PSYKHE
2022, 31(SI 1), 1-15
https://doi.org/10.7764/psykhe.2021.33531

ISSN 0717-0297
www.psykhe.cl

An Evaluation of the Effects of D-Cycloserine on Operant Learning and Response Recovery

Evaluación de los Efectos de la D-Cicloserina en el Aprendizaje Operante y la Recuperación de Respuesta

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D-cycloserine (DCS) is a drug that has generated great interest for its association with improvements in both learning and memory. Few studies have evaluated the effect of DCS on learning, extinction, and response recovery in operant conditioning. The present study aimed to evaluate, over three experiments with rats, the effect of DCS on the spontaneous recovery of a simple operant, and on the resurgence of operant behavior. DCS was expected to strengthen the extinction, and that a decrease in spontaneous recovery and resurgence would also be observed. The results showed a faster extinction in the groups that received DCS during the extinction; however, no differences were observed in the recovery of the response. Based on the present results, it is not possible to conclude that DCS is a supportive drug for learning processes such as exposure therapy.

Keywords: D-cycloserine, operant learning, response recovery.

La D-cicloserina (DCS) es un fármaco que ha producido gran interés por su asociación con mejoras tanto en el aprendizaje como en la memoria. Pocos trabajos han evaluado el efecto de la DCS en el aprendizaje, extinción y recuperación de respuesta en el condicionamiento operante. El presente estudio tuvo como objetivo evaluar, a lo largo de tres experimentos con ratas, el efecto de la DCS en la recuperación espontanea de una operante simple y en la resurgencia de la conducta operante. Se esperaba que la DCS fortaleciera la extinción y que se observara además una disminución de la recuperación espontánea y resurgencia. Los resultados mostraron una extinción más rápida en los grupos que recibieron DCS durante la extinción; sin embargo, no se observaron diferencias en la recuperación de la respuesta. En base a los presentes resultados, no es posible concluir que la DCS sea un fármaco de apoyo para procesos de aprendizaje tales como la terapia de exposición.

Palabras clave: D-cicloserina, aprendizaje operante, recuperación de respuesta.

D-cycloserine (DCS) is a N-methyl-D-aspartate (NMDA) agonist that in recent years has attracted some research interest because of its association with improvements in learning and memory processing (e.g.,Guastella et al., 2007; Hofmann et al., 2006; Norberg et al., 2008). The evidence suggests that DCS enhances the effectiveness of NMDA receptors that are relevant in memory processing; thus, DCS could improve processing of different types of learning, including extinction (e.g., Bouton et al., 2008; Ledgerwood et al., 2005), as well as post-extinction response recovery phenomena.

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This research was supported by FONDECYT grant #1160132 awarded by CONICYT to G. Miguez, and by a National PhD Scholarship awarded by CONICYT's Advanced Human Capital Training Program (Scholarship #21150074) to C. San Martín. There is no conflict of interest to disclose.

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Operant (or instrumental) conditioning is a type of associative learning which involves an association between a response (e.g., lever press), and a specific consequence (e.g., food pellet). We refer to this response as "goal directed" or "operant" behavior, as a response is necessary to produce consequences on the environment. An appetitive consequence will "reinforce" the behavior, making it more likely to occur, while an aversive consequence will "punish" it, making it less likely to occur. An already established response can be diminished by omitting the reinforcer, a process called extinction. However, extinction is not permanent, and as in Pavlovian conditioning (e.g., Alfaro et al., 2019; Bustamante et al., 2019; González et al., 2016; Miller et al., 2015; Miguez et al., 2014; San Martín et al., 2020) under several circumstances an extinguished operant response can return. For instance, extinguished operant responses have shown to recover after a context change from the context of extinction (renewal; e.g., Bouton et al., 2012), after a time has elapse since extinction training (spontaneous recovery; e.g., Bernal-Gamboa et al., 2014; Graham & Gagné, 1940); and after extinction of an alternative response, in a phenomenon called "resurgence" (e.g.,Winterbauer & Bouton, 2010).

Experimental basic research on operant conditioning, extinction, and response recovery procedures constitutes the foundation of behavior therapy and provide an explanation for the frequent relapses observed in patients (Craske et al., 2014). Operant conditioning in particular is an important model for the etiology of different problematic behaviors, such as avoidance behavior (Guastella et al., 2007, 2008; Hayes et al., 1996; Lovibond, 2007; Thompson & Waltz, 2010), substance abuse (Aigner & Balster, 1978; Bigelow et al., 1981; Dudai et al., 1976; Silverman, 2004) and eating disorders (Farmer et al., 2001; Harrison et al., 2011, 2016; Keating et al., 2012), and contributes to understanding their onset and maintenance. There are several psychotherapeutic techniques based on research on operant conditioning (Craske et al., 2018; Culver et al., 2018). For instance, positive reinforcement is used with patients who have problems with alcohol or other substance (Pelchat, 2002), with patients with eating disorders (Steinglass et al., 2012), and with people that show avoidance behavior (Hunt et al., 2017; Krypotos et al., 2015, 2018; San Martín et al., 2020; Vervliet et al., 2013).

Since operant extinction is subject to relapse, it is relevant to examine potential manipulations to improve the treatment's long-term effect. DCS has been shown to have a positive effect on learning (e.g., Guastella et al., 2007, 2008); thus, it might also help improve the effect of behavior therapy in humans and operant extinction in animals (e.g., Langton & Richardson, 2010; Ledgerwood et al., 2003). Much of the research on the DCS effect has been conducted with Pavlovian preparations, with the aim of examine whether DCS is able to improve fear extinction (e.g., Ledgerwood et al., 2003, 2004, 2005). However, to date few studies have examined the DCS effect on extinction and recovery of an operant behavior (e.g., Vurbic et al., 2011). Vurbic and colleagues conducted three experiments in order to assess whether DCS had an effect on operant renewal; the result showed no DCS effect on an operant response renewal, even after manipulating the administered DCS dose (Experiments 1A and 1B), after the introduction of non-contingent reinforcement during extinction training (Experiment 2), and after discriminative training (Experiment 3). Moreover, it has been shown that the DCS delivery prior to the extinction session can increase lever pressing and, thus, decrease the amount of extinction (Peters & De Vries, 2013; Port & Seybold, 1998). A DCS effect has also been observed on operant responding only in presence of a Pavlovian cue associated with the reinforcer (Nic Dhonnchadha et al., 2010; Shaw et al., 2009; Vengeliene et al., 2008).

Given the limited literature on the DCS effects in operant conditioning, the goal of the present study is extending the previously observed results in a renewal preparation (e.g.,Vurbic et al., 2011) to other recovery phenomena (i.e., spontaneous recovery and resurgence). Examining different types of response recovery phenomena is relevant to assess the scope in which DCS might be an important tool for therapeutic use in extinction-based therapy (e.g., Siegmund et al., 2011). Thus, three experiments examined whether DCS had an effect on extinction and recovery of a free operant response. Based on the evidence in Pavlovian preparations, DCS should enhance extinction and thus decrease recovery; however, based on the existing literature on operant conditioning, it is likely that DCS will not affect extinction in the expected direction.

Experiment 1

The goal of this experiment was to examine the DCS effects on extinction and spontaneous recovery of a simple operant response. One group of animals received DCS during extinction, and a second group received a saline solution in an equivalent volume. If DCS improves extinction memory, then a better extinction and reduced spontaneous recovery should be observed in the group that received DCS, compared to the control group on saline solution. Table 1 summarizes the design of Experiments 1 and 2. Experiment parameters were based on the procedure by Vurbic et al. (2011).

