Effects of multiple exposures to D-cycloserine on extinction of conditioned fear in rats

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Abstract

Previous research has shown that an acute, post-training injection of D-cycloserine (DCS) facilitates extinction of conditioned fear in rats; however, the effects of multiple exposures to DCS in this situation are not known. In Experiment 1, rats were conditioned (light-shock pairings) and 24 h later given six extinction (light-alone) trials followed by an injection of DCS (15 mg/kg) or saline. The next day, all rats were tested for light-elicited freezing. In Experiment 2, the effect of DCS on extinction was tested in the same manner, except that rats were pre-exposed to DCS (0, 1, or 5 injections) just prior to conditioning. In Experiment 3, rats received five pre-exposures of DCS but conditioning occurred either 2 or 28 days after the last pre-exposure. The results showed that DCS facilitated extinction of conditioned freezing to the light CS when no drug pre-exposure had occurred, but pre-exposure to DCS just prior to conditioning disrupted the facilitation of extinction effect. When 28 days were interposed between pre-exposure and conditioning, the facilitatory effects of DCS on extinction were restored. These findings suggest that DCS has significant clinical value but that behavioral desensitization may occur with multiple exposures; however, desensitization is not permanent and is reduced by the passage of time.

Keywords: Extinction; D-Cycloserine; Learned fear; Rats; Freezing

1. Introduction

In the laboratory, Pavlovian fear conditioning involves presenting rats with pairings of an innocuous conditioned stimulus (CS; e.g., a light) and an aversive unconditioned stimulus (US; e.g., footshock). When the CS is subsequently presented alone, a fear reaction is elicited. However, over successive presentations of the CS alone, the rat gradually ceases to exhibit fear behaviors. This reduction in CS-elicited fear is thought to occur because the rat learns that the CS no longer predicts an aversive outcome, and thus be fear of the CS is ‘extinguished.’

This animal model of fear extinction has provided the basis for some current treatments of anxiety disorders in the clinic. Specifically, one behavioral technique that is widely used to treat anxiety disorders such as Panic Disorder, Posttraumatic Stress Disorder, Obsessive-Compulsive Disorder, and Phobia, is exposure therapy (Andrews, Grino, Hunt, & Page, 1994; Barlow, 2001; Foa & Kozak, 1986; Thyer, Baum, & Reid, 1988; Zarate & Agras, 1994). Because intense fear of an object (or a situation) is often associated with significant avoidance, exposure therapy involves presenting the anxiety-eliciting object in a safe environment so that the client learns...
that aversive consequences are not going to occur. Although the effects of exposure therapy in humans may be interpreted in a number of ways, the extinction paradigm offers a potentially useful framework (Bouton, 1988; Dadds, Bovbjerg, Redd, & Cutmore, 1997; Marks & Tobena, 1990; Mineka & Cannon, 1999). Thus, treatments that enhance fear extinction in animal models may also be useful for alleviating anxiety disorders in humans.

Recent studies with rats have indicated that extinction of particular fear responses, such as freezing (Ledgerwood, Richardson, & Cranney, 2003) and fear potentiated startle (Walker, Ressler, Lu, & Davis, 2002), can be enhanced pharmacologically with the glycine partial agonist d-cycloserine (DCS). DCS increases excitatory neurotransmission by binding to the strychnine-insensitive glycine recognition site of the N-methyl-D-aspartate (NMDA) receptor complex, without inducing neurotoxicity. Indeed, DCS has been used in human populations in attempts to treat the cognitive impairments typically observed in Alzheimer’s disease (e.g., Schwartz, Hashtroudi, Herting, Schwartz, & Deutsch, 1996; Tsai, Falk, Gunther, & Coyle, 1999) and schizophrenia (e.g., Goff et al., 1999; Heresco-Levy et al., 2002). Further, and of more direct relevance, Ressler et al. (2004) have recently reported that DCS facilitates fear extinction in people with an anxiety disorder. Specifically, it was found that patients suffering from acrophobia displayed significantly reduced levels of fear if they had received DCS in combination with exposure therapy. Indeed, patients who received DCS after two exposure sessions showed a level of fear that was similar to patients who received a placebo and eight exposure sessions.

