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A randomized controlled trial of the effect of D-cycloserine on exposure therapy for spider fear

Adam J. Guastella [a,*], Mark R. Dadds [a], Peter F. Lovibond [a], Philip Mitchell [b], Rick Richardson [a]

[a] School of Psychology, University of New South Wales, Kensington, Sydney, NSW 2052, Australia
[b] School of Psychiatry, University of New South Wales, Kensington, Sydney, NSW 2052, Australia

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Abstract

Previous research [Hofmann SG, Meuret AE, Smits JA, Simon NM, Pollack MH, Eisenmenger K, et al. Augmentation of exposure therapy for social anxiety disorder with D-cycloserine. Archives of General Psychiatry 2006;63:298–304; Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Archives of General Psychiatry 2004;61:1136–44] suggests that D-cycloserine (DCS) facilitates the reduction of clinical fear in humans. We used a well established intervention to evaluate the effectiveness of administering DCS as an adjunct to exposure therapy in a heightened, but sub-clinical, fear population. Over two studies, 100 spider-fearful participants were allocated to DCS or placebo before treatment and were assessed at pre-, immediate post-, and 3.5 weeks post-treatment. Significant treatment effects and return of fear was observed at follow-up, particularly in non-treatment contexts; however, both studies failed to demonstrate any enhancing effects of DCS (50 or 500 mg). DCS did not enhance the reduction of spider fears or the generalisation of treatment of a single session of exposure-based therapy. These results suggest that DCS may not enhance loss of non-clinical levels of fear in human populations.

Keywords: Anxiety disorders; D-Cycloserine; Exposure therapy; Phobia; Extinction; Generalisation

1. Introduction

The NMDA partial agonist D-cycloserine (DCS) facilitates extinction of learned fear in rats when administered before, after, or 60 min post-extinction training (Richardson et al., 2004; Walker et al., 2002), while it has no impact in the absence of extinction training. It has been suggested that DCS strengthens extinction memories so they may be more easily retrieved during subsequent exposures to fear-relevant cues. Recent research has also suggested that DCS may facilitate the therapeutic effects of exposure therapy (ET) for clinical anxiety in humans. In a first pilot study (Ressler et al., 2004), 27 height-phobic subjects were assigned to three conditions: placebo, 50 mg DCS, or 500 mg DCS, and all received two sessions of virtual reality (VR) ET. At 1 week and 3-months post-treatment, participants in the DCS condition, regardless of dose, experienced less fear as indicated by fear levels in a virtual reality environment, self-reported attitudes and beliefs about acrophobia, and the number of self-exposures to real-world environments. A second study by Hofmann et al. (2006) also found that DCS given before each of four ET sessions decreased social anxiety symptoms reported one month post-treatment.

These findings have the potential to significantly advance the practice of fear/anxiety management, and warrant careful replication in varying populations. The aim of this study was to use a well developed laboratory-based

* Corresponding author. Tel.: +61 2 9552 3681; fax: +61 2 9385 3641.
E-mail address: a.guastella@unsw.edu.au (A.J. Guastella).

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treatment to test the efficacy of combining DCS with ET for spider fears. These laboratory-based exposure therapy treatments have been used previously to demonstrate the impact of internal and external context shifts, stimulus shifts, and session-spacing effects on exposure outcomes (Mineka et al., 1999; Mystkowski et al., 2003; Rodriguez et al., 1999; Rowe and Craske, 1998a,b). Our aim was to test whether DCS would enhance exposure therapy treatment effects in a heightened spider fear population. Ressler et al. (2004) results also suggest that DCS effects generalise to settings outside of the treatment context (i.e., number of self-exposures), so we tested whether the hypothesised benefits of DCS generalised to non-treatment settings in our participants.

2. Study 1

2.1. Method and materials

Following the procedures of previous research[1] (Mineka et al., 1999; Rodriguez et al., 1999), university students participated in this study if (1) they scored 15+ ($M = 21.02$, range = 15–28) on the Spider Phobia Questionnaire (SPQ; Klorman et al., 1974) or (2) they were unable to approach within a metre of a clear perspex box containing a spider (final sample = 49 female, 14 male; age = 20.9 years SD = 5.76, range = 17–56). High scoring SPQ participants were identified and contacted from screening assessments conducted on all first-year students at UNSW ($N = 900$). All participants received ET, and were randomly assigned, in a double-blind design, to receive a 50 mg dose of DCS ($n = 33$) or placebo ($n = 30$). After a medical screen, each participant was randomly assigned two contexts, (1) a spider and room for *assessment and treatment (the treated context)* and (2) a spider and room presented only at *assessment (the non-treated context)*. Trapdoor (slow-moving) and Huntsman (fast-moving) spiders (leg spread ~8 cm) were used. Participants were provided with a written description of the study, written consent was obtained, and participants were free to withdraw at any stage.

