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A randomized controlled trial of the effect of D-cycloserine on extinction and fear conditioning in humans

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Abstract

Previous research has shown that D-cycloserine (DCS) facilitates extinction of Pavlovian fear conditioning in rats and enhances exposure therapy in humans. The aim of this study was to test the effect of DCS on extinction of fear conditioning in humans. In three experiments, 238 participants were given either DCS (50 or 500 mg) or placebo 2–3 h before extinction training following a differential shock conditioning paradigm. Clear extinction and recovery (return of fear) effects were observed on both skin conductance and self-reported shock expectancy measures in three studies. DCS had no influence on these effects. The same pattern was observed when the analysis was restricted to aware participants or to good conditioners, when fear-relevant cues (pictures of snakes) were used as the conditioned stimuli, or when analysis was restricted to heightened snake-fearful participants. These results suggest that DCS may not enhance the extinction, or prevent the recovery, of learned fear in a differential Pavlovian conditioning paradigm in humans. Further experimental research is needed to better understand the mechanisms underlying the therapeutic effects of DCS.

Keywords: Fear; Conditioning; Extinction; Cycloserine; DCS; Skin conductance

Introduction

The most effective current treatments for anxiety disorders are based on the process of extinction. Experimental methods to study the fear extinction process in animals and humans are well developed and usually involve Pavlovian conditioning procedures. Studies using this sort of procedure involve three phases: conditioning, extinction, and test. In the first phase, an initially neutral stimulus (conditioned stimulus; CS), such as a tone or picture, is paired with an aversive unconditioned stimulus (US), such as shock. As a consequence of these pairings, the CS elicits a fear response. In the second phase, the CS is presented without the US. Repeated CS-alone presentations result in a gradual reduction of the fear response elicited by the CS. In the final test phase, the residual fear response to the CS after extinction is assessed, relative to responding to

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various control stimuli. In most circumstances, the participants show partial recovery of fear during the test phase, usually referred to as spontaneous recovery. These procedures have also been used to demonstrate the phenomenon of reinstatement (return of fear following unsignalled US presentation; Hermans et al., 2005) and protection from extinction (no loss of fear to CS when it has been repeatedly presented in combination with a safety signal during extinction; Lovibond, Davis, & O'Flaherty, 2000).

In non-human animals, studies using Pavlovian conditioning procedures have shown that NMDA receptors are critical in the extinction of learned fear. First, it was demonstrated that NMDA antagonists blocked extinction of learned fear in rats (e.g., Falls, Miserendino, & Davis, 1992). Second, it was recently demonstrated that D-cycloserine (DCS), a partial NMDA agonist, facilitates extinction of learned fear in rats when administered immediately before or even shortly (up to 60 min) after extinction training (Ledgerwood, Richardson, & Cranney, 2004, 2005; Walker, Ressler, Lu, & Davis, 2002; Yang & Lu, 2005). In contrast, DCS administered in the absence of extinction training has no impact on subsequent fear responding to the CS. As a result of these findings, it has been suggested that DCS strengthens the extinction memory so that it may be more easily retrieved during subsequent exposures to the CS. These findings are important because (1) they inform our understanding of the neural bases of extinction, and (2) they suggest that a combined behavioural/pharmacological approach to the treatment of fear and anxiety disorders in humans may lead to improved efficacy.

In humans, two pilot studies have provided suggestive evidence that DCS facilitates treatment outcome following exposure therapy in clinical populations. The first used a virtual reality exposure-based therapy for height phobia (Ressler et al., 2004) and the second used a brief exposure-based intervention for social phobia (Hofmann et al., 2006). However, it is not completely clear that human phobias are based on a prior conditioning episode (e.g., Menzies & Clarke, 1995). It is therefore important to directly test the effect of DCS on extinction of conditioned fear in humans.

There have been some recent studies on the effects of various pharmacological agents on the acquisition of fear in humans (e.g., Grillon, Cordova, Morgan, Charney, & Davis, 2004). However, to our knowledge, there have not been any studies examining the effects of DCS on the extinction of learned fear in humans. Testing the drug in controlled human conditioning paradigms better replicates what has been found in the animal studies and has the potential to more accurately elucidate the operating mechanisms involved in DCS facilitating extinction of fear. Examination of effects on autonomic measures and explicit cognitive expectancy measures may also tell us whether DCS operates on both the unconscious and conscious processes involved in extinction, or just one type of process.