Table 1
Experiments 1 and 2 Design

Groups	Acquisition	Extinction	Ho	Delay	Test	Ho
DCS	L+	L-DCS	cr	21 days	L-	cr
No DCS		L-Saline	Cr			CR

Note. L = lever, + = reinforcement, - = no reinforcement; CR, Cr, cr = expected levels of conditioned response, from highest to lowest. In Experiment 1 we used the number of bar pressing per minute as a dependent variable, and in Experiment 2, we added the inter-response intervals.

Method

Subjects

Twenty-four Sprague-Dawley rats (12 males and 12 females), obtained from the Pontificia Universidad Católica de Chile's vivarium, were used in this experiment. According to an a priori analysis, an n of 24 subjects allows a statistical power of .80 for an effect size of .25 using Cohen's f, which is considered a small effect size. This analysis was based on an unpublished review by the author regarding the use of the drug, where a small effect size was observed in non-human animals (d = .437; a moderate effect size is considered to start from .50).

All subjects weighted at least of 200 grs at the beginning of the experiment. Subjects were housed in group cages (three animals in each cage) with free access to water and in a light-dark cycle of 16:8 hours. Two weeks before starting the experiment, the subjects were gradually deprived of food until they reached 80% of their original weight. Animals then were assigned to each condition in a semi-randomized fashion, so that each condition consisted equally of males and females and were of similar average body weight. All procedures in this and the following experiments were approved by the Institutional Committee of Care and Use of Animals (CICUA) from Universidad of Chile.

Stimuli and Apparatus

Two sets of six experimental chambers with 32 × 25 × 26 cm dimensions (Med Associates Deluxe Package) were used in this and the following experiments. Each set was located in adjacent rooms. All chambers consisted of transparent Plexiglas® roof, front and back walls, and two stainless steel side walls. The floor was made of 0.5 cm diameter stainless steel bars, separated from each other by 1.2 cm. On top of the right wall a lickometer was placed, and on the left side, two 30 v and 4 w lights. A food magazine was located on the center of this wall through which pellets were dispensed by a feeder, and to the right and left side of the food magazine were each of two levers, left and right levers, which were counterbalanced as Lever 1 (L1) and Lever 2 (L2). Each lever was separated 3.2 cm away from the feeder and by 6.4 cm from the floor of the chamber. A speaker was placed in each of the steel walls. 45 mg chocolate-flavored sugar pellets (BioServ) were used as reinforcement for lever pressing.

DCS (Sigma-Aldrich, St. Louis, MO) was administered in doses of 30 mg/kg, diluted in physiological serum, and then injected intraperitoneally in a volume of 1 ml/kg. For the control groups, the same volume of a saline solution was injected in. All administrations were conducted in a room contiguous to the

experimental ones and used exclusively for that purpose. After each administration, subjects were immediately brought into the experimental chambers.

Procedure

Magazine Training. On day 1 all subjects received a 30 min session of magazine training. Throughout the session two pellets were delivered every 120 s, starting 2 min after beginning the session. A total of 15 pairs of food pellets were delivered.

Acquisition of L1 Pressing. For 5 days (2, 3, 4, 5 and 6) all subjects received one daily lever pressing training session. Training began with lever pressing in a continuous reinforcement schedule (that is, each response was reinforced). After subjects produced 30 responses, the schedule changed to a fixed-ratio-3 schedule (FR3), with a pellet delivered every 3 responses. After 30 responses in FR3, subjects were then switched to a fixed-ratio-7 schedule (FR7). Subjects remained in FR7 until 5 pellets were delivered, after which animals were switched to a 30 s variable interval schedule (VI30 s), in which they remained for the rest of the experiment. After finishing this phase, both groups were matched based on performance during the fifth session.

Extinction. All subjects received one daily extinction session for 3 days (days 7, 8, 9). Half of the subjects received 30 mg/kg of DCS, and the other half received saline solution in the same volume, 15 minutes prior to the extinction session, in a separate room. Each session lasted 30 min.

Spontaneous Recovery Test. Twenty-one days after the last extinction session (day 30), subjects received a 30-minute session with the available lever. No reinforcement was delivered in this phase.

Data Analysis

The number of lever pressings was recorded individually for each subject. Sessions were divided into 5-minute bins and mean responses per bin per subject were calculated. Lever pressing during both acquisition and extinction were analyzed with a mixed ANOVA with Session (mean responses of each in 5 acquisition sessions) as a within-subjects factor and DCS (DCS vs No-DCS) as a between-subjects factor. The first four extinction bins were also assessed with a mixed ANOVA with Bin (first 4 bins) as a within-subjects factor and DCS (DCS vs No-DCS) as a between-subjects factor, in order to examine whether the effect of DCS on extinction might be transient to the start of extinction. The spontaneous recovery test was analyzed with a mixed ANOVA with Phase (last 5 min bin of Extinction vs first 5 min bin of Spontaneous Recovery) as within-subject factor, and DCS (DCS vs No-DCS) as between-subject factor.

Results

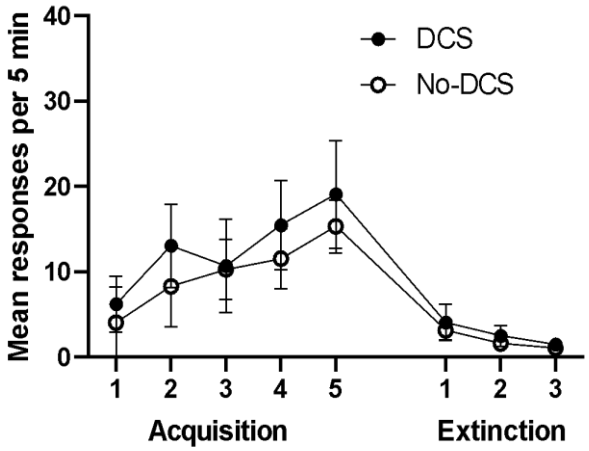
Acquisition

Lever press acquisition progressed steadily each session. The analysis showed that animals increased their lever pressing along training, $F(4,88) = 22.32$, $p < .001$, MSE = 21.174., $\eta_p^2 = .504$, IC 95% [0.33, 0.59], and that groups did not differ from each other, $F = 1.59$, $p = .220$. No interaction was observed, $F < 1$. Response means can be seen in Figure 1.

Extinction

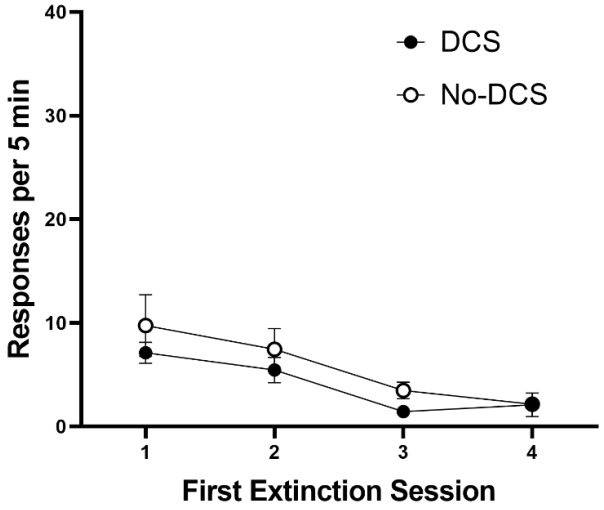
Lever pressing decreased across extinction sessions. The analysis showed an effect of Session, $F(2, 44) = 20.219$, $p < .001$, MSE = 1.681, $\eta_p^2 = .479$, IC 95% [0.24, 0.61]. No DCS effect was observed, $F(2, 44) = 1.583$, $p = .217$, and no interaction, $F < 1$. Mean responses during extinction can be seen in Figure 1. A mixed ANOVA conducted on the first 4 bins of first extinction phase (Figure 2) yielded an effect of Bin, $F(3, 66) = 12.458$, $p < .001$, MSE = 18.305, $\eta_p^2 = .362$, IC 95% [0.16, 0.48], but no other effects were observed, all Fs < 1.

