—or more generally, learning from non-reinforcement—contributes to the symptomatology of a number of mental health disorders. By focusing on the development of highly translational touchscreen-based tasks, these authors argue that is possible to develop a deep understanding of the transdiagnostic psychological processes affected by changes in extinction learning.

Conclusions

The number and quality of the papers comprising this special issue is indicative of the interest in extinction as a phenomenon, and the exciting developments occurring in this field. The breadth of the research presented highlights not only the importance of extinction to a wide range of psychological phenomena—Pavlovian and instrumental learning, aversive and appetitive motivational systems—but also the progress that can be made at the interface of psychological, psychopharmacological and neuropsychopharmacological research. We hope that you find the papers herein as informative and energising as we have as we enter an exciting phase in defining the psychopharmacology of extinction in the basic and clinical realms.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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