A Randomized Controlled Trial of D-Cycloserine Enhancement of Exposure Therapy for Social Anxiety Disorder

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Background: Pilot research has suggested that D-cycloserine (DCS) enhances treatment outcomes for anxiety disorders when employed as an adjunct to exposure therapy (ET). The aim of this study was to determine whether 50 mg of DCS enhances ET for social anxiety disorder (SAD) according to a comprehensive set of symptom and life impairment measures.

Methods: In a randomized double-blind placebo-controlled trial, we administered 50 mg of DCS or placebo in combination with ET to 56 participants who met primary diagnosis for SAD.

Results: Participants administered DCS reported greater improvement on measures of symptom severity, dysfunctional cognitions, and life-impairment from SAD in comparison with placebo-treated participants. Effect sizes were mostly in the medium range. Results also indicated that the amount of adaptive learning about one's ability to give speeches in front of an audience interacted with DCS to enhance treatment outcome.

Conclusions: This study shows that the administration of DCS before ET enhances treatment outcomes for SAD. Results also provide the first preliminary evidence to suggest that DCS moderates the relationship between a reduction in negative appraisals about one's speech performance and improvement in overall SAD symptoms.

I n nonhuman animals, Pavlovian conditioning studies have shown that the partial N-methyl d-aspartate (NMDA) agonist D-cycloserine (DCS) facilitates the extinction of learned fear when administered immediately before or even shortly after extinction training (1). It has been suggested that DCS strengthens extinction memories so they might be more easily retrieved during subsequent exposures to fear-relevant cues. On the basis of these pre-clinical studies, it was suggested that DCS might enhance the extinction of fear in humans when combined with exposure-based therapy (ET) procedures (2).

Research shows that DCS has no effect on symptoms of anxiety when administered chronically to patients over weeks and months (3). However, when administered acutely in combination with exposure-based procedures, pilot studies suggest that DCS enhances treatment outcome. In a first study (4), 27 patients diagnosed with height phobia (acrophobia) were assigned to three conditions: placebo, 50 mg DCS, or 500 mg DCS; and all received two sessions of virtual reality ET. At 1-week and 3-months post-treatment, participants assigned to the DCS condition, regardless of dose, experienced less fear as indicated by self-reported fear levels in a virtual reality environment, acrophobic beliefs, and an increased number of self-exposures to heights in real-world environments. In a second study (5), 27 patients diagnosed with social anxiety disorder (SAD) were randomly

assigned to receive DCS (50 mg) or placebo 1 hour before each of four public speaking tasks. Speeches were recorded and then viewed. At the conclusion of therapy and at 1-month follow-up, participants who received DCS showed larger improvements relative to participants who received a placebo, as measured by clinician-rated and self-report ratings of symptom severity. In a third study (6), 32 patients diagnosed with obsessive-compulsive disorder were assigned to receive DCS (125 mg) or placebo 2 hours before each of 10 exposure and ritual prevention therapy sessions. Results indicated that DCS facilitated anxiety reduction of obsession-related distress after four sessions of ET. The DCS effects were, however, weaker and nonsignificant over the following six therapy sessions. The authors concluded that DCS might be best applied as an adjunct to brief therapy treatment programs.

Our research group has published two studies investigating DCS effects on fear extinction in non-clinical samples (7,8). In the first study (7), non-clinical students ($n = 100$) who reported heightened spider fear were given DCS (50 mg or 500 mg) or placebo in combination with a single-session of ET. Across two experiments, results showed that DCS did not enhance treatment outcomes as indicated by behavioral, physiological, or self-report fear measures taken in the presence of spiders at 3.5 weeks after treatment. In the second study (8), 238 participants were given either DCS (50 or 500 mg) or placebo 2–3 hours before extinction training with a differential shock conditioning paradigm (9). Over three experiments, DCS was shown to have no clear influence on fear-extinction as assessed by skin conductance and self-reported shock expectancy measures. To explain discrepancies between clinical and non-clinical findings, some researchers (10) have suggested that DCS effects might be more difficult to show in non-clinical studies, because of potential floor effects from extinction procedures and/or the use of only a single administration of DCS in this population.