Therefore, given the recent findings that DCS facilitates loss of fear following an exposure-based therapy procedure, the primary aim of the present study was to examine the effect of two doses of DCS, 50 and 500 mg, on extinction and return of fear in humans. These doses were selected on the basis of previous research demonstrating their efficacy in increasing the effectiveness of exposure therapy in humans. Another reason for trialling the 500 mg dose is that there is some evidence in humans that 50 mg may not consistently activate NMDA receptors (D'Souza et al., 2000; van Berckel et al., 1997). We used a well-developed autonomic fear conditioning paradigm with an electric shock as the US (Lovibond, 1992; Lovibond et al., 2000) and the impact of DCS was assessed using two measures of conditioning: skin-conductance and a self-report measure of shock expectancy.

Method

Participants

In the first study, 97 undergraduates were randomly assigned to the 50 mg DCS ($n = 50$) or placebo ($n = 47$) condition (53 females, 44 males). DCS capsules (250 mg; Aspen Pharmacare, Sydney) were reformulated into 50 mg capsules by a compounding chemist; identical placebo capsules were also used.

In the second study, 44 undergraduates were randomly assigned to the 500 mg DCS ($n = 22$) or Placebo ($n = 22$) condition (26 females, 18 males). The compounding chemist purchased DCS powder directly from Eli-Lilly (Indianapolis, USA) to make the 500 mg capsules, along with identical placebos.

All participants volunteered for course credit. Participants were provided with a written description of the study, a medical screen was conducted, and written consent was obtained. Participants were free to withdraw at any time. All procedures and materials were identical for both studies.

Apparatus

The conditioning apparatus was the same as that described in Lovibond et al. (2000). Briefly, the conditioned stimuli (CSs) were coloured blocks (Blue, Red, Yellow, and Green) presented on a computer monitor. Shock was delivered through electrodes on the proximal and medial segments of the index finger on the participant's non-preferred hand. Skin conductance was measured through electrodes on the second and third fingers of the same hand. Participants used their preferred hand to record their subjective expectancy of shock during each CS on a continuous, 180°, rotary dial. The left extreme was labelled *Certain no shock*, the centre position was labelled *Uncertain*, and the right extreme was labelled *Certain shock*.

Procedure

The conditioning procedure followed that described by Lovibond (1992). Briefly, participants first self-selected their maximum tolerable shock intensity, and were then instructed in use of the expectancy dial. CS durations varied randomly between 11 and 30 s, and shock duration was 0.5 s. Inter-trial intervals varied randomly between 20 and 50 s. Colours for CSs A, B, and C were randomly selected from the four available colours. The design is shown in Table 1. The experiment was conducted over three separate sessions. There was a 2–3 h delay between the Acquisition and the Extinction sessions, and the Test session occurred on the following day. The DCS group received DCS immediately after Acquisition, whereas the Control group received placebo.

In the Acquisition session, A and C were both paired with shock while B was presented without shock. In the Extinction session, C was presented alone (extinguished) across four trials while A was again paired with shock and B was presented without shock (one time each). In the Test session, A, B and C were all presented once. Trial order within all phases was randomized. Expectancy ratings were converted to a 0–100 scale, and skin conductance scores for each trial were calculated as change in mean log skin conductance level (SCL) from baseline to CS (see Lovibond, 1992).

Participants were administered a capsule of either DCS or placebo under double-blind conditions immediately after the Acquisition session. They returned 2–3 h later, at which point their serum DCS levels should have been maximal (Hardman & Limbird, 2001) and completed the Extinction session. The following day they returned for the Test session. After the Test session, participants were given a brief structured interview to determine their explicit knowledge of the CS-shock relationships. Participants were asked what information they used to predict shock in the first session. They were also asked if they believed each of three coloured squares always, sometimes, or never led to shock. They were then fully debriefed. Data were analysed by a set of planned, orthogonal contrasts using a multivariate, repeated measures model (O'Brien & Kaiser, 1985).

Table 1
Experimental design

Phase		
Acquisition	Extinction	Test
A+ (3)	A+ (1)	A+ (1)
B− (4)	B− (1)	B− (1)
C+ (3)	C− (4)	C− (1)

Note: Letters A–C refer to conditioned stimuli (CSs); + and − refer to the presence and absence, respectively, of electric shock after the CS; numbers in parentheses give the number of trials of each type; within each phase, trial types were intermixed. The same experimental design was used for both the DCS and Placebo groups.

