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

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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

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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).