

# Effects of D-Cycloserine on Extinction: Translation From Preclinical to Clinical Work

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*Administration of benzodiazepines or serotonin reuptake inhibitors in combination with behavior therapy for the treatment of many anxiety disorders has generally lead to only modest gains. In this article we suggest that pharmacotherapy aimed not at treating the symptoms of anxiety but instead aimed at improving the learning that takes place in exposure therapy might actually improve the effectiveness of exposure therapy. This idea was based on animal work showing that the partial N-methyl-D-aspartate (NMDA) agonist D-cycloserine (DCS) facilitated extinction of fear when given either before or shortly after exposure to fearful cues, reduced return of fear that is normally seen when extinction training is followed by stress, and led to generalized extinction, where DCS given in combination with exposure to one fearful cue led to extinction to another cue previously paired with the same aversive event. These findings suggested that DCS might facilitate exposure-based psychotherapy, which was verified in a small clinical study showing that DCS facilitated exposure therapy for fear of heights in a well-controlled virtual reality environment.*

**Key Words:** Amygdala, fear, anxiety, psychotherapy

It has been suggested that the use of anxiolytics is contraindicated in combination with behavior therapy for the treatment of many anxiety disorders, especially phobias, because these medications might interfere with the effectiveness of exposure therapy, although more work in this area is needed. However, in this article we suggest that pharmacotherapy aimed not at treating the symptoms of anxiety but instead aimed at improving the learning that takes place in exposure therapy might actually improve the effectiveness of exposure therapy. This idea grew out of animal studies looking at the role of the neurotransmitters involved in a process called extinction, which is very similar in many respects to the process of exposure therapy. Extinction of fear refers to the reduction in the measured level of fear to a cue previously paired with an aversive event when that cue is presented repeatedly in the absence of the aversive event. Actually, the term extinction is used in several different ways in the literature. Extinction might refer to: 1) the experimental procedure used to produce a decrement in the fear response; 2) the decremental effect of this procedure on the fear response, which can be measured both at the time the cue is presented in the absence of the aversive event and at a later time; or 3) the hypothesized associative or cellular process responsible for that effect. As suggested elsewhere (Myers and Davis 2002) we will define the experimental procedure as “extinction training,” the decrement in the fear response measured during extinction training as “within-session extinction,” and the decrement measured at some interval after extinction training as “extinction retention.” The term “extinction” will be reserved for the process underlying the loss of the fear response.

In exposure therapy the patient is repeatedly exposed for prolonged periods to a feared object or situation in the company of a supportive therapist and hence in the absence of aversive consequences (extinction training). As a result, the patient is now

able to face their feared cues or situations with less fear and avoidance (extinction retention) by virtue of the learning that took place during exposure therapy (extinction). Consistent with the idea that pharmacotherapy given to treat the symptoms of anxiety might interfere with the effectiveness of exposure therapy, it has been shown in rats that benzodiazepines given during extinction training reduce extinction retention (Bouton et al 1990). But what if we could find a drug that improves extinction in animals; would this drug also improve the effectiveness of exposure-based psychotherapy?