Results

Study 1

Data from 13 participants were excluded due to experimenter error, data corruption or failure to follow instructions. Mean shock expectancy ratings and change in log SCL for the remaining 84 participants across all three experimental sessions are shown in Fig. 1. We first analysed the skin conductance data. Averaged over drug conditions, responding to A and C was higher than to B during Acquisition [$F(1, 82) = 19.2$, $p < 0.05$]. In the Extinction phase, responding to C declined markedly over trials [$F(1, 82) = 17.1$, $p < 0.05$]. Finally, there was a substantial return of skin conductance responding to C in the Test phase [$F(1, 82) = 20.8$, $p < 0.05$]. None of these effects interacted with drug condition [all F's < 1]. In order to control for individual differences in skin conductance reactivity, an additional contrast was tested that compared responses to C with the average of A and B (representing upper and lower bounds of associative responding, respectively). This contrast also did not interact with groups [$F < 1$], confirming that DCS did not influence responding to the extinguished stimulus C relative to control stimuli.

Analysis for the expectancy ratings were similar to that found with the skin-conductance response. Specifically, averaged over drug conditions, there was clear evidence of differential expectancy ratings to the

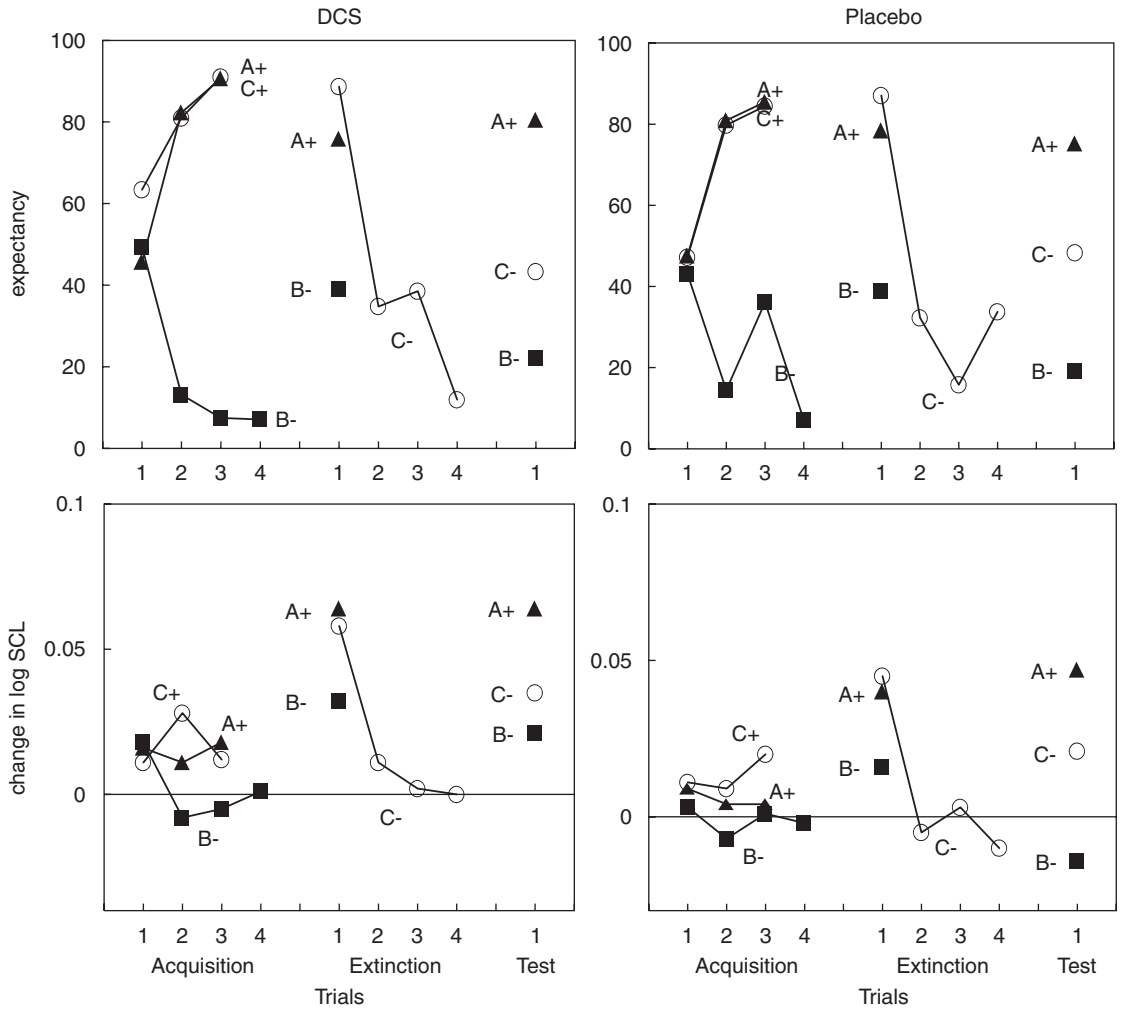

Fig. 1. Mean shock expectancy ratings (top panels) and change in log skin conductance level (bottom panels) as a function of trials within phases for the 50 mg DCS group (left) and Placebo group (right) in Study 1.

shocked stimuli A and C compared to the non-shocked stimulus B in the Acquisition phase [$F(1, 82) = 147.8$, $p < 0.05$]. In the Extinction phase, expectancy ratings to C declined to near-zero over the four non-reinforced trials [$F(1, 82) = 289.6$, $p < 0.05$]. In the Test session, expectancy ratings of shock in the presence of stimulus C increased substantially in comparison to the final extinction trial on the previous day [$F(1, 82) = 69.5$, $p < 0.05$]. These effects did not interact with drug condition (all F's < 1). As in the skin conductance analysis, the contrast comparing C to the average of A and B did not interact with drug condition [$F(1, 82) = 1.1$, $p > 0.05$], again confirming the absence of any effect of DCS on the associative status of the extinguished stimulus C.

Restricting the analyses to those participants who had explicit awareness of the stimulus contingencies in the post-experimental interview ($n = 78$) improved the degree of discrimination observed on both dependent measures, but did not alter the overall pattern or reveal any effect of DCS. Similarly, restricting analysis to participants who showed good skin conductance discrimination in Acquisition ($n = 38$) did not alter the pattern of results. Good discrimination was simply defined as greater responding to CS+ than CS− at the end of acquisition.