Although there is promising evidence that DCS enhances exposure-based treatments for clinical anxiety disorders, clinical

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studies have been limited by small sample size. To have strong evidence that DCS augments anxiety treatments, there is a need for replication with significantly larger sample sizes. Furthermore, there is a need for process measures to understand how DCS facilitates ET. The aim of this study was to conduct the first major replication of DCS-enhanced treatment of SAD for a large sample of community patients. Social anxiety disorder has an estimated lifetime prevalence of 12.1% (11). Patients with this disorder suffer significant impairment in functioning characterized by social fear, avoidance, dysfunctional cognitions, and life-impairment (12,13). We also aimed to extend previous studies by tracking weekly changes in symptoms to identify the point in treatment at which DCS enhances ET. This information might be used by researchers to plan the number of treatment sessions needed to show DCS effects on outcome. Finally, we wanted to test the effect of DCS on patients learning to reduce negative self-appraisals of speech performance. If DCS works by enhancing adaptive learning during exposure, then reductions in anxiety and avoidance should be associated with a reduction in negative self-appraisals about how one appears and communicates in front of an audience during an in-session speech exposure task. We predicted that patients receiving DCS would display larger reductions in negative self-appraisals across treatment sessions and that this learning would be more strongly associated with SAD symptom reduction than in those patients given a placebo.

Methods and Materials

Participants

Following the procedures of previous research (5), we recruited participants recruited from the community if they met DSM-IV diagnosis for SAD with the Anxiety Disorder Interview Schedule for Adults (ADIS-IV [14]) and also reported fear of public speaking on self-report measures. All participants were recruited through the University of New South Wales (UNSW) Psychology Clinic between May and October 2006 (all procedures were approved by the UNSW Human Research Ethics Committee [#04145]; this trial was registered on the Australian Clinical Trials Registry [012606000352505]). All assessment and treatment sessions were conducted by therapists who were registered or provisionally registered clinical psychologists. All therapists were supervised and trained by a senior clinical psychologist (AJG).

A total of 110 participants self-referred to the UNSW Psychology Clinic from advertisements in local media. Participants who seemed eligible after an initial phone screen were then assessed for SAD with the ADIS-IV clinical interview. Exclusion criteria included: a primary diagnosis of major depression, bipolar disorder, psychotic disorders (such as schizophrenia), severe kidney disease, epilepsy, reported pregnancy, current substance dependence, and current participation in any other psychological therapy. Non-psychiatric exclusion criteria were determined by self-report. Participants were asked to refrain from caffeine, nicotine, and alcohol on days that they received treatment. Of the 110 participants, 80 adults were eligible for treatment and were offered participation; 65 accepted (signed informed consent and completed initial assessments). Trial sample size was based on previous studies that report moderate–large effects from DCS in combination with ET (4–6). After the first treatment session (before drug assignment), 9 participants failed to return for the second and third treatment session and were not included in the analysis. The remaining 56 participants were randomly assigned

to DCS (*n* = 28) or placebo (*n* = 28) at the start of the second therapy session. After drug assignment, 6 participants (1 = DCS; 5 = placebo) failed to attend at least three group exposure sessions between session 2 and 5 and dropped out of treatment. The χ^2 analysis showed the difference between the two groups in drop-out rates after drug assignment approached significance, (*p* = .08). No drop-outs occurred over the 1-month follow-up assessment period. The progress of participants is shown in Supplements 1 and 2.

Of the 56 participants (mean age = 35.48, SD = 11.35, range = 18–60) recruited, 57% were male, 76.8% Caucasian, 66.1% single, and 53.5% had a tertiary degree. The other major ethnic origin was Asian (10.7%). The *t* tests and χ^2 analysis indicated that there were no differences across drug condition on any sample characteristics such as gender, age, baseline clinical ratings, ethnicity, education, or antidepressant use. All participants met criteria for SAD, and 30.34% of the participants (*n* = 17) were given an additional secondary diagnosis. Of these, 8 participants were diagnosed with an additional anxiety disorder, 8 were diagnosed with an additional secondary mood disorder, and 1 was diagnosed with an additional anxiety and mood disorder. Only 21% (*n* = 12) of participants were taking medication, and they were evenly distributed across DCS and placebo groups. They were stabilized for a period of at least 6 weeks on antidepressant drugs (including sertraline hydrochloride [*n* = 2], mirtazapine [*n* = 2], and paroxetine hydrochloride [*n* = 1]) (*n* = 5), immune-suppressant drugs (*n* =2), appetite suppressant drugs (*n* = 2), blood pressure medication (*n* = 2), or herbal preparations (*n* = 1).

Medication

D-cycloserine is approved as an antibiotic for treatment of tuberculosis by the Therapeutic Goods Administration (15) and the Food and Drug Administration (United States). Peak blood levels are reported within 2–8 hours after dosing, and half-life is estimated at 10 hours (16). The compounding chemist purchased DCS powder directly from Eli-Lilly (Indianapolis, Indiana) to make 50-mg DCS capsules, along with identical placebo. We used 50 mg of DCS in combination with ET, because previous research had shown it to be an effective dose (4,5) and differences in treatment efficacy have not been reported between 50 mg and 500 mg (4). A random allocation sequence was generated by numbering containers with the medication. This randomization sequence was developed by the compounding chemist before the trial and concealed from all individuals involved in patient care, evaluation, or supervision until follow-up assessments were completed.