Figure 1
Experiment 1 Acquisition and Extinction



Note. Each point represents the session mean responding in 5-min time bins. Each group is a different line. Error bars represent 95% CI.

Figure 2
First Extinction Session

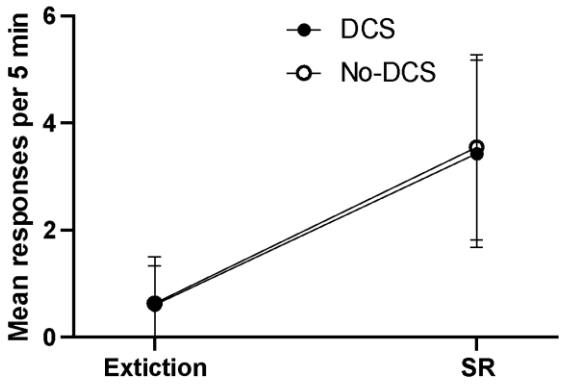


Note. Each point represents 5-min time bins during the first session of extinction. Each group is a different line. Error bars represent 95% CI.

Spontaneous Recovery

The analysis showed an effect of Bin, indicating spontaneous recovery, $F(1, 22) = 21.977$, $p < .001$, MSE = 4.513, $\eta_p^2 = .493$, IC 95% [0.29, 0.6], but no other effects were detected, all $Fs < 1$, indicating similar levels of recovery in both groups. The results are shown in Figure 3.

Figure 3
Experiment 1 Spontaneous Recovery Test



Note. Each point represents the mean responding in 5-min time bins of the last extinction bin and the first SR bin. Each group is a different line. Error bars represent 95% CI.

Discussion

Spontaneous recovery was observed, but it was not affected by DCS. Additionally, no DCS effect was observed on extinction. Procedurally, the present study was similar to the previous report in renewal by Vurbic et al. (2011), which also failed to detect a DCS effect on response recovery. Compared to other DCS effect reports (e.g., Shaw et al., 2009), several differences in procedure, parameters and experimental design might help explain their different results. For instance, Shaw et al. (2009) removed the lever each time pellets were delivered, and added the sound of a bell, which would make the extinction context perceptually different to that of acquisition and thus make their procedure as a renewal one. Extinction was also more extensive, with 8 sessions, 20 min each, every 3 or 4 days; finally, their experimental subjects were mice instead of rats, and their dependent variable was the inter-response interval (IRI) instead of average lever pressing.

Another potential issue concerns the sensitivity of a 21-days long retention interval to the DCS effects. Previous evidence in other and similar preparations (e.g., Bouton et al., 2008; Vurbic et al., 2011; Woods & Bouton, 2006) suggests that the DCS effect might be transient, or at least limited to the extinction context. If that is the case, then a 21-days delay before testing might not be sensitive to the DCS effect, and a shorter interval would be more appropriate.

Based on this, it is possible that a different dependent variable might be more sensitive to a potential DCS effect. In Experiment 1, we registered the number of responses per minute; however, we did not record the time between these responses, limiting our analysis. Thus, in Experiment 2 both individual levers pressing as well as IRIs were registered. Experiment 2, as Experiment 1, aimed to examine the DCS effect on the extinction of a free operant. IRI was defined as the time interval between each lever press; short intervals indicate a higher responding level, while longer intervals indicate less responses. The spontaneous recovery test was also changed to a within-extinction test, that is, to the recovery that occurs between extinction sessions, in order to assess whether DCS is able to attenuate this short-term recovery.

Experiment 2

Experiment 2 was similar to Experiment 1, excepting the inclusion of IRI as dependent variable (Shaw et al., 2009). IRIs was defined and registered as different intervals: less than 0.5 s, between 0.5 s and 1 s, etc. The categories established were: 0.5 - 1 s, 1 - 1.5 s, 1.5 - 2 s, 2 - 2.5 s, 2.5 - 3 s, 3 - 3.5 s, 3.5 - 4 s, 4 - 4.5 s, 4.5 - 5 s, and > 5 s or pauses. Each interval frequencies were recorded for each subject and averaged across groups for a response profile of each group, which were then analyzed. The final part of the lever training was also changed from IV30 to RF5, since a variable interval schedule may be more difficult to extinguish (Lattal et al., 2013). Lever training and extinction were identical to Experiment 1 (Vurbic et al., 2011). Spontaneous recovery was assessed between extinction sessions because of the lack of an effect on spontaneous recovery

after 21 days, during experiment 1, and since the transient effects of DCS observe on previous studies (e.g., Vurbic et al., 2011).

Method

Subjects, Stimuli and Apparatus

Subjects, stimuli and apparatus were similar to Experiment 1.

Procedure

Magazine Training. Magazine training was similar to the previous experiment.

Acquisition of L1 Pressing. This phase was similar to the Experiment 1 acquisition phase, with the exception that training finished when subjects were switched to a FR5 schedule.

Extinction and Spontaneous Recovery. The extinction and spontaneous recovery phases were identical to the previous experiment. However, spontaneous recovery was analyzed as the amount of response recovery between extinction sessions. A new way of assessing spontaneous recovery was used due to the failure of the previous experiment in finding spontaneous recovery evidence.

Data Analysis

Data was collected as in Experiment 1, with the addition of IRIs. The session average presses per 5 min bins was used to analyze acquisition with a mixed ANOVA with Group (DCS vs. No-DCS) as a between-subject factor and session (each of the 5 acquisition sessions) as a within-subject factor. Extinction analysis was a mixed ANOVA where the factors were group (DCS vs. No-DCS) as a between-subject factor and session (3 sessions) as a within-subject factor. Responses during extinction were also examined through the frequency distribution of their IRIs. All individual frequencies of the first extinction session were analyzed with a mixed ANOVA with DCS (DCS vs No-DCS) as a between-subject factor and frequency (all 11 frequency categories from 0.5 to 5 plus a >5 category) as a within-subjects factor. Spontaneous recovery was analyzed with a mixed ANOVA with DCS (DCS vs No-DCS) as between-subjects factor and bin (last 5 minutes of the first extinction session vs first 5 minutes of second extinction session) as a within-subjects factor.