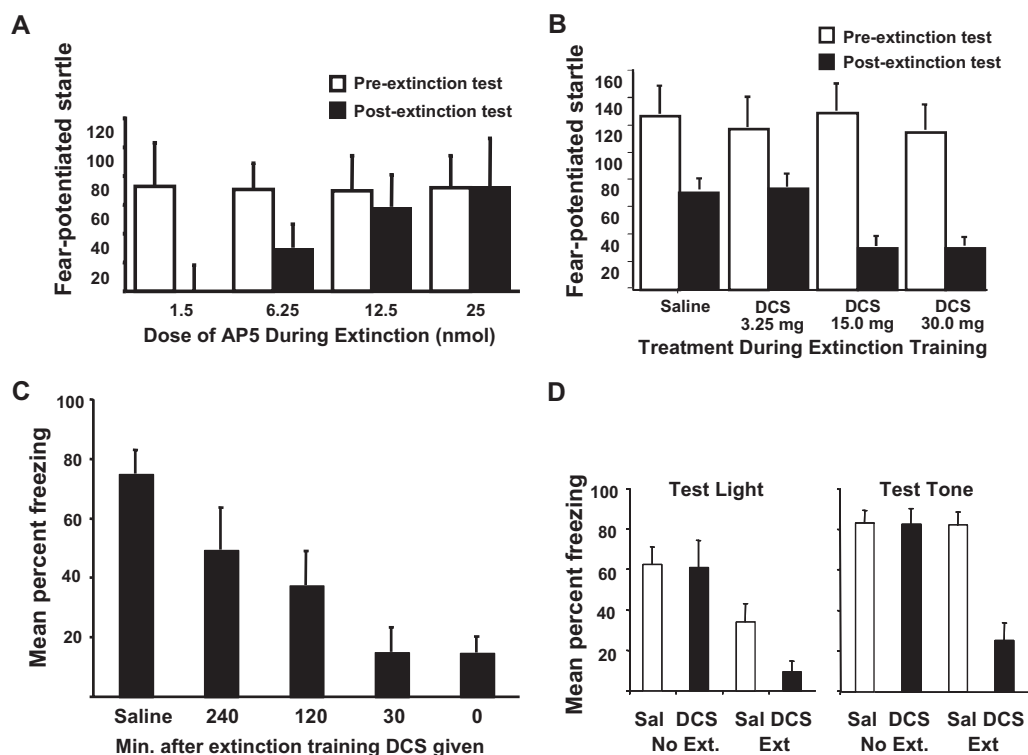
## The Role of N-Methyl-D-Aspartate Receptors in Extinction

Extinction typically does not result from an erasure of the original fear memory but instead represents a new form of learning that acts to inhibit or suppress the original fear memory (Bouton and Bolles 1979a; Konorski, 1967; Pavlov 1927). A large body of literature suggests that glutamate acting at the N-methyl-D-aspartate (NMDA) receptor is critically involved in learning and memory (Bear 1996; Castellano et al 2001; Morris et al 1990; Newcomer and Krystal 2001). For example, Miserendino et al (1990) found that blockade of the NMDA glutamate receptor in the amygdala, known to be critical for fear conditioning, blocked the acquisition but not the expression of conditioned fear. Hence, we wondered whether the same treatment would block the development of extinction (Falls et al 1992). Rats were first exposed to a standard fear conditioning protocol (10 pairings of a visual cue with a footshock on each of 2 days). Several days later, separate groups of rats received intra-amygdalar infusions of different concentrations of the NMDA antagonist 2-amino-5-phosphonopentanoic acid (APV) immediately before extinction training, which took place on each of 2 days and consisted of 30 presentations of the light in the absence of shock. Extinction retention was then tested the following day. The APV produced a dose-dependent blockade of extinction retention that could not be attributed to antagonism of NMDA receptors outside of the amygdala, damage to the amygdalar complex, or an impairment of sensory transmission during extinction training (Figure 1A). A similar blockade of extinction retention of contextual fear conditioning, inhibitory avoidance, and eyeblink conditioning has since been reported with administration of APV or other NMDA antagonists (Kehoe et al 1996; Lee and Kim 1998; Szapiro et al 2003), and additional studies have confirmed that these effects cannot be explained by state dependency—a return of the fear

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Received September 12, 2005; revised March 28, 2006; accepted March 28, 2006.



**Figure 1.** Glutamate antagonists block and glutamate agonists facilitate extinction. **(A)** Percent fear-potentiated startle measured 24 hours before (pre-extinction test) and 24 hours after (post-extinction test) extinction training. On each of 2 successive days, various doses of the N-methyl-D-aspartate (NMDA) antagonist AP5 (1.5, 6.25, 12.5, or 25 nmol/side) were infused into the basolateral amygdala 5 min before presentation of 30 lights in the absence of shock. Fear potentiated startle was then measured 24 hours later in the absence of drug (values are means  $\pm$  SEM) (Falls et al 1992). **(B)** Percent fear-potentiated startle measured 24 hours before (pre-extinction test) and 24 hours after (post-extinction test) extinction training. Saline or D-cycloserine (DCS; 3.25, 15, or 30 mg/kg, IP) was administered 30 min before a single session of extinction training. Fear potentiated startle was then measured 24 hours later in the absence of drug (values are means  $\pm$  SEM) (Walker et al 2002). **(C)** Effect of varying the delay of DCS administration after extinction training. Mean ( $\pm$  SEM) percent of time rats spent freezing during one 2-min presentation of the light conditioned stimulus during an extinction retention test. Rats were given five pairings of a light with a shock on Day 1; on Day 2, all rats were given six, 2-minute non-reinforced presentations of the light and saline or DCS was administered 240, 120, 30 min, or immediately after extinction training; on Day 3, the extinction retention test was given (Ledgerwood et al 2003). **(D)** Effect of DCS on conditioned freezing during test. Left panel: Mean ( $\pm$  SEM) percent of time rats spent freezing during presentations of the light after either extinction training to the light or handling. Sal, saline; No Ext, no extinction; Ext, extinction. Right panel: Mean ( $\pm$  SEM) percent of time rats spent freezing during presentations of the tone after either extinction training to the light or handling. All rats were given pairings of the light and the tone with a loud noise US on Day 1; on Day 2, some rats were given non-reinforced presentations of the light (i.e., extinction training) and then injected with either saline or DCS; on Day 3, all rats were tested for fear of the light and the tone (in a counterbalanced order) (Ledgerwood et al 2005).