Study 2

Data from one participant were excluded due to equipment malfunction. Mean shock expectancy ratings and change in log SCL across the three experimental sessions are shown in Fig. 2 for the DCS and Placebo groups. Averaged over drug conditions, there was clear evidence of differential conditioning on the skin conductance measure. Responding to A and C was higher than to B during Acquisition [$F(1, 41) = 8.9$, $p < 0.05$]. In the Extinction phase, responding to C declined markedly over trials [$F(1, 41) = 19.1$, $p < 0.05$]. Finally, there was a return of skin conductance responding to C in the Test phase [$F(1, 41) = 4.2$, $p < 0.05$]. None of these effects interacted with drug condition (all F's < 1). Nor was there any interaction between drug condition and a contrast comparing C with the average of A and B in the Test phase ($F < 1$).

A similar pattern of results was found for the shock expectancy ratings. Differential conditioning was found between the shocked stimuli A and C compared to the non-shocked stimulus B in the Acquisition phase [$F(1, 41) = 374.4$, $p < 0.05$]. In the Extinction phase, expectancy ratings to C declined to near-zero over the four trials [$F(1, 41) = 327.1$, $p < 0.05$]. In the Test session, expectancy ratings for C increased substantially in comparison to the final extinction trial on the previous day [$F(1, 41) = 23.5$, $p < 0.05$]. A similar pattern of results was observed for the DCS and Placebo groups, and there were no significant interactions between the above contrasts and drug condition (all F's < 1). A contrast comparing C with the average of A and B in the Test phase also failed to interact with drug condition [$F < 1$].

Discussion

The results of this study replicate several previous findings in humans that have used Pavlovian conditioning and extinction procedures (Lovibond et al., 2000). Participants showed higher shock expectancy and SCLs at test for stimuli A and C, which had been paired with shock, than for stimulus B, which was never paired with shock. There was clear evidence of loss of fear to stimulus C during extinction and there was a strong return of fear to stimulus C at test on both measures. Results provide what may be one of the first demonstrations of spontaneous recovery using a human fear conditioning apparatus (see also Marescau & Vansteenwegen, 2006). Most importantly, however, the present data do not provide any evidence that pre-extinction administration of 50 or 500 mg of DCS facilitated extinction of learned fear in humans. That is, participants given DCS exhibited (1) a similar loss of fear to stimulus C across the 4 non-reinforced trials in the Extinction session, and (2) a similar return of fear to stimulus C at test, as did participants given placebo. This pattern was observed on both skin-conductance and self-reported shock expectancy.