The finding that DCS facilitates fear extinction in acrophobia suggests that it may have considerable value in the treatment of anxiety disorders. However, important questions about the efficacy of DCS as a treatment adjunct remain. For example, no experimental studies to date have explicitly assessed the effects of multiple administrations of DCS on extinction of fear. This is of considerable interest because the treatment protocol for anxiety disorders often involves multiple exposure sessions (Andrews et al., 1994; Barlow, 2001; Thyer et al., 1988). Moreover, there is some pre-clinical evidence to suggest that long-term exposure to DCS leads to a significant decrease in the effects of DCS on behavior (Lopes, Neubauer, & Boje, 1997; Quartemain, Mower, Rafferty, Herting, & Lanthorn, 1994; Wlaz, Baran, & Loscher, 1994). For example, Lopes et al. (1997) examined the effects of DCS on the Porsolt swim test (PST; which is used as a pre-clinical drug screen to examine antidepressant properties of pharmacological agents). Rats given DCS prior to the swim test displayed less immobility during the PST than did rats given saline. However, if given five pre-exposures to DCS, then DCS-treated rats did not differ from saline-treated rats on the PST. In other words, the reduction in immobility that was observed after a single DCS administration was not maintained after multiple exposures to the drug.

To date, there have been no explicit tests of whether multiple exposures to DCS affect its ability to enhance extinction of conditioned fear. If DCS is to be used as an adjunct to exposure therapy, then it would be important to know whether repeated administrations of the drug reduce its effectiveness at enhancing extinction of learned fear. The aim of the present study, therefore, was not only to replicate previous findings showing that DCS promotes fear extinction in rats but also to examine whether this effect remains after pre-treatment with the drug.

2. General methods

2.1. Subjects

Experimentally naive, adult (90–150 days of age) male Sprague-Dawley rats obtained from the breeding colony maintained by the School of Psychology at the University of New South Wales were used. The rats were housed in groups of eight in plastic boxes (67 cm long × 40 cm wide × 22 cm high) in a colony room maintained on a 12-h light–dark cycle. Food and water were continuously available. All experimental procedures were approved by the Animal Care and Ethics Committee of the University of New South Wales and adhered to the ethical guidelines established by the American Psychological Association. Prior to experimentation, all rats were handled for approximately 5 min for three consecutive days.

2.2. Apparatus

Two types of cages were used. Fear conditioning occurred in one of four identical conditioning cages, each measuring 20 cm long × 12 cm wide × 12 cm high. The front wall, rear wall, and ceiling of each conditioning cage were made of clear Perspex, and the side walls and floor consisted of stainless steel bars, with 13 mm between each bar. Each pair of cages was located within a sound attenuating wood cabinet and each cage was separated from the other by a solid timber partition. A ventilation fan provided a 60-dB ambient noise level in each cabinet and a red lamp provided illumination. Underneath each cage was a tray of bedding that was cleaned between sessions. Unscrambled 50-Hz AC shock from a constant current generator (constructed at The University of New South Wales) could be delivered to the floor of each chamber. All programming, timing, and shock stimulus presentations were computer controlled.
Extinction training and testing occurred in one of two identical cages (30 cm long × 22.5 cm wide × 30 cm high) with a clear Perspex front, black and white striped side and rear walls, and a wood hinged lid. The floor consisted of stainless steel bars, with 10 mm between each bar, and was raised 8.5 cm above the base. Each cage was located within its own sound attenuating cabinet and a ventilation fan in the cabinets provided a low, constant background noise (60-dB). A red light bulb in each cabinet provided low-level illumination at all times, and a tray of bedding was placed underneath each cage. Between sessions, the chambers were wiped with 0.5% eucalyptus solution and the bedding was changed. Test sessions were videotaped for later assessment.

The conditioned stimulus (CS) was a white light that was mounted inside of each cabinet housing the conditioning and extinction/test cages. The intensity of the light CS was equivalent (approximately 16–17 lx) across the two sets of cages.

2.3. Drugs

D-Cycloserine (15 mg/kg; Sigma–Aldrich, Castle Hill, New South Wales) was freshly dissolved in sterile isotonic saline (0.9%) and injected subcutaneously in a volume of 1 ml/kg. The drug dose was chosen on the basis of the results of previous behavioral studies with DCS (Ledgerwood et al., 2003; Walker et al., 2002). Control animals were injected with 1 ml/kg saline.