Results

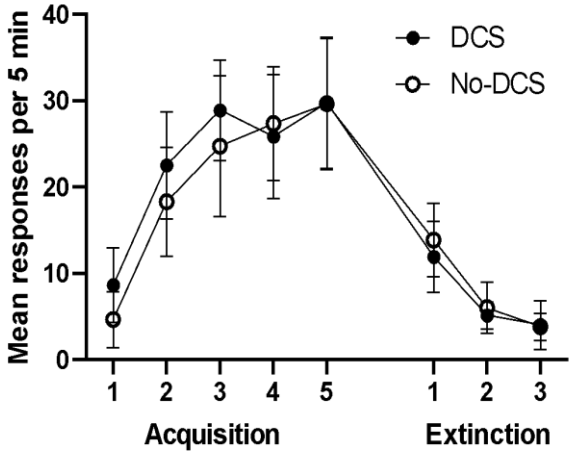
Acquisition

Lever press responses gradually increased across acquisition sessions, as shown by the following analysis. There was an effect of session, $F(4, 88) = 72.437$, $p < .001$, MSE = 28.306, $\eta_p^2 = .767$, IC 95% [0.66, 0.81], but no effect of group, $F < 1$, or interaction, $F(4, 88) = 1.552$, $p = .194$, were found. Figure 4 shows average responses across sessions.

Extinction

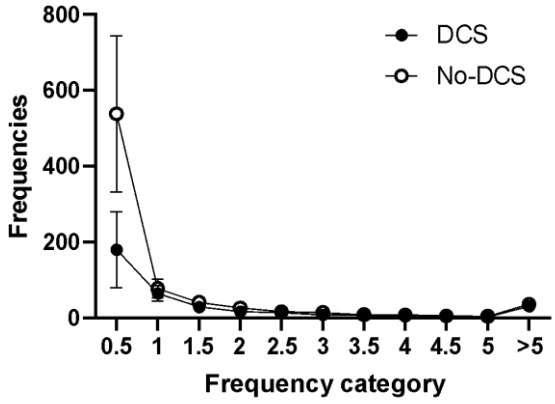
Lever press responses decreased across sessions, as shown in Figure 5. The analyses showed an effect of session, $F(2, 44) = 32.2$, $p < .001$, MSE = 16.949, $\eta_p^2 = .594$, IC 95% [0.37, 0.7]. No other effect or interaction were found, all Fs < 1. Regarding IRIs, there was a main effect of DCS, $F(10, 220) = 12.84$, $p = .002$, MSE = 7.279, $\eta_p^2 = .368$, IC 95% [0.24, 0.43], a main effect of frequency, $F(10, 220) = 43.58$, $p < .001$, MSE = 5.957, $\eta_p^2 = .664$, IC 95% [0.57, 0.70], and also a DCS x Frequency interaction, $F(10, 220) = 11.42$, $p < .001$, MSE = 5.957, $\eta_p^2 = .341$, IC 95% [0.21, 0.40]. As depicted in Figure 5, results show that, overall, the faster responses were, the higher the frequency and that in the fastest category (0.5), the No-DCS group had higher frequency than the DCS Group.

Figure 4
Experiment 2 Acquisition and Extinction



Note. Each point represents the session mean responding in 5-min time bins. Each group is a different line. Error bars represent 95% CI.

Figure 5
Experiment 2 IRI Frequencies during Extinction

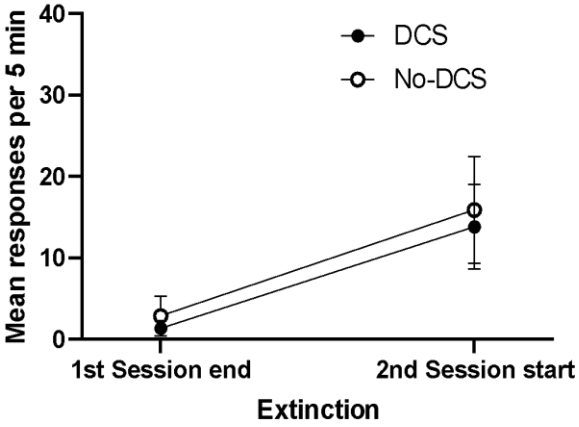


Note. Each point represents the inter-response interval frequency mean corresponding to each category. 0.5 is 0.5 or below, 1 is 1 or below, etc. Error bars represent 95% CI. 0.5 or below represents the fastest responding possible, more than 5 represents the slowest responding possible.

Spontaneous Recovery

The analyses yielded an effect of bin (last 5 minutes of the first extinction session vs first 5 minutes of second extinction session), $F(1, 22) = 57.782$, $p < .001$, MSE = 33.760, $\eta_p^2 = .724$, IC 95% [0.46, 0.82]. No DCS effect nor an interaction were found, all Fs < 1 (see Figure 6).

Figure 6
Spontaneous Recovery Test of Experiment 2



Note. Each point represents mean responding in 5-min time bins of the first extinction session's last bin and the first bin of the second extinction session. Each group is a different line. Error bars represent 95% CI.

Discussion

Experiment 2 showed that, as observed by Shaw et al. (2009), DCS produces a more pronounced extinction when measured as frequency of IRIs. That is, the DCS group showed slower responses while subjects in the control group responded quicker, as if they were expecting the omitted reinforcer. This increased extinction is observed as the frequency of fast (IRI < 1 s) responses, indicating a faster reduction of this IRI in the DCS group. On the other hand, between-session recovery was observed at similar levels in both groups, suggesting that this short-term recovery was not affected by the DCS. Thus, DCS appears to have a significant but limited effect on extinction and does not transfer to sessions other than the one in which the application took place. This is consistent with the Experiment 1 results and suggest that the lack of an effect on spontaneous recovery after 21 days was not due to a low sensitivity of the test, and also agrees with previous studies showing transient DCS effects (e.g., Vurbic et al., 2011).

Experiment 3

Although the data appears to suggest that response recovery in operant conditioning is not sensitive to DCS, one phenomenon remains thus far unexplored. Resurgence is an operant recovery phenomenon that occurs when a response is reinforced while concurrently extinguishing another, previously reinforced operant response. Then, in a test phase, while both responses are in extinction and produce no reinforcement, a responding resurgence to the first previously reinforced response is observed (Bouton et al., 2012). In the case of lever pressing, a lever is first reinforced in a phase (e.g., L1+), and in a second phase, a second lever is reinforced while extinguishing the first lever (L1-/L2+). In the test phase, both levers are present producing no reinforcement (L1-/L2-). Resurgence occurs when responses to L1 increase.

Experiment 3 aimed at examining whether DCS affects the extinction and resurgence of an operant response. To our knowledge, no study has examined the DCS effect on resurgence; thus, the present experimental design was based on previous reports of resurgence, more specifically the study of Winterbauer & Bouton (2010). Experiment 3 implemented a factorial design with a resurgence procedure and its control (extinction) as one factor, and the DCS presence or absence as another factor, for a total of four conditions. The resurgence factor is different in the second phase, L2 is either reinforced (R) or not-reinforced (NR), and the DCS factor is the administration of DCS during the second phase (DCS) or its absence (No-DCS). DCS is expected to deepen the extinction of a free operant and prevent resurgence. Table 2 shows the Experiment 3 design.

Table 2
Experiment 3 Design

Group	Acquisition	Extinction/Acquisition	Test	Ho	
R-No DCS	L1+	L1-/L2+ Saline	L1- vs. L2-	L1	RC
R-DCS		L1-/L2+ DCS		L1	rc
EXT-No DCS		L1-/L2- Saline		L1 = L2	Rc
EXT-DCS		L1-/L2-DCS		L1 = L2	rc

Note. L1 and L2 = levers, + = reinforcement, - = no reinforcement; CR, Cr, cr = expected level of expected conditioned response, from highest to lowest.

Method

Subjects

Thirty-two Sprague-Dawley rats were used as subjects, in similar conditions to those used in Experiments 1 and 2. According to an a priori analysis, an *n* of 32 subjects allows a statistical power of .90 for an effect size of .25 using Cohen's f.