Before concluding that DCS does not facilitate fear extinction in a Pavlovian conditioning paradigm we thought it important to address three issues. Firstly, in the pre-clinical studies, the rats are not shocked during the Extinction phase. In contrast, our participants received a shock to a single presentation of the reinforced stimulus during extinction. In terms of the impact of DCS, however, this may be a particularly important

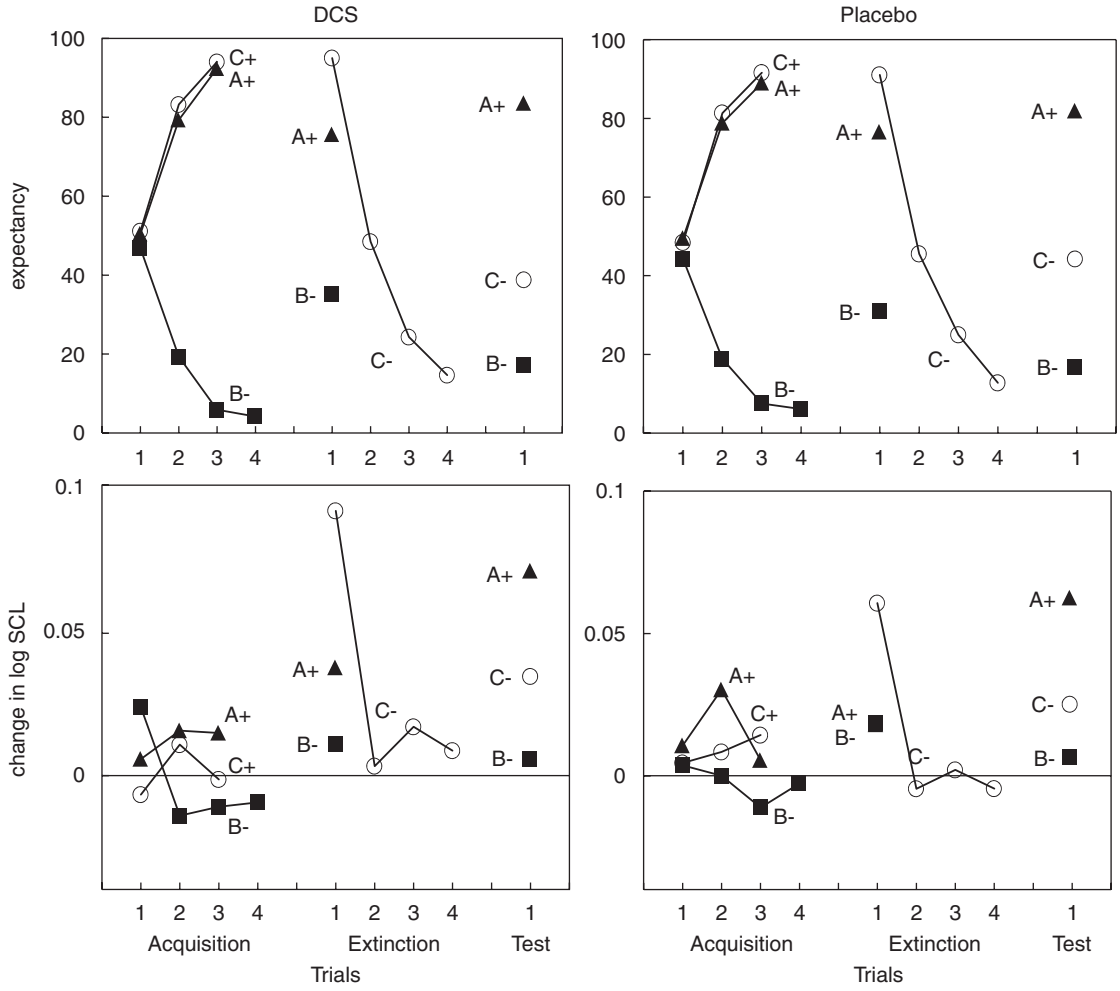

Fig. 2. Mean shock expectancy ratings (top panels) and change in log skin conductance level (bottom panels) as a function of trials within phases for the 500 mg DCS group (left) and Placebo group (right) in Study 2.

procedural difference since the US is presented during the period when DCS is thought to be active. It is possible that this may have resulted in the lack of observed effect of DCS on extinction by, for example, altering the activation of the US memory or the amount of contextual conditioning.