response when the animal is later tested in the absence of the drug given during extinction training (Baker and Azorlosa 1996; Cox and Westbrook 1994).

### Facilitation of Extinction With an NMDA Partial Agonist

Because the blockade of the NMDA receptor impairs extinction, it was logical to wonder if enhancing the functioning of that receptor would enhance extinction. To test this we administered a compound called D-cycloserine (DCS) either systemically or directly into the rats' amygdala before extinction training and then tested retention of extinction the next day (Walker et al 2002). D-cycloserine does not bind to the NMDA receptor itself but to another receptor on the NMDA protein called the glycine regulatory site. Activation of this site improves the ability of the NMDA receptor protein to flux calcium, which initiates a variety of intracellular events that are critical for learning. As predicted, when DCS was given in combination with repeated exposure to the feared stimulus without a shock, extinction retention was enhanced (Figure 1B). This did not occur in control rats that received the drug alone, without extinction training. On the basis of these results we concluded that the positive effects of the DCS were specifically connected with extinction and did not result

from a general dampening of fear expression. These results have now been replicated with freezing as the measure of conditioned fear (Ledgerwood et al 2003).

Preclinical information about the effects of DCS on extinction of learned fear has continued to accumulate. Previously it was reported that NMDA antagonists given after extinction training reduced subsequent extinction retention (Santini et al 2001), suggesting that NMDA receptors are involved in the consolidation of extinction. If so, then one might expect that DCS given after extinction training would also facilitate extinction retention. To test this, Ledgerwood et al (2003) trained rats to be afraid of a light and 24 hours later gave them extinction training consisting of six 2-min exposures to the light with no shock. They then injected rats with either saline or DCS either immediately or 30, 60, 120, or 240 min after extinction training; all rats were tested for the level of freezing to the light 24 hours after extinction training. Rats given DCS after extinction training exhibited less fear of the light at test than rats given saline. Increasing the delay between the end of extinction training and administration of DCS led to a linear decrease in the enhancement effect with significant facilitation of extinction occurring only when the DCS was administered

< 4 hours after extinction training (Figure 1C). These data are thus consistent with the idea that DCS causes a time-dependent facilitation of extinction consolidation.

Recently, Yang and Lu (2005) replicated the finding that DCS facilitates extinction of learned fear in rats. More importantly, their work provides information about some of the processes by which DCS facilitates extinction of learned fear. For example, they showed that intra-amygdalar protein synthesis was involved in the DCS effect. That is, rats given a protein synthesis inhibitor in combination with DCS did not exhibit facilitated extinction. Furthermore, Yang and Lu (2005) also reported that the phosphoinositide-3 kinase (PI-3K) and mitogen-activated protein kinase (MAPK)-dependent signaling cascades are involved in the DCS effect. That is, rats given, for example, a MAPK inhibitor in combination with DCS did not exhibit the DCS effect. Although we don't yet fully understand the molecular processes involved in the facilitation of extinction by DCS, this paper by Yang and Lu (2005) provides a very good foundation for further exploration of this issue.