3. Experiment 1

Experiment 1 aimed to replicate the findings of Ledgerwood et al. (2003) where an acute injection of DCS administered immediately after an extinction session was found to facilitate the extinction of conditioned freezing to a light CS.

3.1. Method

3.1.1. Procedure

A 2 × 2 factorial design was employed, where the first factor was drug condition (DCS or saline) and the second factor was training condition (extinction or no extinction). This produced four groups (all with n = 8): extinction + DCS (E-DCS), extinction + saline (E-Sal), no extinction + DCS (NE-DCS), and no extinction + saline (NE-Sal).

On day one, rats were pre-exposed to the conditioning cages for 20 min. Two to three hours later, rats were returned to the cages and after a 2-min adaptation period, received 5 pairings of a 10s white light and a conterminating 0.8s shock (0.8 mA). Each light-shock pairing was separated by 60s. Following the fifth light-shock presentation, rats remained in the cage for another 2 min before being returned to their home cage.

Extinction training occurred on day two, where after a 2-min baseline, rats were presented with 6 × 2-min presentations of the light in the absence of shock. Each light presentation was separated by 2-min. This amount of extinction training has previously been shown to produce moderate levels of fear extinction on the following day in saline-injected rats, allowing for an enhancing effect of DCS to be detected (Ledgerwood et al., 2003).

Immediately following extinction training, half the rats were injected with DCS and the other half with saline. The two groups that did not receive extinction training were handled for 5 min on day two, injected with either DCS or saline, and returned to their home cage.

On day three, all rats were placed in the extinction cages for the post-extinction test. The test session was 4 min long: 2 min without the light, and then 2 min with the light.

3.1.2. Data analysis

Each rat was scored for freezing during the six extinction trials1 and the post-extinction test. Freezing was characterized by an absence of all bodily movements except those required for breathing (Fanselow, 1994), and was measured using a time sampling method. That is, an observation was made every 3s and a positive or negative count was made. A percentage score was calculated for the proportion of the total observation period spent freezing. An additional observer, who was unaware of the group conditions of each rat, scored 50 percent of the testing sessions across the three experiments. The inter-rater reliability between these two scorers was high (r = 0.93).

For both the extinction and test sessions, the 2 min prior to the first CS presentation comprised the baseline score. Pilot studies had indicated a relatively high baseline level of freezing (i.e., freezing during the pre-CS period) during the post-extinction test for some rats. It was therefore decided to allow multiple baselines. Specifically, if a rat froze more than 50% during the 2-min period before the test presentation of the light, the rat was taken back to the colony room for a 5 min period after which it was tested again. If, after three separate baseline trials, the rat continued to freeze more than 50% at baseline, the animal was removed from the experiment.

Analysis of variance (ANOVA) was the primary statistical approach, and post hoc comparisons were made with Tukey’s Honestly Significant Difference test.

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1 The extinction data from Experiment 2 were not scored because of equipment malfunctions. Specifically, the extinction training sessions for eight rats, distributed unequally across groups, was not recorded.
3.2. Results and discussion

Data from two rats in the E-Sal group were lost due to equipment failure during the extinction session (therefore, they did not contribute any data to the extinction analysis; but they did provide data for the test analysis). In addition, data from one rat in the NE-DCS condition was excluded because it froze more than 50% during baseline in the post-extinction test.

During the first 2 min of the extinction training session, prior to the first light presentation (i.e., baseline), there was no difference in levels of freezing between rats that were to be injected with DCS and rats to be injected with saline \( t(13) = .47; p = .64 \). During the first light CS presentation, levels of freezing were high for both the DCS and the saline group, and freezing levels significantly decreased for both groups across the six extinction trials \( F(5, 60) = 26.0; p < .001 \); see Fig. 1A]. There were no group differences in freezing levels during the six CS presentations \( F < 1.0 \). That is, rats in both groups exhibited similar levels of conditioned fear, and similar rates of fear extinction.

Analysis of CS-elicited freezing at the post-extinction test 24 h later (see Fig. 1B), with a 2 × 2 ANOVA, revealed a significant interaction of extinction and drug condition \( F(1, 27) = 10.52, p = .003 \). The main effects of extinction and drug condition were not significant [both \( F s < 1 \)]. Post hoc tests (\( p < .05 \)) revealed that the rats that had received extinction training followed by DCS exhibited significantly less freezing than those rats given saline after extinction training, and those rats given DCS but not the extinction training. No other group differences in CS-elicited freezing were significant. There were no group differences in the level of freezing during the pre-CS period \( F < 1.0 \).