Assessments were conducted at pre-, post-treatment, and at follow-up by an assessor blind to drug condition. A behavioural-approach-task (BAT) tested the closest distance that participants were able to approach the spiders at each phase in treatment and assessment contexts. Distance to approach ratings have a long history in anxiety assessments and are found to be highly valid in terms of convergence with self-reports and psychophysiology (i.e., Borkovec and Craighead, 1971). Participants reported (1) fear levels before, during, and after BAT tasks on a 100-point scale; and (2) level of confidence in their ability to complete each BAT. Heart rate, averaged over 5 s periods, was taken for 2 min pre-, during, and for 5-min after each assessment session using a Polar belt and watch receiver unit (Model 610i).

Given the demonstrated efficacy of DCS at 50 mg (Ressler et al., 2004), DCS capsules (250 mg; Aspen Pharmacare, Sydney) were reformulated into 50 mg. Identical placebo capsules were also made. Participants attended pre-treatment, treatment, and post-treatment on the same day, while follow-up was conducted approximately 3.5 weeks later. As DCS serum should peak approximately 2–3 h post-administration (Hardman and Limbird, 2001), capsules were given at the start of assessment so participants engaged in ET close to the expected peak time. There was no drop-out.

After assessment, a single session treatment was administered that included 1 h of education about cognitive, behavioural, and physiological aspects of ET, as well as some cognitive-therapy, and then an 11-step exposure session. The 11-step exposure session was set for a maximum time of 2 h. The first step was based on the proximity attained during the first BAT, while the last step was to place a gloved hand on the floor of a Perspex box and move the spider over the hand with a chopstick. A gloved hand was used as all spiders of sufficient size in Australia can produce a painful bite. All participants were able to place their gloved hand in the box by the end of treatment. Post-treatment assessment was then conducted. Follow-up assessments were conducted with a different therapist. Participants were debriefed.

2.2. Results

Demographic and pre-treatment variables did not differ across drug conditions; there were no group differences in variables such as exposure duration ($M = 65$ min), therapist, or context. Pre-treatment levels of spider fear were consistent with previous research (Rodriguez et al., 1999); on average, participants were able to stand 68.44 cm (SD = 92.25) away from the spider, predicted experiencing 56/100 fear level (SD = 11.03), and had 43% (SD = 27.79) confidence of being able to touch the perspex container. On average, participants reported 81/100 fear level (SD = 11.60) during the pre-treatment BAT.

Fig. 1 presents scores on average fear reported (SUDS) and heart-rate during the BAT of closest proximity in both the treated and non-treated contexts. Results suggested significant overall ET effects similar to those reported previously (Rodriguez et al., 1999). To examine the effect of context on treatment response, change SUDS and heart-rate scores were created by subtracting post-treatment and follow-up assessment scores from pre-treatment scores within each context. *T*-tests comparing the difference scores in each context suggested that there was a greater treatment response within the same context in comparison to the different context. Results were significant at both post-treatment and follow-up assessment only for SUDS scores (smallest $t(62) = 6.80$, $p < 0.001$).

[1] All procedures were approved by the University of New South Wales Human Research Ethics Committee (#04145).