Secondly, Acquisition and Extinction phases were placed on the same day in the present study but not in the pre-clinical studies. While the Acquisition phase occurred before DCS was administered, the animal literature shows that post-training administration of DCS is just as effective as giving it pre-training (Ledgerwood, Richardson, & Cranney, 2003). We chose to do this because we wanted to be as conservative as possible with the spacing between sessions. We cannot rule out the possibility, however, that DCS may strengthen the acquisition memory as well as the extinction memory, and therefore, weaken any potential effect at test. Thirdly, DCS has been found to be effective in the extinction of fear-relevant stimuli (e.g., heights). Our two studies used coloured squares as conditioned stimuli. It may be that the effects of DCS on extinction of fears may be more easily observed with stimuli that are more biologically relevant.

The third study was designed to address these concerns. We removed the shocked CS during the extinction phase; we used a stronger US; we used fear-relevant stimuli (pictures of snakes) as the CS+ stimuli; we conducted acquisition, extinction, and test phases on separate days; and we recruited individuals with a heightened fear of snakes.

Study 3: method

Participants

A total of 97 undergraduates were randomly assigned to the 50 mg DCS ($n = 50$) or Placebo ($n = 47$) condition (60 females, 37 males). Data from 10 were excluded due to experimenter error, data corruption, failure to follow instructions or drop-out.

Of the 87 remaining participants, 40 (21 = DCS; 19 = Placebo) scored 15+ ($M = 19.38$, range = 15–29) on the Snake Phobia Questionnaire (SPQ; Klorman, Hastings, Weerts, Melamed, & Lang, 1974). These 40 participants had been identified using the SPQ as a screening questionnaire for all UNSW first year psychology students at the start of semester ($N = 900$). DCS capsules (250 mg; Aspen Pharmacare, Sydney) were reformulated into 50 mg capsules by a compounding chemist in the same manner as described earlier. All participants volunteered for course credit. Participants were provided with a written description of the study, a medical screen was conducted, and written consent was obtained. Participants were free to withdraw at any time.

Apparatus and procedure

The apparatus was similar to previous studies except that the reinforced and extinguished stimuli, A and C, were pictures of snakes and the non-reinforced stimulus, B, was a picture of a flower. We also modified the US to enhance the potency of the US by combining shock with a simultaneous 0.5 s 105-db tone on stereo headphones. The procedure was exactly the same as for Study 2, except that the reinforced cue (stimulus A) was not presented during extinction and a space of 1 day was placed between acquisition and extinction tests. DCS was administered 2–3 h before the extinction training on day 2.

Results

Mean shock expectancy ratings and change in log SCL across the three experimental sessions are shown in Fig. 3. Averaged over drug conditions, there was clear evidence of differential conditioning on the skin conductance measure. Responding to A and C was higher than to B during Acquisition [$F(1, 86) = 80.49$, $p < 0.05$]. In the Extinction phase, responding to C declined markedly over trials [$F(1, 86) = 68.93$, $p < 0.05$]. Finally, there was a return of skin conductance responding to C in the Test phase [$F(1, 87) = 20.84$, $p < .05$]. None of these effects interacted with drug condition (all F's < 1). Nor was there any interaction between drug condition and a contrast comparing C with the average of A and B in the Test phase [$F(1, 86) = 2.25$, $p > 0.05$].

A similar pattern of results was found for the shock expectancy ratings. Differential conditioning was found between the shocked stimuli A and C compared the non-shocked stimulus B in the Acquisition phase [$F(1, 86 = 1254.48$, $p < 0.05$]. In the Extinction phase, expectancy ratings to C declined to near-zero over the four trials [$F(1, 86) = 214.51$, $p < 0.05$]. In the Test session, expectancy ratings for C increased substantially in comparison to the final extinction trial on the previous day [$F(1, 86) = 58.25$, $p < 0.05$]. A similar pattern of results was observed for the DCS and Placebo groups, and there were no significant interactions between the above contrasts and drug condition (all F's < 1). A contrast comparing C with the average of A and B in the Test phase also failed to interact with drug condition [$F < 1$].

High snake anxious participants

All analyses were re-run with high snake anxious participants. Similar results were observed. The critical tests comparing C with the average of A and B in the Test phase did not interact with drug condition on skin conductance scores [$F(1, 38) = 3.12$, $p = 0.09$], or expectancy measures [$F < 1$].