These data demonstrate that systemic DCS administration immediately following extinction training facilitates extinction of conditioned freezing. Further, because rats that received DCS in the absence of extinction training displayed significant levels of freezing at test, DCS appears to act specifically to enhance extinction, rather than on simply interfering with response expression.

4. Experiment 2

As noted in Section 1, there is pre-clinical evidence that long-term exposure to DCS may lead to a significant decrease in the effects of DCS on behavior (Lopes et al., 1997; Quartermain et al., 1994; Wlaz et al., 1994). Experiment 2 aimed to determine whether multiple exposures to DCS have any effect on the facilitatory effects of DCS on extinction of conditioned fear.

4.1. Method

4.1.1. Procedure

The training, extinction, and testing procedures were all as described in Experiment 1. This experiment employed a non-factorial design with 4 experimental conditions (all with \( n = 8 \)). The groups varied with regard to the number of DCS injections before conditioning (i.e., 5, 1, or 0) and the drug administered after the extinction training session (i.e., DCS or saline) (see Table 1). Specifically, rats in group Pre5-DCS received five DCS injections before conditioning and a DCS injection after extinction training. Rats in group Pre5-Sal received five DCS injections before conditioning and a saline injection after extinction. Rats in group Pre1-DCS received four saline injections followed by one DCS injection before conditioning and a DCS injection after extinction. Rats in group Pre0-DCS received five saline injections prior to conditioning and DCS after extinction.

Fig. 1. (A) Mean (+SEM) percentage freezing during extinction training for rats that were injected with DCS or saline following the extinction session. Freezing levels are shown for each of the six 2-min non-reinforced presentations of the light CS. (B) Mean (+SEM) percentage freezing to the light CS during the post-extinction test of rats that received extinction training followed by an injection of DCS (E-DCS) or saline (E-Sal), and rats that received DCS or saline without extinction training (NE-DCS & NE-Sal, respectively).
4.2. Results and discussion

To determine whether the basic DCS effect on extinction reported in Experiment 1 was replicated, a comparison was made between group Pre0-DCS (five saline pre-exposures followed by DCS after extinction) and group Pre5-Sal (five DCS pre-exposures followed by saline after extinction). The Pre5-Sal group froze significantly more to the light CS at test than the Pre0-DCS rats \[t(14) = 3.95; \ p < .001; \text{see Fig. 2A}\]. Thus, a DCS injection administered after extinction training facilitated extinction of conditioned freezing at test the following day (replicating the results of Experiment 1). Further, DCS pre-exposures did not appear to interfere with, or enhance, the acquisition or expression of conditioned freezing. That is, rats in group Pre5-Sal in the present experiment exhibited a very similar level of performance at test as did rats in group E-Sal in Experiment 1 (i.e., both groups exhibited just over 60% freezing at test).

To test the effects of multiple administrations of DCS, subsequent analyses focused on the three groups given DCS after extinction training. These groups differed in terms of the number of prior exposures to DCS: 0, 1, or 5. The results of this analysis revealed a significant linear trend \[F(1,21) = 7.2, \ p < .01\] (see Fig. 2B). Specifically, it was found that rats that received five DCS pre-exposures (Pre5-DCS) displayed significantly higher levels of conditioned freezing on the post-extinction test than rats that received no prior exposure to DCS (Pre0-DCS) \[p < .05\]. Rats that received one pre-exposure to DCS (Pre1-DCS) exhibited intermediate levels of freezing in comparison to the other groups. Post hoc tests revealed that this group was not statistically different to either of the other two groups.

Overall, the results of Experiment 2 demonstrate that pre-exposure to DCS disrupts the facilitatory effect of DCS on extinction, and that the level of disruption is proportional to the number (or amount) of pre-exposures.

5. Experiment 3

Experiment 2 demonstrated that repeated exposure to DCS decreases the facilitatory effects of DCS on subsequent fear extinction. Therefore, the aim of Experiment

<table>
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<td>12</td>
<td>Light alone + DCS</td>
<td>Light alone + DCS</td>
<td>Light alone + Saline</td>
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Immediately following extinction training the animals received either a DCS or saline injection. Group labels indicate how many DCS injections the rats received before conditioning and the drug administered after extinction training.