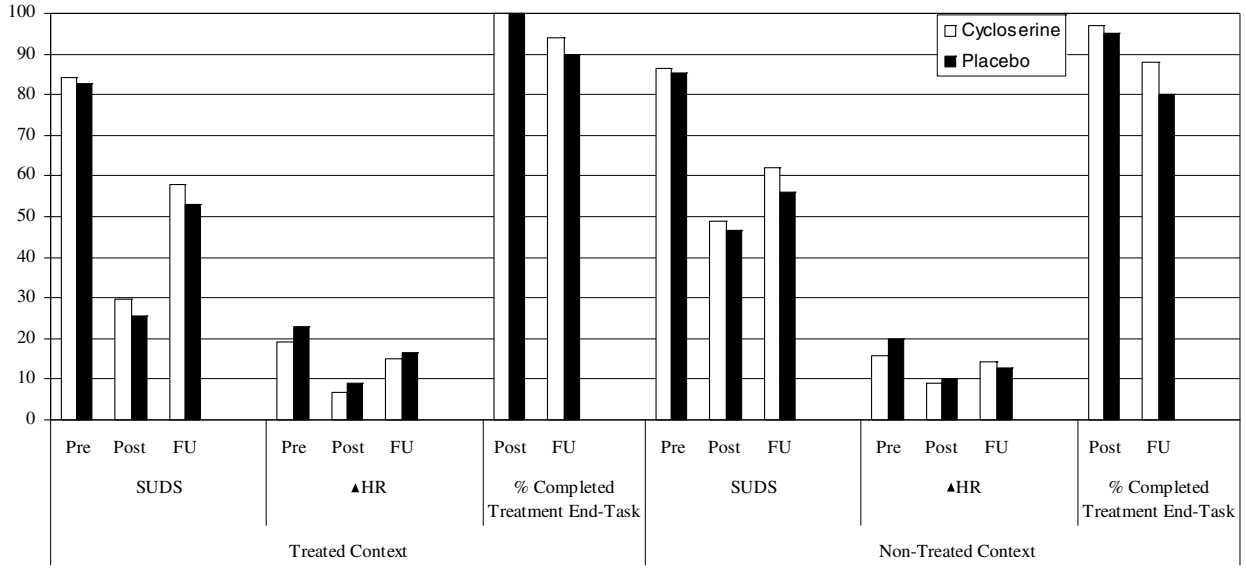

Fig. 1. The effect of drug condition on the closest proximity BAT scores at pre, post-treatment, and follow-up assessments. ▲HR = the difference between the average heart rate recorded during each BAT and the average heart rate recorded during baseline. The treated context refers to the context in which participants received treatment. To test generalisation of treatment, the non-treated context refers to a spider and room that differed from the treatment context.

To examine the effect of drug condition on treatment response, the data were analysed with a mixed-design ANOVA, with drug condition (Placebo, DCS) and time (pre, post, follow-up) as factors. This analysis showed a main effect for time on SUDS and heart-rate measures (smallest $F(2,60) = 7.25$, $p = 0.001$). Analysis indicated a significant drop on both SUDS and heart rate measures from pre to post-treatment. There was also a significant increase on all measures, except heart rate in the different context, from post-treatment to follow-up assessment. Follow-up assessments were significantly lower than at the pre-treatment assessments on all measures. Overall, these results suggest that there were significant treatment gains, and partial return of fear in the follow-up test.

Analysis showed that there was no main effect of drug, on either SUDS or heart rate measures in either context (largest $F(1,61) = 2.32$, $p > 0.05$). Analysis also indicated there was no interaction between drug and time (largest $F(2,60) = 0.69$, $p > 0.05$). Further, analysis suggested there was no difference between Placebo and DCS groups in the number of individuals able to complete the treatment end-point task at follow-up, or the number of self-exposures from post-treatment to follow-up assessment (largest $F(1,61) = 0.63$, $p > 0.05$). The same pattern of results was observed when the analysis was restricted to the most severe 20% of spider-fearful participants (based on SPQ or initial BAT scores) or the 20% of participants who achieved the least amount of change during exposure therapy. At the post-experiment interview, 51% of participants correctly guessed the central hypothesis and 27% of participants believed they had taken DCS, however; these rates did not differ between drug conditions.

2.3. Discussion

The results of this study do not support the hypothesis that ET treatment of non-clinical spider fears are enhanced by DCS. Both DCS- and placebo-treated groups showed substantial reductions in spider fear following treatment, but these two groups did not differ on self-reports, behavioural proximity tasks, or heart rate responses following treatment. However, before concluding that DCS does not enhance therapeutic outcomes of a single-session exposure therapy treatment in this setting, we felt it necessary to address two issues. First, our study differs significantly from the previous treatment trials (Hofmann et al., 2006; Ressler et al., 2004) in the strength of the exposure treatment provided to the placebo condition. In the two previous studies, the placebo group barely improved as a result of treatment. In contrast, in our study the effect of exposure therapy was substantial in the placebo condition. It could be that because our treatment was so effective, we may not have had the opportunity to detect any treatment enhancing effects of DCS. Countering this suggestion, however, was the fact that we did observe some return of fear at follow-up, and an analysis of only those participants showing the lowest levels of improvement across the treatment session still failed to yield any evidence of a DCS effect. Nonetheless, it still possible that enhancement of treatment outcome by DCS is most obvious when ET is conducted in a minimalist manner.