Discussion

Participants in this study showed higher shock expectancy and skin conductance for stimuli A and C at test, in contrast to stimulus B, which was never paired with shock. There was clear evidence of loss of fear to

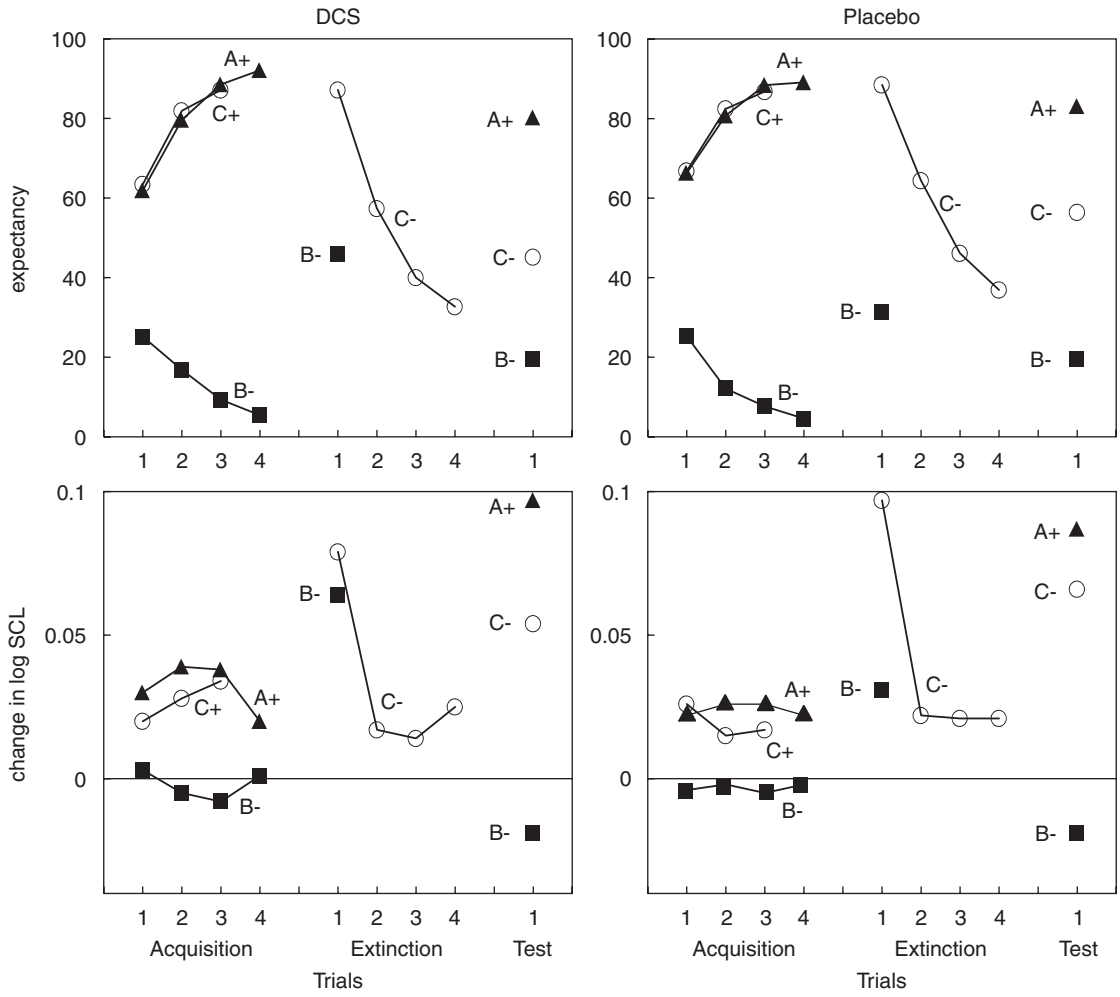

Fig. 3. Mean shock expectancy ratings (top panels) and change in log skin conductance level (bottom panels) as a function of trials within phases for the 50 mg DCS group (left) and Placebo group (right) in Study 3.

stimulus C during extinction and there was a strong return of fear to stimulus C at test on both measures. The present data, however, do not provide any evidence that pre-extinction administration of 50 mg of DCS facilitated extinction of fear in humans. This same pattern of results was seen when we focused only on heightened snake fearful participants. It should be noted that since this latter study used prepared fear cues as conditioned stimuli, the experiment should not be considered a pure test of the extinction of conditioned fear.

General discussion

The data from the three studies do not provide any evidence that pre-extinction administration of DCS facilitates extinction of learned fear in humans. That is, participants given DCS exhibited (1) a similar loss of fear to stimulus C across the 4 non-reinforced trials in the Extinction session, and (2) a similar return of fear to stimulus C at test, as did participants given placebo. This pattern was observed on both skin-conductance and self-reported shock expectancy.