Stimulus and Apparatus

L1 and L2 were available to the subjects, counterbalanced. Chambers were otherwise the same as in the previous experiments. All sessions lasted 30 min.

Procedure

Magazine Training. Magazine training was similar to Experiments 1 and 2.

Acquisition of L1 Pressing. This phase was similar to that of the previous experiments.

Acquisition and Extinction of L2. All subjects received four sessions of L2 instrumental conditioning and L1 extinction (days 7, 8, 9, 10). L2 delivered reinforcement following the same schedule used previously for L1; the groups of the extinction condition had both levers available with no reinforcement delivered. For the DCS condition, DCS was injected in the first two sessions, 15 minutes before starting the session; subjects that received the saline solution underwent a similar procedure.

Resurgence Test. All animals received a final test session, in which both levers were present without reinforcement availability.

Data Analysis

Lever presses were registered in 5-min bins and averaged across each session. The L1 acquisition was analyzed using a mixed ANOVA with DCS (DCS vs NO-DCS) and condition (Extinction vs. Resurgence) as between-subject factors, and session (each of 5 acquisition sessions) as within-subject factor. Additionally, category frequencies were obtained from IRI data, and analyzed with an analogous mixed ANOVA. Two animals were excluded from all analysis due to failure to learn lever pressing (one from the E-DCS Group and one from the R-DCS Group). The second resurgence phase, L2 acquisition and L1 extinction were analyzed with two ANOVAs. First, a mixed ANOVA was performed on L1 responses with DCS (DCS vs NO-DCS) and condition (Extinction vs. Resurgence) as between-subject factors, and session (each of 3 sessions) as within-subject factor. Then, the same analysis was performed on L2 responses. Resurgence was analyzed with two types of data. First, a mixed ANOVA with DCS (DCS vs NO-DCS) and condition (Extinction vs. Resurgence) as between-subject factors, and bin (six 5-min each, time bins during test session) as within-subject factor was performed on lever presses per 5 minutes on L1. Second, IRI of L1 responses were separated into 11 categories as previously described. A mixed ANOVA was used with frequency (all 11 IRI

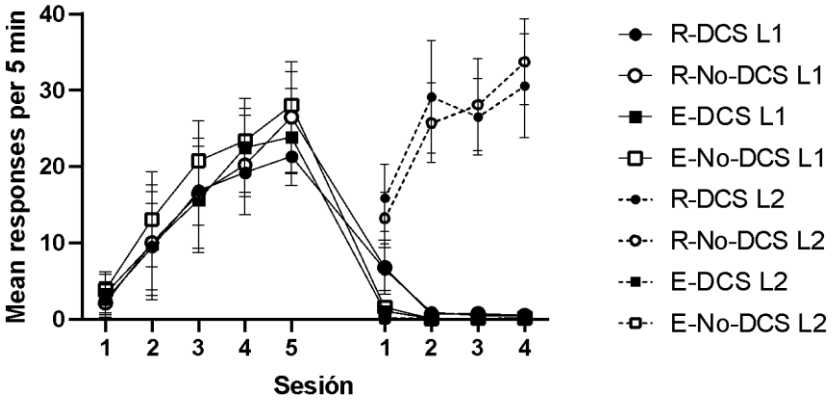
categories from 0.5 to > 5 and pause) as a within-subjects factor and DCS (DCS vs No-DCS) and condition (Extinction vs Reinforcement) as between-subject factors.

Results

L1 Acquisition

Lever pressing responses on L1 increased regularly across sessions, as shown in Figure 7. The analysis was performed with a Huynh-Feldt correction due to a sphericity violation. There was a session effect, $F(3.355, 140.908) = 144.730$, $p < .001$, MSE = 29.028, $\eta_p^2 = .775$, IC 95% [0.7, 0.81]; no other effects or interactions were detected, all $Fs < 1$, except for a session x DCS interaction, $F(3.355, 140.908) = 1.431$, $p = .233$.

Figure 7
Experiment 3 L1 Acquisition and Extinction and L2 Acquisition



Note. Each line represents either responding to L1 or L2 of each of 4 groups. Error bars represent 95% CI.

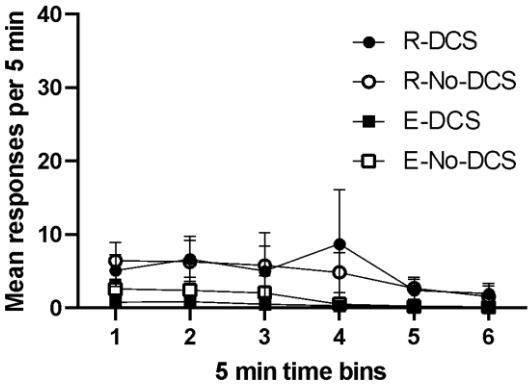
L2 Acquisition and L1 Extinction

All the analysis were Huynh-Feldt corrected due to a sphericity assumption violation. L1 responses decreased along sessions, as shown in Figure 7. A session effect was observed, $F(1.052, 44.2) = 49.026$, $p < .001$, MSE = 8.773, $\eta_p^2 = .538$, IC 95% [0.32, 0.66], as well as a session x condition interaction, $F(1.052, 44.2) = 21.697$, $p < .001$, MSE = 8.773, $\eta_p^2 = .34$, IC 95% [0.12, 0.51], indicating that responses in the reinforcement condition were higher than in the extinction condition. Animals in the reinforcement condition had overall higher response levels, as shown by a main effect of condition, $F(1, 42) = 36.215$, $p < .001$, MSE = 3.802, $\eta_p^2 = .463$, IC 95% [0.23, 0.61]. No other effects or interaction were found, all $Fs < 1$. A similar analysis was performed on L2 responses. There was a main effect of condition, $F(1, 42) = 252.624$, $p < .001$, MSE = 115.860, $\eta_p^2 = .857$, IC 95% [0.76, 0.89], and of session, $F(2.431, 102.087) = 66.302$, $p < .001$, MSE = 12.175, $\eta_p^2 = .612$, IC 95% [0.48, 0.68]. A session x condition interaction was also observed, $F(2.431, 102.087) = 66.831$, $p < .001$, MSE = 12.175, $\eta_p^2 = .614$, IC 95% [0.48, 0.68], a session x DCS interaction, $F(2.431, 102.087) = 3.104$, $p = .04$, MSE = 12.175, $\eta_p^2 = .614$, IC 95% [0.48, 0.68], as well as a marginal session × DCS × condition triple interaction, $F(2.431, 102.087) = 2.845$, $p = .052$. No other effects or interactions were observed, all $Fs < 1$.

Lever Pressing in Resurgence

Responses overall decreased across the session as depicted in Figure 8. The analysis showed a bin effect, $F(2.917, 128.350) = 7.951$, $p < .001$, MSE = 17.573, $\eta_p^2 = 0.15$, IC 95% [0.4, 0.25], and condition, $F(1, 44) = 32.251$, $p < .001$, MSE = 31.093, $\eta_p^2 = 0.42$, IC 95% [0.19, 0.57]. There was also a condition x bin interaction, $F(2.917, 128.350) = 3.004$, $p = .034$, MSE = 17.573, $\eta_p^2 = 0.06$, IC 95% [0.0, 0.14], but no bin x DCS interaction, $F(27.195, 17.573) = 3.004$, $p = .206$. No other effects or interactions were detected, all $Fs < 1$.