### Does DCS Cause "Generalized" Extinction?

Perhaps the most surprising result from the recent preclinical studies on DCS and extinction is that DCS seems to lead to generalized extinction (Ledgerwood et al 2005). In that study, rats were initially trained with two different cues (i.e., a light and a tone), each paired with a loud aversive noise. The next day some rats were given two sessions (separated by 2 hours) of extinction training with the visual cue (six non-reinforced exposures to the 2-min light in each session). Immediately after the second extinction training session, some rats were injected with DCS, whereas others were injected with saline. Other rats were injected with saline or DCS on the same day but not given extinction training. Twenty-four hours later, the light and the tone were each presented separately (test order was counterbalanced) and level of freezing was measured. The results obtained with the visual conditioned stimulus (CS) replicated earlier findings where shock had been the aversive unconditioned stimulus (US). Specifically, rats given DCS after extinction training exhibited less fear of the light than rats given saline after extinction training or rats injected with DCS but not given extinction trials to the light (left side of Figure 1D). The most interesting result came from the test with the tone CS, the response to which had not been extinguished. Rats given extinction training to the light and injected with DCS exhibited reduced fear of the tone as well (right side of Figure 1D). That is, the DCS-treated rats exhibited generalized extinction of fear. This effect was not observed in rats injected with saline after extinction training to the light or in rats injected with DCS but not given the extinction training.

One interpretation of this finding of "generalized extinction" after DCS administration is that DCS facilitates extinction by enhancing the devaluation of the US representation elicited by the presentation of the light CS. The notion of US devaluation is best illustrated by a study by Rescorla (1973) in which rats received pairings of a cue with a loud noise. After this, some rats were habituated to the loud noise. Those rats habituated to the noise exhibited less fear of the cue (measured by lick suppression) than those rats not habituated to the noise. In a subsequent study, Rescorla and Heth (1975) suggested that extinction after non-reinforced presentations of the cue could result from the same process. That is, the cue elicits a representation of the loud noise during the extinction trials. However, given that no noise

US is presented, the representation of the noise US becomes devalued. After several such trials, the cue elicits a devalued representation of the noise, one that is incapable of eliciting learned fear responses. In other words, the cue-noise association is still intact, but now the cue activates a representation of the noise that is too weak to elicit fear responses. More recently, Ledgerwood et al (Ledgerwood, Cranney, and Richardson, unpublished data) extended this work by giving rats separate pairings of a visual and an auditory cue with a loud noise. Some rats were then habituated to the loud noise. The rats habituated to the loud noise exhibited much less freezing to both cues than did rats not habituated to the loud noise. In other words, the rats habituated to the noise before test exhibited a pattern of performance just like that seen in rats given DCS after extinction training with a visual cue but then tested later with both a visual and auditory cue.

### Clinical Implications

Not only does DCS facilitate extinction of learned fear (Ledgerwood et al 2003; Walker et al 2002; Yang and Lu 2005) but it also seems to produce generalized extinction (Ledgerwood et al 2005). Indeed, DCS-treated rats exhibit a pattern of performance at test that is exactly like that seen in rats that are habituated to the aversive stimulus before test. Therefore, DCS might facilitate extinction of learned fear by somehow affecting the devaluation of the representation of the aversive events associated with conditioned cues. Specifically, DCS might not only enhance the rate of devaluation (which leads to a faster rate of extinction; i.e., fewer extinction training sessions required to produce extinction retention) but also increase the strength of this effect that would lead to a loss of fear to any cue previously paired with that aversive event. Clinically this could be very beneficial, because it would predict that exposure-based psychotherapy aimed at reducing fear to certain cues might generalize to other associated cues not directly dealt with in therapy.

### DCS Reduces Reinstatement of Learned Fear After Extinction

In another study, Ledgerwood et al (2004) found that DCS might block relapse (i.e., a return of the learned fear response) that normally occurs when extinction training is followed by a stress, a phenomenon referred to as reinstatement. In that study, rats were first trained to be afraid of a light by pairing it with a footshock and then, the next day, given extinction training followed by injection of either DCS or saline. To equate levels of fear before stress, the saline-treated rats were given an additional day of extinction training. Some rats were then re-exposed to the shock 24 hours before test. If this shock re-exposure occurred in the test context, then rats in the saline condition exhibited a return of conditioned freezing; rats treated with DCS did not exhibit this return of learned fear after the pre-test shock treatment.