A second issue that needs to be addressed relates to the dosage of DCS that was selected in our study. Ressler et al. (2004) reported no difference between 50 and 500 mg DCS groups, and so combined the two groups; however, it may not have been possible to detect a dose difference with their

relatively small sample size. While Hofmann et al. (2006) also used a 50 mg dose of DCS and found significant effects, there is neurological evidence to suggest that 50 mg of DCS may not consistently activate NMDA receptors in humans (D'Souza et al., 2000; van Berckel et al., 1997). More consistent effects may be observed with a larger dose of DCS.

3. Study 2

The aim of this study was to test the effects of both the 50 and 500 mg dose of DCS in a heightened spider fearful sample when only partial ET treatment is provided. Like the first study, this study aimed to assess whether DCS could enhance the effects of ET by increasing treatment response and the generalisation of treatment.

3.1. Method and materials

Participants ($n = 37$) were recruited in the same way as the previous study.[1] All participants received ET, and were randomly assigned, in a double-blind design, to receive DCS or placebo. The first 21 participants who entered the study received 50 mg DCS ($n = 10$) or placebo ($n = 11$). The next 16 participants received 500 mg DCS ($n = 8$) or placebo ($n = 8$).

The materials and procedures were identical to Study 1 except for the fewer number of BAT steps required for completion of the exposure treatment. After assessment, a single session treatment was administered. This session included 1 h of education about cognitive, behavioural, and physiological aspects of ET, as well as some cognitive-therapy, and then an 8-step exposure session. The maximum time for ET was set at 2 h. The first step was based on the proximity attained during the first BAT, while the last step consisted of moving the spider with a chopstick. In order to reduce the power of exposure therapy treatment, we removed the three most difficult BAT steps that were part of the exposure treatment in study 1. These difficult BAT steps were placed into a challenge task that was completed at follow-up for assessment.

The first two BAT assessments at follow-up were identical to those in Study 1. The third BAT in both contexts was a challenge task and tested how far participants could approach the spider beyond the treatment end-point. Participants were told that we were interested in how close they could approach the spider before feeling too uncomfortable to continue. The task began with dangling their fingertips in the box, then placing their gloved hand in the clear perspex box, and finally moving the spider over their gloved hand with a chopstick. The degree of approach in this task was given a rating between 0 (completed task by placing hand in box and moving spider over gloved hand) and 14 (standing 300 cm away unable to approach further). Fear ratings on this BAT were taken, pre-, point of maximum approach, and post.

3.2. Results

Demographic and pre-treatment variables did not differ across drug conditions; there were no group differences in variables such as exposure duration ($M = 42$ min), therapist, or context. Pre-treatment levels of spider fear were consistent with Study 1 and with previous research (Rodriguez et al., 1999); on average, participants were able to stand 78.49 cm (SD = 69.44) away from the spider, predicted experiencing an average 72/100 fear level (SD = 14.98), and had 49% (SD = 24.66) confidence of being able to touch the perspex container. On average, participants reported 78/100 fear level (SD = 10.72) during the pre-treatment BAT.

Fig. 2 presents scores on most fear reported (SUDS) and heart rate during the BAT of closest proximity. Two SUDS ratings are listed at follow-up. The first set of ratings are for the BAT treatment end-point (max = move spider with chopstick), while the second are for the ratings provided during the challenge BAT of closest proximity (max = move spider with chopstick over gloved hand inside the Perspex box). To examine the effect of context on treatment response, SUDS and heart-rate change scores were created by subtracting post-treatment and follow-up assessment scores from the pre-treatment score within each context. *T*-tests comparing the two sets of difference scores between each context suggested that there was a greater treatment response within the same context in comparison to the different context at both post-treatment and follow-up assessment (smallest $t(36) = 2.19$, $p = 0.03$). This was shown on both SUDS and heart-rate measures in all but one case, the change in heart-rate from pre-treatment to follow-up. Results on this measure suggested a trend, however, in the same direction as the other analysis ($t(36) = 1.75$, $p = 0.09$).