Figure 8
Experiment 3 Resurgence Test

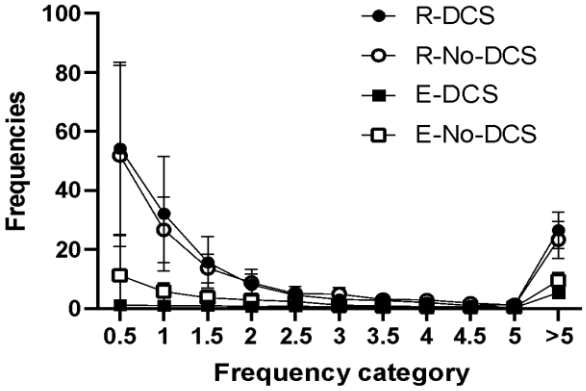


Note. Each line represents L1 mean responding from each group. Error bars represent 95% CI.

Inter-Response Interval in Resurgence

IRIs during the resurgence test are shown in Figure 9. As depicted, the reinforcement condition had overall a higher frequency of responses; this is supported by a main effect of condition, $F(1, 42) = 36.12$, $p < .001$, MSE = 428.02, $\eta_p^2 = .462$, IC 95% [0.23, 0.61]. A main frequency effect, $F(1, 42) = 32.404$, $p < .001$, MSE = 120.33, $\eta_p^2 = .435$, IC 95% [0.35, 0.48] was also observed, indicating a higher presence of fast responses than of slow ones. Finally, there was also a condition x frequency interaction, $F(1, 42) = 19.65$, $p < .001$, MSE = 120.33, $\eta_p^2 = .318$, IC 95% [0.23, 0.55], indicating a flatter distribution of frequencies in the extinction condition. No other effects or interactions were found, all $Fs < 1$.

Figure 9
Experiment 3 IRI f = Frequencies of Resurgence



Note. Each point represents the mean response IRI frequency corresponding to each category. 0.5 is 0.5 or below, 1 is 1 or below, etc. Error bars represent 95% CI.

Discussion

Experiment 3 results showed a basic resurgence phenomenon, indicated by the amount of responding to L1 during the resurgence test. However, no difference was observed between the groups with and without DCS, regardless of the dependent variable. DCS might improve memory and learning (Guastella et al., 2007; Norberg et al., 2008), but with the results of the present experiment the hypothesis that DCS might improve operant extinction and thus help prevent resurgence failed to be supported. Interestingly, Experiment 3

design was based on one of two possible resurgence designs; resurgence can be sequential (Epstein, 1983; Winterbauer & Bouton, 2010) or concurrent (e.g., Winterbauer & Bouton, 2010). The present experiment implemented a concurrent design, in which acquisition and extinction are conducted simultaneously in phase 2. A DCS effect on either of these memories (or both) could have affected the response recovery effect (responses of L1 at test). The failure to observe such an effect strongly indicates that DCS did not affect the L1 memory of extinction or L2 acquisition.

General Discussion

Three experiments sought to examine whether DCS affects the extinction and recovery of a free operant; experiments 1 and 2 were aimed at assessing the DCS effect on spontaneous recovery, and experiment 3 on resurgence. However, only a transient DCS effect was observed in experiment 2 when analyzing IRIs during extinction; no DCS effect was detected on responses per minute during extinction, nor on any variable in either spontaneous recovery or resurgence. Thus, the present study results strongly suggest that, while DCS might have an effect on extinction learning, this effect does not transfer to post-extinction recovery. These DCS results, on the other hand, are consistent with previous evidence in similar tasks (e.g., Port & Seybold, 1998; Vurbic et al., 2011; Woods & Bouton, 2006).

At an associative level, our task did produce acquisition, extinction, and recovery. First, these findings are coherent with the literature in both operant learning (Bernal-Gamboa et al., 2014; Bouton et al., 2012; Graham & Gagné, 1940; Winterbauer & Bouton, 2010) and Pavlovian conditioning (e.g., Alfaro et al., 2019; Bustamante et al., 2019; González et al., 2016; Miller et al., 2015; Miguez et al., 2014; San Martín et al., 2020. Second, these effects allow us to explore the further DCS effect on them. We were able to observe them using two dependent measures, IRIs and response frequency.

The finding that IRIs may be more sensitive to differences in extinction is an interesting fact for future research regarding extinction phenomena. In experiment 2, the DCS group showed during extinction a lower frequency of fast responses compared to the control group. An extinction procedure might eliminate first fast responses as it lowers the overall response frequencies; thus, it appears that with IRIs small differences in the velocity at which extinction proceeds could be observed, which with other variables would not be detected by the analyses due to them being confounded with the overall reduction in responses that occurs during extinction.

Concerning the results, a central resurgence feature is that it extinguishes an operant response while at the same time reinforces another. DCS was administered during this crucial phase but no effects were observed in the L1 resurgence, even if it might have affected both L1 acquisition and L2 extinction, which should have facilitated the recovery of L1. One possible explanation for this failure comes from the "renewal" hypothesis by Winterbauer & Bouton (2010). Winterbauer and Bouton suggested that resurgence can be explained as a special case of renewal. The alternative behavior and its reinforcement (i.e., L2) would provide an extinction context for L1. When the alternative behavior is no longer reinforced, it constitutes a context change, leading to the recovery of the first learned behavior as in renewal (Bouton et al., 2012). In experiment 3, the DCS administration as well as all the associated procedure can be considered as an interoceptive stimulus, which would have enhanced the perceptual difference between contexts, leading to a failure in preventing resurgence (e.g., Vurbic et al., 2011). One interesting implication of this hypothesis is that DCS should not be able to prevent any response recovery phenomenon; response recovery, be it spontaneous recovery or resurgence, would occur because there is a change of context between extinction and testing (e.g., Bouton et al., 2012). Thus, DCS would at most enhance the memory of extinction within its own context.

A second possible explanation is associated with the so-called "response prevention" hypothesis. Leitenberg et al. (1975) suggested that the source of resurgence was that L1 extinction is prevented because L2 acquisition is conducted at the same time; thus, when the alternative behavior is extinguished, the first one reappears, since it was never really extinguished. In this case, it is possible that DCS indeed enhanced the L2 learning (but not of L1), meaning that during the test responding to L1 would also be observed. L1 extinction would not be affected by DCS because, according to this hypothesis, extinction never happened.

The design of experiment 3 does not allow examining this hypothesis. An interesting design for future research would be examining resurgence in sequential phases, that is, conducting L1 extinction and L2 acquisition at different times. This manipulation would facilitate L1 extinction by avoiding the L2 simultaneous training (Leitenberg et al., 1975), while also retiring any context that the reinforcer might be

providing (Winterbauer & Bouton, 2010). Two issues are however more difficult to resolve: first, it is possible that the DCS administration still provides a context to extinction and in this case, recovery would still occur; second, in spontaneous recovery the context is also given by the passage of time, and thus it is not possible to test recovery without a context. The first case can be at least partially solved by reducing the paraphernalia associated with DCS administration when possible. The second issue can be addressed by reducing the time interval between extinction and test, but as the result of experiment 2 suggests, it is likely that the DCS effect is too transient to extend beyond one extinction session.

The evidence presented in this study concerning the DCS effects on response recovery phenomenon could be relevant regarding its use as an effective tool for therapeutic use. The usefulness of a drug capable of enhancing extinction is diminished if it does not translate into a concordant effect on response recovery. Thus, a probable DCS application as a therapy aid might be limited to a transient effect on the first few sessions of extinction-based therapy, but would not be helpful in preventing relapse, which is one of the main problems of this approach (e.g., Vervliet et al., 2013).