### Clinical Implications

Not only does DCS facilitate extinction of learned fear (Ledgerwood et al 2003; Walker et al 2002; Yang and Lu 2005) and seem to produce generalized extinction (Ledgerwood et al 2005) but it also seems to reduce post-extinction reinstatement after a stressful event. Clinically this could be very beneficial, because it would mean that fewer patients would relapse after successful completion of exposure-based psychotherapy. However, it must be noted that the finding of post-extinction reinstatement does not fit well with the US devaluation explanation of extinction. That is, if extinction of learned fear is due to a devaluation of the

US representation, then reinstatement should occur no matter where the pre-test shock is presented (i.e., the US representation would be “revived” regardless of the context in which the shock was presented). However, that is not the case. To observe reinstatement after extinction, the shock and the subsequent test have to occur in the same context (Bouton and Bolles 1979a). This effect was also found by Ledgerwood et al (2004). Thus, reinstatement must involve something more than just a reversal of devaluation. One possibility here, suggested by Richardson et al (2004), is that DCS-injected rats develop an extremely strong (and possibly context-independent) inhibitory CS-US association during extinction training. For example, Denniston et al (2003) reported that massive extinction (i.e., 800 extinction trials) reduced renewal of fear (return of fear when rats are tested in a context different from that during extinction training; Bouton and Bolles 1979b). If DCS causes extinction to become context independent after only a few trials, then reinstatement might be more difficult to demonstrate in these rats compared with saline-treated rats. That is, it might be necessary to provide stronger shock exposures or more shock exposures to observe reinstatement in the DCS-treated animals. Clearly, further research is required to examine these issues.

### DCS Does Not Seem to Facilitate Fear Conditioning and Might Even Reduce It

If DCS is so effective in facilitating learning, then one might wonder whether it could actually be harmful if combined with exposure-based psychotherapy. For example, bringing to mind awful memories of a traumatic event can lead to sensitization rather than extinction if a full therapeutic exposure is not carried out (Bisson et al 1997; Mayou et al 2000). Perhaps sensitization would be exacerbated by DCS by reinstating the fearful memories. Thus far none of us have seen any evidence of this in our rodent studies; nor was any evidence of this observed in our clinical study (see following). In fact, we have found that DCS does not facilitate fear conditioning under the conditions we use but might instead interfere with it (Walker and Davis, unpublished observations). Why might that be so?

D-cycloserine is an analogue of a naturally occurring chemical in the brain, D-serine. D-serine and glycine bind to the same site on the NMDA receptor as DCS. So it is possible that NMDA receptors involved in fear conditioning are already saturated with D-serine or glycine, making these receptors work optimally. This optimal functioning would be adaptive, because it is very important for all animals to learn quickly what stimuli are dangerous so as to avoid them in the future. If the receptors are already saturated, DCS would not be able to have any further effect. In fact, DCS is actually less effective than either D-serine or glycine; so if the site on the NMDA receptors involved in fear conditioning is fully saturated, DCS might actually reduce the activity of the receptors by displacing the more effective endogenous chemicals. This could explain why DCS seems to actually inhibit fear conditioning in some situations.

But how does this explain the ability of DCS to facilitate extinction? Perhaps the NMDA receptors involved in extinction are different from those involved in fear conditioning (e.g., on different neurons), and perhaps those involved in extinction are not saturated with glycine or D-serine. This would suggest that these particular NMDA receptors do not work as efficiently, an explanation for why extinction takes much longer to develop than fear conditioning. But because these receptors are not already saturated with natural chemicals, then the effect of giving

DCS would be to facilitate NMDA transmission and, therefore, extinction.