Treatment was far less effective than the treatment provided in Study 1. As can be seen, only 20% of participants in this study were able to reach the final step of moving the spider over their gloved hand at follow-up. In fact, on average, participants in this study were only able to reach dangling their fingertips in the box in the treated context. In the non-treated context, on average, participants experienced even greater difficulty completing the challenge task and were not able to move beyond moving the spider with a chopstick. In contrast, about 90% of participants in Study 1 were able to move the spider over their gloved hand in both the treated and non-treated context.

To test the effect of drug on treatment response, the data were analysed with a mixed-design ANOVA, with drug condition (Placebo, DCS) and time (pre, post, follow-up treatment end-point BAT) as factors. This analysis showed a main effect of time on SUDS and heart-rate measures (smallest $F(2, 35) = 10.88$, $p < 0.001$). There was a significant drop on SUDS and heart rate from pre to post-treatment and then an increase on both measures from post-treatment to follow-up assessment. Follow-up assessments were significantly lower than at the pre-treatment

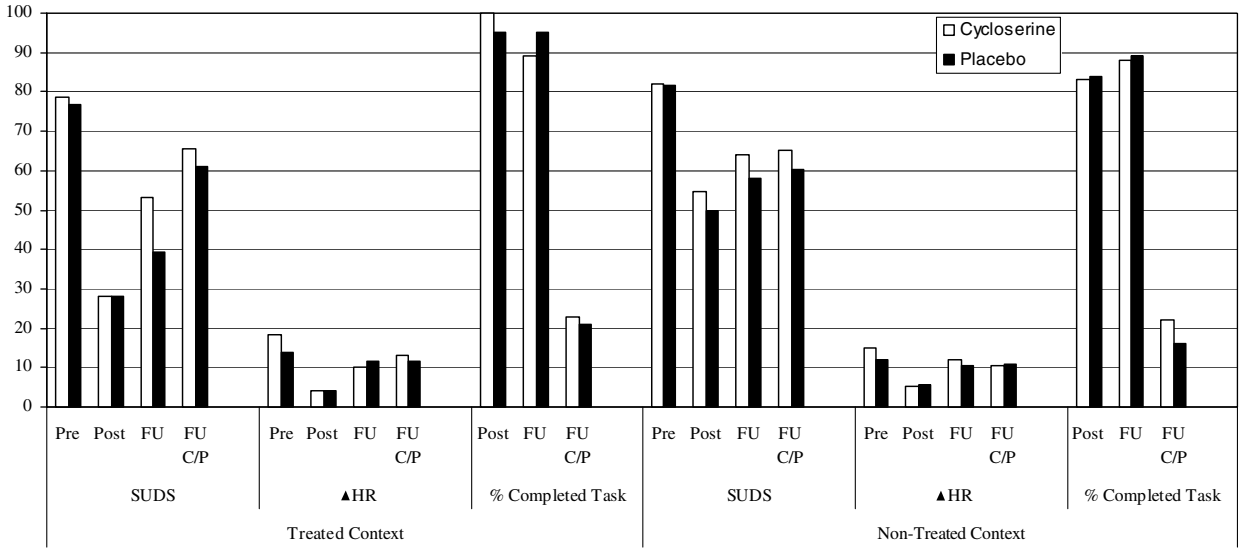

Fig. 2. The effect of drug condition on the closest proximity BAT scores at pre, post-treatment, and follow-up assessments, where FU, treatment endpoint; FU/CP, follow up closest proximity task, and ▲HR, the difference between the average heart rate recorded during each BAT and the average heart rate recorded during baseline. The treated context refers to the context in which participants received treatment. To test generalisation of treatment, the non-treated context refers to a spider and room that differed from the treatment context.

assessment on all measures except heart-rate in the different context. These results suggest that there were significant treatment gains, and significant of return of fear, particularly on heart-rate in the different context. Analysis also showed that there was no main effect of drug on SUDS or heart rate measures in either context (largest $F(1,36) = 0.92$, $p > 0.05$). This analysis also indicated there was no interaction between drug and time (largest $F(2,35) = 0.82$, $p > 0.05$). Further, analysis suggested there was no difference between Placebo and DCS groups in the number of individuals able to complete the treatment endpoint task or the challenge task at follow-up, the physical distance from challenge task completion, or the number of self-exposures from post-treatment to follow-up assessment (largest $F(1,36) = 2.13$, $p > 0.05$). At the post-experiment interview, 33% of participants correctly guessed the central hypothesis and 31% of participants believed they had taken DCS; however, these rates did not differ between drug conditions.