References

Aigner, T. G., & Balster, R. L. (1978). Choice behavior in rhesus monkeys: Cocaine versus food. *Science*, *201*(4355), 534–535. https://doi.org/10.1126/science.96531

Alfaro, F., Navarro, V. M., Laborda, M. A., Betancourt, R., & Miguez, G. (2019). Rol de estímulos asociados a las claves de extinción en la recuperación de respuesta. *Psykhe*, *28*(1), 1–15. https://doi.org/10.7764/psykhe.28.1.1282

Bernal-Gamboa, R., Carrasco-López, M., & Nieto, J. (2014). Contrasting ABA, AAB and ABC renewal in a free operant procedure. *Spanish Journal of Psychology*, *17*, Article E67. https://doi.org/10.1017/sjp.2014.68

Bigelow, G. E., Stitzer, M. L., Griffiths, R. R., & Liebson, I. A. (1981). Contingency management approaches to drug self-administration and drug abuse: Efficacy and limitations. *Addictive Behaviors*, *6*(3), 241–252. https://doi.org/10.1016/0306-4603(81)90022-8

Bouton, M. E., Vurbic, D., & Woods, A. M. (2008). D-cycloserine facilitates context-specific fear extinction learning. *Neurobiology of Learning and Memory*, *90*(3), 504–510. https://doi.org/10.1016/j.nlm.2008.07.003

Bouton, M. E., Winterbauer, N. E., & Todd, T. P. (2012). Relapse processes after the extinction of instrumental learning: Renewal, resurgence, and reacquisition. *Behavioural Processes*, *90*(1), 130–141. https://doi.org/10.1016/j.beproc.2012.03.004

Bustamante, J., San Martín, C., Laborda, M. A., & Miguez, G. (2019) An extinction cue does not necessarily prevent response recovery after extinction. *Learning and Motivation*, *67*, 101576. https://doi.org/10.1016/j.lmot.2019.101576

Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014). Maximizing exposure therapy: An inhibitory learning approach. *Behaviour Research and Therapy*, *58*, 10–23. https://doi.org/10.1016/j.brat.2014.04.006

Craske, M., Hermans, D., & Vervliet, B. (2018). State-of-the-art and future directions for extinction as a translational model for fear and anxiety. *Philosophical Transactions of the Royal Society B: Biological Sciences, 373*, Article 20170025. https://doi.org/10.1098/rstb.2017.0025

Culver, N. C., Stevens, S., Fanselow, M. S., & Craske, M. (2018). Building physiological toughness: Some aversive events during extinction may attenuate return of fear. *Journal of Behavior Therapy and Experimental Psychiatry*, *58*, 18–28. https://doi.org/10.1016/j.jbtep.2017.07.003

Dudai, Y., Jan, Y. N., Byers, D., Quinn, W. G., & Benzer, S. (1976). dunce, a mutant of Drosophila deficient in learning. *Proceedings of the National Academy of Sciences of the United States of America*, *73*(5), 1684–1688. https://doi.org/10.1073/pnas.73.5.1684

Epstein, R. (1983). Resurgence of previously reinforced behavior during extinction. *Behaviour Analysis Letters*, *3*, 391–397.

Farmer, R. F., Nash, H. M., & Field, C. E. (2001). Disordered eating behaviors and reward sensitivity. *Journal of Behavior Therapy and Experimental Psychiatry*, *32*(4), 211–219. https://doi.org/10.1016/S0005-7916(01)00036-2

George, S. A., Rodriguez-Santiago, M., Riley, J., Abelson, J. L., Floresco, S. B., & Liberzon, I. (2018). D-cycloserine facilitates reversal in an animal model of post-traumatic stress disorder. *Behavioural Brain Research, 347*, 332–338. https://doi.org/10.1016/j.bbr.2018.03.037

González, V. V., Navarro, V., Miguez, G., Betancourt, R., & Laborda, M.A. (2016). Preventing the recovery of extinguished ethanol tolerance. *Behavioural Processes, 124*, 141–148. https://doi.org/10.1016/j.beproc.2016.01.004

Graham, C. H., & Gagné, R. M. (1940). The acquisition, extinction, and spontaneous recovery of a conditioned operant response. *Journal of Experimental Psychology*, *26*(3), 251–280. https://doi.org/10.1037/h0060674

Guastella, A. J., Lovibond, P. F., Dadds, M. R., Mitchell, P., & Richardson, R. (2007). A randomized controlled trial of the effect of d-cycloserine on extinction and fear conditioning in humans. *Behaviour Research and Therapy*, *45*(4), 663–672. https://doi.org/10.1016/j.brat.2006.07.005

Guastella, A. J., Richardson, R., Lovibond, P. F., Rapee, R. M., Gaston, J. E., Mitchell, P., & Dadds, M. R. (2008). A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. *Biological Psychiatry*, *63*(6), 544–549. https://doi.org/10.1016/j.biopsych.2007.11.011

Harrison, A., Sternheim, L., O'Hara, C., Oldershaw, A., & Schmidt, U. (2016). Do reward and punishment sensitivity change after treatment for anorexia nervosa? *Personality and Individual Differences*, *96*, 40–46. https://doi.org/10.1016/j.paid.2016.02.051

Harrison, A., Treasure, J., & Smillie, L. D. (2011). Approach and avoidance motivation in eating disorders. *Psychiatry Research*, *188*(3), 396–401. https://doi.org/10.1016/j.psychres.2011.04.022

Hayes, S. C., Wilson, K. G., Gifford, E. V., Follette, V. M., & Strosahl, K. (1996). Experiential avoidance and behavioral disorders: A functional dimensional approach to diagnosis and treatment. *Journal of Consulting and Clinical Psychology*, *64*(6), 1152–1168. https://doi.org/10.1037/0022-006X.64.6.1152

Hofmann, S. G., Meuret, A. E., Smits, J. A. J., Simon, N. M., Pollack, M. H., Eisenmenger, K., Shiekh, M., & Otto, M. W. (2006). Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Archives of General Psychiatry*, *63*(3), 298–304. https://doi.org/10.1001/archpsyc.63.3.298

Hunt, C., Cooper, S. E., Hartnell, M. P., & Lissek, S. (2017). Distraction/suppression and distress endurance diminish the extent to which generalized conditioned fear is associated with maladaptive behavioral avoidance. *Behaviour Research and Therapy*, *96*, 90–105. https://doi.org/10.1016/j.brat.2017.04.013

Keating, C., Tilbrook, A. J., Rossell, S. L., Enticott, P. G., & Fitzgerald, P. B. (2012). Reward processing in anorexia nervosa. *Neuropsychologia, 50*(5), 567–575. https://doi.org/10.1016/j.neuropsychologia.2012.01.036

Krypotos, A.-M., Effting, M., Kindt, M., & Beckers, T. (2015). Avoidance learning: A review of theoretical models and recent developments. *Frontiers in Behavioral Neuroscience*, *9*, Article 189. https://doi.org/10.3389/fnbeh.2015.00189

Krypotos, A.-M. M., Vervliet, B., & Engelhard, I. M. (2018). The validity of human avoidance paradigms. *Behaviour Research and Therapy*, *111*, 99–105. https://doi.org/10.1016/j.brat.2018.10.011