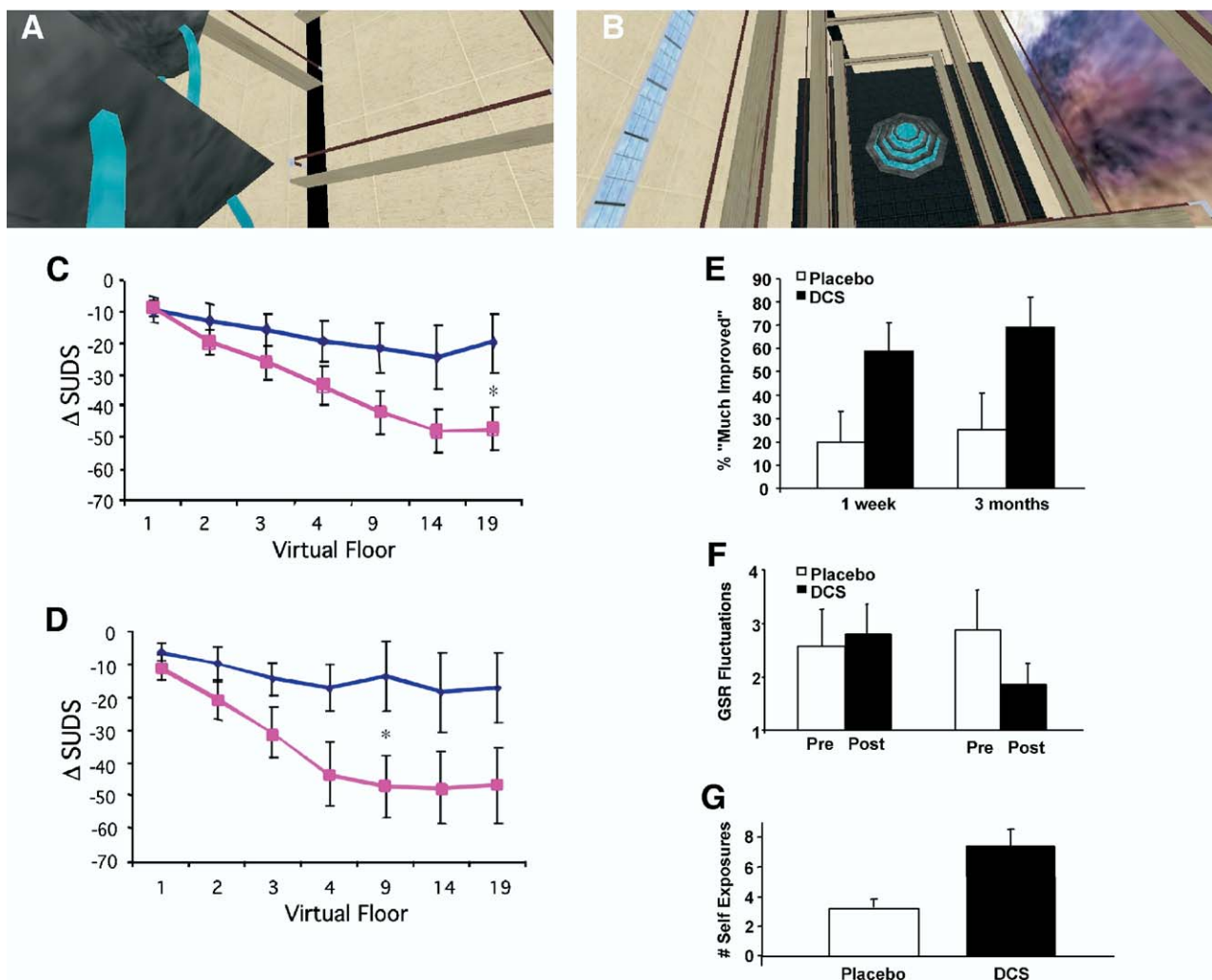
### A Clinical Test of Combining DCS With Behavioral Exposure Therapy for Acrophobia

Recently we tested whether DCS given in combination with exposure therapy for the treatment of specific phobia in humans would improve the effectiveness of this therapy (Ressler et al 2004). We wished to examine the ability of DCS to enhance exposure therapy in humans with the most optimally controlled form of psychotherapeutic learning available. Virtual reality exposure (VRE) therapy is ideal for clinical research assessment because exposure and testing is identical between patients, is well controlled by the therapist, and occurs within the spatial and temporal confines of the limited therapy environment (Rothbaum et al 1995). This method has proven to be successful for the treatment of specific phobias as well as post-traumatic stress disorder (Rothbaum et al 1995, 2000, 2001). With VRE for fear of heights, we used a virtual glass elevator in which participants stood while wearing a VRE helmet and were able to peer over a virtual railing (Figures 2A and 2B). Previous work has shown improvements on all acrophobia outcome measures for treated as compared with untreated groups after seven weekly therapy sessions (Rothbaum et al 1995). To examine whether DCS would enhance the learning that occurs during exposure therapy for humans with specific phobia, we enrolled 28 volunteer participants who were diagnosed with acrophobia by DSM-IV (Ressler et al 2004). Participants were randomly assigned to three treatment groups, Placebo + VRE Therapy or DCS + VRE Therapy at two different doses of DCS (50 mg or 500 mg). The high dose was chosen because we knew, on the basis of its prior use for the treatment of tuberculosis, that it would be well tolerated. The lower dose was chosen because it is in the range of doses that have been tried as cognitive enhancers in Alzheimer’s disease and schizophrenia. Treatment condition was double-blinded, such that the subjects, therapists, and assessors were not aware of assigned study medication condition. Although we used two different doses of DCS, preliminary analysis of our data indicated that there were no significant differences between the 50 mg and 500 mg drug groups for the primary outcome measures of acrophobia. Therefore we combined the two drug groups for analysis.