3.3. Discussion

These results once again show that a single ET session reduces fear of spiders (Rodriguez et al., 1999), but fail to support the hypothesis that DCS enhances the extinction of fear in a non-clinical sample. No effects of DCS were found on self-reported fear, behavioural proximity, or heart-rate. There was also no effect of DCS on the generalisation of treatment to different contexts. These results were the same as in Study 1, even though we trialled two doses of DCS, less time was allocated to exposure therapy, and only a partial exposure therapy treatment was given. In fact, most participants remained afraid of spiders at follow-up with only about 20% of participants able to complete the final BAT. This is a dramatic reduction in treatment efficacy from Study 1 where approximately 95% were able to complete this same BAT step.

4. General discussion

The results of these studies indicate that DCS does not enhance the reduction of fear in a heightened spider fear population. DCS-treated subjects were no different to placebo controls on self-reports, behavioural proximity tasks, and heart rate responses post-treatment or at follow-up. Despite a failure to find an effect of DCS, this study was able to replicate the effects of other variables thought to impede ET, specifically, stimulus and context shifts (Rodriguez et al., 1999; Rowe and Craske, 1998b). In both of the present studies, the results showed that changing stimulus or context had a significant negative effect on treatment efficacy, even at the immediate post-treatment assessment. This negative effect was more pronounced in the second study, where exposure treatment had been scaled back.

The results reported here contrast with the numerous studies in laboratory animals (for review see, Richardson et al., 2004), as well as two human clinical trials (Hofmann et al., 2006; Ressler et al., 2004) that have found DCS facilitates extinction of fear. We must therefore consider the unique factors in this study which may account for these inconsistent results. The first, and most obvious, consideration relates to our use of a non-clinical sample. There may have been some clinically phobic participants in our sample, but most would have been considered

sub-clinical. Although sub-clinical participants are routinely used to test clinical models of anxiety and are particularly useful for the evaluation of mechanisms associated with extinction and return of fear (Rodriguez et al., 1999), it may be that the biological mechanisms on which DCS operates are particularly sensitive in participants with clinical-level fears. The second major issue relates to our exposure therapy treatment. It partially reduced fear in the placebo condition. Previous DCS clinical treatment studies have shown very little, if any, treatment effects from exposure therapy in the placebo condition. It may be that the impact of DCS is only obvious when exposure therapy is ineffective. We tried to evaluate this factor by restricting analysis to participants who improved least over treatment. However, this analysis was limited by self-selection and participants who report less therapeutic learning from exposure therapy may also be less likely to benefit from DCS. In any case, the present findings suggest that researchers planning to conduct future DCS studies in humans may not want to use non-clinical samples.

There were three other significant methodological differences between our study and the other two human studies. First, participants in the present study received DCS just before the pre-treatment assessment whereas participants in the other studies received their DCS after the pre-treatment assessment session. It is difficult to see how this difference could potentially impact upon DCS treatment effects. DCS takes at least 2 hours to peak after oral administration (Hardman and Limbird, 2001), and our participants were receiving exposure treatment during this time. Second, pre-treatment assessment and ET took place on the same day whereas previous studies have separated assessment and treatment. Third, we used a single exposure therapy session while the two previous human trials employed at least two exposure therapy sessions. However, Ressler et al. (2004) data suggest benefits from DCS were apparent after the first exposure session. It is unclear how these design differences could explain our failure to replicate the previously reported effect of DCS on loss of fear following ET, however, these differences should be noted.

In conclusion, the current studies show that a single DCS dose used in conjunction with ET in a heightened spider fear sample does not enhance treatment. These effects were not found despite testing a large sample, the use of a well-characterised and researched exposure paradigm, and clear evidence of context manipulation effects on ET outcomes. The present studies suggest that DCS may only be effective as an adjunct to exposure therapy in clinical populations.

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