The results of the present study are in contrast to previous pre-clinical studies with rats where DCS has been shown to reliably facilitate extinction of learned fear following a Pavlovian conditioning procedure (Ledgerwood et al., 2003, 2004; Walker et al., 2002; Yang & Lu, 2005). Further, these results are contrary to

what might have been predicted from clinical exposure treatment studies (Hofmann et al., 2006; Ressler et al., 2004) where it was found that DCS enhanced treatment outcomes for exposure therapy.

These discrepancies might raise questions about the procedures used in the present study. However, these general procedures have been found to be sensitive to other manipulations, such as protection from extinction and reinstatement (Hermans et al., 2005; Lovibond et al., 2000). The present study differed from these other studies in that acquisition, extinction, and test occurred in separate sessions, rather than in a single continuous session. This alteration was necessary in order to test the possible effects of DCS on the expression and extinction of learned fear. The introduction of this spacing between sessions does not appear to have had a significant impact on the results, however, because standard conditioning and extinction effects were demonstrated. That is, the placebo-treated participants exhibited similar conditioning, extinction, and recovery of fear effects as has been observed in earlier studies without spaced sessions. It should also be noted that in all the pre-clinical studies showing that DCS facilitates extinction of learned fear the acquisition, extinction and test sessions were all spaced in time (i.e., not in a single continuous session).

There are some potentially important differences in the exact Pavlovian conditioning procedures used in the rat DCS studies and those reported here with humans. Firstly, in the rat studies, the rats are presented with only one CS throughout the experiment. In contrast, our participants were presented with three stimuli during the acquisition phase: two reinforced stimuli and one non-reinforced stimulus. Secondly, this procedural difference results in a difference in the method chosen to analyse the extinguished CS during the Test phase. In humans, the non-extinguished reinforced CS and the non-reinforced CS provide an upper and lower limit upon which the extinguished stimulus can be assessed. Without these stimuli, the interpretation of skin conductance data would be near impossible due to quite significant individual differences in SCLs. Studies 1 and 2 differed from the animal studies in that conditioning and extinction were carried out on the same day, but Study 3 separated these phases by 1 day with no impact on the results obtained.

We based our timing and doses for drug administration on previous research. It should be noted, however, that we did not use any direct test to check DCS serum levels at the time of extinction training. The results of this study may also raise questions about the use of non-clinical participants to test the mechanisms by which DCS facilitates loss of fear. We used normal and heightened fear populations and there is some additional evidence that DCS may not reduce fear in non-clinical populations (Guastella, Dadds, Lovibond, Mitchell, & Richardson, in press). The two previous human treatment trials that have found positive effects of DCS used clinically fearful participants. There is little evidence that conditioning effects differ between clinical and non-clinical participants (Lissek et al., 2005), but nonetheless it is possible that the mechanism mediating facilitated loss of fear following DCS may be specific to clinical fear. Replication of this study in a clinical population using fear-relevant stimuli in real world environments may be warranted. The use of virtual reality conditioning methods offers particular promise for these purposes (Baas, Nugent, Lissek, Pine, & Grillon, 2004).

It can be assumed that DCS exerts its effects on extinction by facilitating learning. Given the present results, however, we think it is less likely that DCS exerts its effects by decreasing conditioned associations between the CS and the US. Instead, it is possible that DCS may facilitate extinction through some form of context learning or inhibition of the US memory, rather than through discrimination learning per se. That is, the conditioning procedure we used in the above studies is based on participants discriminating different CS–US relationships and does not tease out CS from context conditioning effects or more general changes in US retrieval (Mineka & Zinbarg, 2006). Future studies using different conditioning procedures would be required to assess these hypotheses.

In conclusion, findings from animal conditioning studies that DCS facilitates the extinction of learned fear (for a review see Richardson, Ledgerwood, & Cranney, 2004) were not replicated using a Pavlovian conditioning paradigm in humans. The findings from this study suggest that DCS does not enhance extinction of learned fear responses, either skin conductance or expectancy ratings, to either neutral or fear-relevant CSs. Further research is required to assess the impact of DCS on extinction using other conditioning paradigms to better understand its underlying mechanisms of action. In the meantime, it may be premature to conclude that DCS facilitates exposure treatment in humans via enhancement of extinction of conditioned fear.

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