Participants underwent two therapy sessions, which is a suboptimal amount of exposure therapy for acrophobia (Rothbaum et al 1995). They were instructed to take a single pill of study medication 2–4 hours before each therapy session, such that only two pills were taken for the entire study. A post-treatment assessment was performed 1 week and 3 months after the second therapy session.

At both 1–2 weeks and 3 months after treatment, subjects who received DCS in conjunction with VRE therapy had significantly enhanced decreases in fear within the virtual environment (Figures 2C and 2D,  $p < .05$ ). Patients who received DCS in conjunction with therapy felt that they had improved significantly more than the placebo group in their overall acrophobia symptoms at the 3-month follow-up (Figure 2E). Furthermore, within the virtual environment, skin conductance fluctuations, a psychophysiological measure of anxiety, were significantly decreased in the group that received DCS in conjunction with therapy (Figure 2F).

One of the cardinal features of extinction in animal models is the context-specificity of the extinction environment. However,



**Figure 2.** Acrophobia within the Virtual Environment is improved with Drug + Exposure. **(A)** View from inside virtual glass elevator looking up. Note the small ledges patients are asked to walk out onto. **(B)** Patient is out on one of the ledges looking down to bottom of building. **(C)** Change in subjective units of discomfort (SUDS) from pre- to post-test after two therapy sessions that occurred approximately 1 week before this short-term follow-up assessment. Decrease in SUDS level (y axis) is shown for each floor (1–19) of the virtual glass elevator. Overall analysis of variance was performed with pre-post difference and floor as within subjects variables and drug group as between subjects variable. Significant overall pre-post changes were seen:  $[F(1,25) = 38, p < .001]$ . Significant effect of floor was found:  $[F(6,150) = 89, p < .001]$ . Most importantly, significant effect of pre-post  $\times$  floor  $\times$  drug interaction was found:  $[F(6,150) = 3.8, p < .001]$ . **(D)** Change in SUDS from pre- to post-test at the 3-month long-term follow-up assessment. Statistics were performed as previously described. Significant overall pre-post changes were seen:  $[F(1,17) = 21, p < .001]$ . Significant effect of floor was found:  $[F(6,102) = 81, p < .001]$ . Most importantly, significant effect of pre-post  $\times$  floor  $\times$  drug interaction was found:  $[F(6,102) = 2.4, p < .05]$ . **(E)** Percent of patients in the D-cycloserine (DCS) or placebo groups reporting “much improved” at 3-month follow-up. **(F)** Number of spontaneous galvanic skin fluctuations in the simulated glass elevator before and 1 week after therapy in the two groups. No change in placebo group; significant change ( $p < .05$ ) in the DCS group. **(G)** Self-report of number of in vivo exposures to heights since the treatment 3 months earlier  $[t(17) = 3.0; p < .01]$ .

Richardson et al have demonstrated that DCS enhancement of extinction in rats seems to lead to generalization across cues (Ledgerwood et al 2005). We therefore wondered whether the decreased fear of heights found within the virtual environment would generalize to other settings. This question was assessed in two ways: first, by asking questions related to the subject’s fear of heights in the real world; and second, by assessing the degree to which the subjects had decreased their avoidance of heights since the treatment. We found that patients’ self-exposure to heights in the “real world” had increased, suggesting decreased avoidance (Figure 2G).