Fig. 2. (A) Mean (+SEM) percentage of freezing to the light CS during the post-extinction test for rats that had received five DCS injections prior to conditioning and a saline injection following extinction training (Pre5-Saline) and rats that received five saline injections prior to conditioning and a DCS injection after extinction training (Pre0-DCS). (B) Mean (+SEM) percentage of freezing to the light CS during the post-extinction test for rats that received either five DCS injections prior to conditioning (Pre5-DCS), 1 DCS injection prior to conditioning (Pre1-DCS), or no DCS injections prior to conditioning (Pre0-DCS). All of these groups received DCS after extinction training.
was to determine whether the reduced effectiveness of DCS after pre-exposure is permanent, or whether it is alleviated with the passage of time. Thus, rats received five DCS exposures either 2 or 28 days prior to fear conditioning and were then tested for the effects of a single dose of DCS on extinction the following day.

5.1. Method

5.1.1. Procedure

As in Experiment 2, all rats received an injection of either saline or DCS on every alternate day for a total of five injections. After the final injection, conditioning occurred either 2 or 28 days later. However, the experiment was implemented in a staggered fashion so that all rats were conditioned on the same day. This procedure produced three groups: D28-DCS, where rats were given five DCS exposures, with the last occurring 28 days prior to conditioning, and DCS after extinction \( (n = 8) \); D2-DCS, where rats were given five DCS exposures, the last occurring 2 days prior to conditioning, and DCS after extinction \( (n = 8) \); and S28/2-Sal, where rats were given five saline exposures either 28 \( (n = 4) \) or 2 \( (n = 4) \) days prior to conditioning and saline after extinction (these two groups were pooled).

Rats were conditioned and extinguished using the same procedures as the first two experiments.

5.2. Results and discussion

Data from one rat in the D2-DCS group was excluded because it failed to show a conditioned response during extinction training (failure to exhibit conditioning was defined as an initial level of freezing <20%).

During extinction training, all rats, regardless of group, displayed a similar level of conditioned freezing at the beginning of the session, as well as a similar rate of extinction over the six light-alone presentations (Fig. 3A). These observations were supported by a significant within-subjects effect of trial \( [\text{ANOVA}, F(5, 100) = 39.8, p < .001] \), a non-significant interaction between group and trial \( [F(10,100) = 1.1, p = .37] \), and a non-significant group effect \( [F < 1.0] \). Thus, previous exposures to DCS did not affect rate of extinction learning.

During the retention test the following day, there were no differences between the two saline conditions on the amount of freezing during either the pre-CS period \( [t(6) = 1.1, p = .31] \), or during exposure to the light \( [t(6) < 1] \), and thus, these groups were pooled. Rats in the S28/2-Sal and D2-DCS groups did not differ in the amount of freezing to the light CS, but both exhibited significantly greater amounts of freezing than rats in the D28-DCS group \( [F(2, 22) = 6.5, p = .007] \), with post hoc comparisons significant at \( p < .05 \); Fig. 3B]. Additionally, no group differed significantly in the amount of freezing during the 2 min pre-CS period \( [F(2, 22) = 2.5, p = .11] \).

These data replicate the findings of Experiment 2 in which repeated exposure to DCS just prior to conditioning reduced the effectiveness of a single dose of DCS on the extinction of conditioned freezing (as shown by the D2-DCS group). However, in this experiment it was also shown that if 28 drug-free days were interposed between DCS pre-exposure and conditioning, the enhancing effects of DCS on extinction were restored (as shown by the D28-DCS group).

![Fig. 3](image-url)
6. General discussion

Experiment 1 demonstrated that DCS, a glycine partial agonist that activates the NMDA complex, facilitates extinction of conditioned fear in rats. Specifically, it was shown that when rats are injected with DCS immediately after an extinction session, they display significantly less conditioned freezing than saline-injected rats. Because DCS was only found to reduce conditioned freezing in rats that had received extinction training, the enhancing effect of DCS cannot be attributed to either DCS-related neurotoxicity or to any properties of the drug that may be present at the time of testing. These findings replicate other studies showing that DCS enhances extinction of fear-potentiated startle (Walker et al., 2002) and conditioned freezing (Ledgerwood et al., 2003, Ledgerwood, Richardson, & Cranney, 2004). In Experiment 2, the enhancing effects of DCS on fear extinction were disrupted after multiple pre-exposures to DCS. Specifically, it was found that five DCS exposures over a 10-day period prior to conditioning entirely eliminated the enhancing effects of DCS on extinction, and further, that even one pre-exposure of DCS prior to conditioning had a slight desensitizing effect. In Experiment 3, the behavioral desensitization seen after five DCS pre-exposures was replicated, but it was also shown that if a drug-free interval of 28 days is interposed between drug pre-exposure and conditioning, the DCS effect on extinction is restored.