Langton, J. M., & Richardson, R. (2010). The effect of D-cycloserine on immediate vs. delayed extinction of learned fear. *Learning and Memory*, *17*(11), 547–551. https://doi.org/10.1101/lm.1927310

Lattal, K. A., St. Peter, C., & Escobar, R. (2013). Operant extinction: Elimination and generation of behavior. In G. J. Madden, W. V. Dube, T. D. Hackenberg, G. P. Hanley, & K. A. Lattal (Eds.), *APA handbook of behavior analysis, Vol. 2: Translating principles into practice* (pp. 77–107). American Psychological Association. https://doi.org/10.1037/13938-004

Ledgerwood, L., Richardson, R., & Cranney, J. (2003). Effects of D-cycloserine on extinction of conditioned freezing. *Behavioral Neuroscience*, *117*(2), 341–349. https://doi.org/10.1037/0735-7044.117.2.341

Ledgerwood, L., Richardson, R., & Cranney, J. (2004). D-cycloserine and the facilitation of extinction of conditioned fear: Consequences for reinstatement. *Behavioral Neuroscience*, *118*(3), 505–513. https://doi.org/10.1037/0735-7044.118.3.505

Ledgerwood, L., Richardson, R., & Cranney, J. (2005). D-cycloserine facilitates extinction of learned fear: Effects on reacquisition and generalized extinction. *Biological Psychiatry*, *57*(8), 841–847. https://doi.org/10.1016/j.biopsych.2005.01.023

Leitenberg, H., Rawson, R. A., & Mulick, J. A. (1975). Extinction and reinforcement of alternative behavior. *Journal of Comparative and Physiological Psychology*, *88*(2), 640–652. https://doi.org/10.1037/h0076418

Lovibond, P. (2007). Fear and avoidance: An integrated expectancy model. In M. G. Craske, D. Hermans, & D. Vansteenwegen (Eds.), *Fear and learning: From basic processes to clinical implications* (pp. 117–132). American Psychological Association. https://doi.org/10.1037/11474-006

Lovibond, P. F., Saunders, J. C., Weidemann, G., & Mitchell, C. J. (2008). Evidence for expectancy as a mediator of avoidance and anxiety in a laboratory model of human avoidance learning. *Quarterly Journal of Experimental Psychology*, *61*(8), 1199–1216. https://doi.org/10.1080/17470210701503229

Miller, R. R., Laborda, M. A., Polack, C. W., & Miguez, G. (2015). Comparing the context specificity of extinction and latent inhibition. *Learning & Behavior*, *43*(4), 384–395. https://doi.org/10.3758/s13420-015-0186-x

Miguez, G., Witnauer, J. E., Laborda, M.A., & Miller, R. R. (2014). Trial spacing during extinction: The role of context–US associations. *Journal of Experimental Psychology: Animal Learning and Cognition, 40*(1), 81–91. https://doi.org/10.1037/a0033203

Nic Dhonnchadha, B. Á., Szalay, J. J., Achat-Mendes, C., Platt, D. M., Otto, M. W., Spealman, R. D., & Kantak, K. M. (2010). D-cycloserine deters reacquisition of cocaine self-administration by augmenting extinction learning. *Neuropsychopharmacology*, *35*(2), 357–367. https://doi.org/10.1038/npp.2009.139

Norberg, M. M., Krystal, J. H., & Tolin, D. F. (2008). A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biological Psychiatry, 63*(12), 1118–1126. https://doi.org/10.1016/j.biopsych.2008.01.012

Pelchat, M. L. (2002). Of human bondage: Food craving, obsession, compulsion, and addiction. *Physiology and Behavior*, *76*(3), 347–352. https://doi.org/10.1016/S0031-9384(02)00757-6

Peters, J., & De Vries, T. J. (2013). D-cycloserine administered directly to infralimbic medial prefrontal cortex enhances extinction memory in sucrose-seeking animals. *Neuroscience*, *230*, 24–30. https://doi.org/10.1016/j.neuroscience.2012.11.004

Port, R. L., & Seybold, K. S. (1998). Manipulation of NMDA-receptor activity alters extinction of an instrumental response in rats. *Physiology and Behavior*, *64*(3), 391–393. https://doi.org/10.1016/S0031-9384(98)00095-X

San Martín, C., Jacobs, B., & Vervliet, B. (2020). Further characterization of relief dynamics in the conditioning and generalization of avoidance: Effects of distress tolerance and intolerance of uncertainty. *Behaviour Research and Therapy*, *124*, Article 103526. https://doi.org/10.1016/j.brat.2019.103526

Shaw, D., Norwood, K., Sharp, K., Quigley, L., McGovern, S. F. J., & Leslie, J. C. (2009). Facilitation of extinction of operant behaviour in mice by D-cycloserine. *Psychopharmacology*, *202*, 397–402. https://doi.org/10.1007/s00213-008-1312-7

Siegmund, A., Golfels, F., Finck, C., Halisch, A., Räth, D., Plag, J., & Ströhle, A. (2011). D-cycloserine does not improve but might slightly speed up the outcome of in-vivo exposure therapy in patients with severe agoraphobia and panic disorder in a randomized double blind clinical trial. *Journal of Psychiatric Research*, *45*(8), 1042–1047. https://doi.org/10.1016/j.jpsychires.2011.01.020

Silverman, K. (2004). Exploring the limits and utility of operant conditioning in the treatment of drug addiction. *Behavior Analyst*, *27*(2), 209–230. https://doi.org/10.1007/BF03393181

Steinglass, J. E., Figner, B., Berkowitz, S., Simpson, H. B., Weber, E. U., & Walsh, B. T. (2012). Increased capacity to delay reward in anorexia nervosa. *Journal of the International Neuropsychological Society*, *18*(4), 773–780. https://doi.org/10.1017/S1355617712000446

Thompson, B. L., & Waltz, J. (2010). Mindfulness and experiential avoidance as predictors of posttraumatic stress disorder avoidance symptom severity. *Journal of Anxiety Disorders*, *24*(4), 409–415. https://doi.org/10.1016/J.JANXDIS.2010.02.005

Vengeliene, V., Kiefer, F., & Spanagel, R. (2008). D-cycloserine facilitates extinction of conditioned alcohol-seeking behaviour in rats. *Alcohol and Alcoholism*, *43*(6), 626–629. https://doi.org/10.1093/alcalc/agn067

Vervliet, B., Craske, M., & Hermans, D. (2013). Fear extinction and relapse: State of the art. *Annual Review of Clinical Psychology*, *9*(1), 215–248. https://doi.org/10.1146/annurev-clinpsy-050212-185542

Vurbic, D., Gold, B., & Bouton, M. E. (2011). Effects of D-cycloserine on the extinction of appetitive operant learning. *Behavioral Neuroscience*, *125*(4), 551–559. https://doi.org/10.1037/a0024403

Winterbauer, N. E., & Bouton, M. E. (2010). Mechanisms of resurgence of an extinguished instrumental behavior. *Journal of Experimental Psychology: Animal Behavior Processes*, *36*(3), 343–353. https://doi.org/10.1037/a0017365

Woods, A. M., & Bouton, M. E. (2006). D-cycloserine facilitates extinction but does not eliminate renewal of the conditioned emotional response. *Behavioral Neuroscience*, *120*(5), 1159–1162. https://doi.org/10.1037/0735-7044.120.5.1159

Fecha de recepción: Julio de 2021.
Fecha de aceptación: Junio de 2022.