Our data indicate that participants receiving DCS experienced no increase in anxiety or fear during the exposure paradigm; so the enhancement of extinction is not due simply to enhanced

intensity of exposure. Participants in the DCS group showed some evidence of enhanced extinction after only a single dose of medication and therapy. After two doses of medication and therapy, they showed significant reductions in levels of fear to the specific exposure environment. Finally, we found that 3 months after the two treatment sessions the DCS participants showed significant improvements on all acrophobia outcome measures, their own self-exposures in the real world, and their impression of clinical self-improvement relative to participants who received placebo (Ressler et al 2004). DCS also has been reported to facilitate exposure-based psychotherapy in patients with social phobia (Hofmann et al 2006).

It is important to note that the timing of dosing of DCS might be critical in the use of this agent in the augmentation of

exposure therapy. Despite animal studies suggesting enhancement of spatial learning by DCS (Baxter et al 1994; Quartermain et al 1994; Schuster and Schmidt 1992; Thompson et al 1992), the studies of human trials in patients with dementia have found only minor improvements (Schwartz et al 1996; Tsai et al 1998) or no significant effect on memory enhancement (Fakouhi et al 1995; Randolph et al 1994). We believe that a principal difference between those studies, our human acrophobia study, and the animal literature is the frequency and chronicity of drug dosing. The human memory enhancement studies used daily dosing for weeks to months compared with single dosing before the learning event in animal experiments and in our exposure study. In fact, Quartermain et al (1994) explicitly examined single versus chronic dosing of DCS in animals for improvement of learning. They found that a single dose of drug before training enhanced the learning of the task, whereas 15 days of drug before the task had essentially no effect on the learning. This has very recently been explicitly tested with extinction by Richardson et al, and they found that rats receiving 5 doses of DCS on an every-other-day schedule received no benefit when given DCS in combination with an extinction training session compared with significant facilitation of extinction with acute dosing (Parnas et al 2005).

Interestingly, it is now accepted that most psychiatric medications have their intended psychotropic effect not through their acute mechanisms but through chronic mechanisms that often involve receptor, cellular, and systemic regulatory mechanisms that are quite distinct from the acute pharmacologic drug effect. However, in the case of DCS augmentation of exposure therapy, chronic treatment might actually result in a loss of efficacy due to tachyphylaxis as well as other regulatory phenomena that are likely to occur with prolonged activation of the NMDA receptor. Thus, in contrast to other psychotropic medication, to achieve the intended effect of enhancing NMDA receptor activity, DCS might need to be taken on an acute schedule specifically in combination with the exposure-based treatment.

In conclusion, we have applied some of the lessons learned in extinction training in animals to humans with exciting results. The use of a specific pharmacologic intervention to enhance the beneficial effects of psychotherapy represents a new paradigm in psychiatry. Although we have focused on the effects of a partial NMDA antagonist in the present review, it should be noted that other agents can enhance extinction of learned fear in non-human animals. Future clinical studies on potential pharmacologic enhancement of exposure-based therapy should focus on agents that enhance the learning that occurs during the exposure sessions rather than on agents that reduce the anxiety experienced during those sessions.

*This work was supported by National Institute of Mental Health grants MH-047840 (to MD), MH55555 (to BOR), and MH069884 (to KJR); a National Science Foundation Grant, IBN-987675 for the Science and Technology Center Program; Center for Behavioral Neuroscience and The Yerkes National Primate Center P-51 Base Grant; a Life Sciences Research Grant to Jacqueline Cranney; and a Faculty of Life Science Postgraduate scholarship to Lana Ledgerwood at the University of New South Wales, Sydney, Australia.*

*MD and KR have submitted a patent for the use of D-cycloserine for the specific enhancement of learning during psychotherapy. BOR receives research funding and is entitled to sales royalty from and owns equity in Virtually Better, which is developing products related to the research described in this*

*paper. The terms of these arrangements have been reviewed and approved by Emory University in accordance with their conflict of interest policies.*

*Aspects of this work were presented at the conference, "Extinction: The Neural Mechanisms of Behavior Change," held February 2–6, 2005, in Ponce, Puerto Rico. The conference was sponsored by the National Institute of Mental Health, National Institute of Drug Abuse, Ponce School of Medicine, University of Puerto Rico COBRE Program, Pfizer Global Pharmaceutical, and the Municipality of Ponce.*

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