One possible explanation for the failure of DCS to enhance extinction after multiple injections is that the DCS pre-exposures had shifted the dose-response curve to the right (i.e., the development of tolerance). However, data from a study investigating the facilitatory effects of DCS on maze learning in mice showed that desensitization to DCS occurs after chronic pre-exposure, but that increasing the dose of DCS did not re-establish its effects on behavior (Quarterman et al., 1994). That is, an acute, post-training injection of DCS in mice was found to significantly improve performance in a maze-learning task. This effect was not observed in mice pre-exposed to 3 mg/kg DCS twice a day for 15 days prior to training. Further, after 15 days of DCS pre-exposure, increasing the dose of DCS administered after training did not reverse the desensitizing effects of pre-exposure. Thus, it may be the case that chronic exposure to DCS abolishes its activity at the NMDA receptor. In that regard, Boje, Wong, and Skolnick (1993) examined the effects of chronic exposure to glycine or partial glycine agonists, like DCS, on cultured granule neurons. They reported that chronic exposure to such agents desensitized the NMDA receptor complex at its strychnine-insensitive receptor site. It will be interesting, and important, for future research to determine the exact biomolecular mechanisms underlying the failure of DCS to enhance extinction after multiple injections of the drug.

Whatever the mechanism underlying the loss of the facilitatory effect of DCS on extinction after multiple administrations, it is clear from the present study that this disruption is not permanent. That is, if a drug-free period is left between drug pre-exposure and conditioning, the facilitatory effects of DCS on fear extinction are restored. In the present study, an arbitrary period of 28 days was chosen between the five DCS exposures and the dose immediately following extinction training. Although the present study showed that two drug-free days are not sufficient to re-establish the DCS effect on extinction, it is possible that a drug-free interval much shorter than 28 days will be effective. In any case, the results of the present study suggest that DCS may be most efficacious as an adjunct to exposure therapy if its use is limited, or if an optimal administration schedule can be developed. Thus, further studies are required to determine the administration parameters necessary for maximizing the effectiveness of DCS as a facilitator of fear extinction.

A clinically relevant question that arises from the results of the present study is whether chronic exposure to DCS affects the efficacy of other compounds that activate the glycine/NMDA receptor, or vice versa. Of particular interest here are drugs that are commonly prescribed to people with anxiety disorders, such as anti-depressants and anxiolytics, as well as drugs of abuse. For example, at least one study has found that long-term treatment with selected anti-depressants modified the function of the glycine/NMDA receptor complex in mice (Popik, Wrobel, & Nowak, 2000). That is, administration of either imipramine or citalopram for 21 days diminished the anxiolytic effects of L-701,324, an antagonist at the strychnine-insensitive glycine site of the NMDA receptor. The same desensitising effects on glycine/NMDA receptor function were found after 8 days of an electroconvulsive shock procedure. Thus, because multiple pre-exposures to agents such as imipramine and citalopram affect the functional activity of glycine-activated NMDA receptors, it would be of interest to determine whether multiple pre-exposures to anti-depressants reduce the effects of DCS on extinction of conditioned fear in rats. Indeed, these issues should be taken into account when clinical trials of DCS are being conducted. That is, the acute effects of DCS on extinction maybe be disrupted, or blocked, by the recent use of other active substances (such as anti-depressants).

In conclusion, DCS has the potential to further our understanding of the processes of extinction at a theoretical level by allowing us to explore in more detail the mechanisms underlying the process of extinction. In addition, research with DCS may eventually enhance the effectiveness of current behavioral treatments for anxiety disorders, such as exposure therapy. However, the present study demonstrates that the effectiveness of DCS at enhancing extinction of fear is eliminated by multiple
exposures to the drug, unless a drug-free period occurs between exposures. Future studies, in both the laboratory and the clinic, must establish an administration schedule that allows DCS to remain effective.

References