Treatment

All participants received a five-session group ET protocol based on that used by Hofmann *et al.* (5). Treatment sessions were scheduled 1 week apart. Participants were provided with an exposure-based model of treatment for SAD in the first treatment session (60 min). At the start of session 2, participants randomly selected one coded bottle that contained the DCS or placebo capsules that were to be taken before each ET session. In sessions 2–5, participants received one blinded-study pill, waited 1 hour, and then began exposure-based group therapy. Sessions 2–5 (90 min each) involved giving increasingly difficult speeches about topics chosen by the therapists in front of the other group members and a video camera. All participants gave a speech, and recorded speeches were played back to the group. At the beginning and conclusion of each exposure-based session,

home-practice exposure strategies were reviewed and encouraged (e.g., giving speeches in front of a mirror). Homework was considered part of treatment. Participants were asked to refrain from alternative treatment until the final assessment session.

Measures

Outcome Measures.   Clinical assessment interviews were conducted within the month preceding the initial treatment session and 1 month after the completion of the last treatment session. The DSM-IV diagnoses were determined with the ADIS-IV (14). The ADIS-IV contains diagnostic questions about each anxiety disorder and other diagnostic categories that are important for differential diagnosis (e.g., affective disorders and substance abuse/dependence). Upon completion of diagnostic assessments, clinicians completed a Global Assessment of Functioning (GAF) on a scale of 0–100, in accordance with Axis-V of the diagnostic axis for DSM-IV (17).

Self-report measures were obtained immediately before the two clinical assessment interviews and immediately after the completion of the last treatment session (treatment session 5). Following previous research (5), we used two self-report measures to assess SAD symptoms: the Social Phobia and Anxiety Inventory (SPAI [18]), and the Liebowitz Social Anxiety Scale (LSAS [19]). In addition, we employed other measures to assess additional dimensions of SAD. Firstly, the Brief Fear of Negative Evaluation Scale (BFNE [20]) assesses how characteristic certain dysfunctional thoughts relating to negative evaluation are to an individual (e.g., "I am afraid that others will not approve of me"). Responses are measured on a 5-point Likert scale of how characteristic the statement is (1 = "not at all," and 5 = "extremely"). Secondly, the Life Interference Scale (LIS [21]) provides a measure of the impact of an individual's social fears on various components of their life, including work, family life, and leisure activities (e.g., "My social anxiety interferes with my home/family life"; "My social anxiety makes my day-to-day living unpleasant"). Scores are assessed on a 9-point likert scale (0 = "not at all," and 8 = "extremely") with the total score ranging from 0 (no interference) to 48 (extreme interference). Past analysis from members of our team shows the scale demonstrates excellent internal consistency (α = .90), and the total score correlates with other life-impairment measures (21).

Process Measures.   We administered the Credibility/Expectancy Questionnaire (CEQ [5]) to measure expectancy and credibility of treatment. Participants were asked to rate the perceived logic of treatment on a 9-point scale (1 = "not at all logical," 9 = "very logical") after the first treatment session. Before each session and before drug administration, participants completed a weekly version of LSAS (19). Participants also completed the Speech Performance Questionnaire (SPQ [22]) immediately after each in-session speech exposure task (Sessions 2–5). The SPQ is thought to tap into the common negative self-appraisals displayed by SAD patients when performing in front of a group (e.g., "Seemed to tremble or shake"; "Seemed nervous"; "Made a good impression" [23]) on a 5-point scale (1 = "not at all," 5 = "very much"). A higher total score (0–68) indicated a more positive view of one's performance. The scale demonstrates good internal consistency (α = .79–.86) and inter-rater reliability (22,24,25) and differentiates between patients with SAD, treated SAD patients, and non-clinical participants (23).

Analysis

Data were entered by a research assistant blind to drug assignment and analyzed with the SPSS statistical software pack-

age (SPSS V14; Chicago, Illinois). Last observation carried forward was used to replace missing data. We employed intention-to-treat analysis for all participants assigned to receive DCS or placebo throughout. For outcome analysis, a Drug (DCS, placebo) × Time (pretreatment, post-session 5 treatment, 1-month follow-up) repeated-measures multivariate analysis of variance (MANOVA) was conducted on total scores from the SPAI, LSAS, BFNE, and LIS. We also conducted a Drug (DCS, placebo) × Time (pretreatment, 1-month follow-up) repeated-measures analysis of variance (ANOVA) on the clinician-rated GAF scores. We computed effect sizes (Cohen's d [26]) by dividing the difference between the mean change of the DCS group and the mean change of the placebo group by the pooled SD. To determine the number of treatment sessions required to show differences between DCS and placebo groups, we ran a Drug (DCS, placebo) × Treatment Session (Sessions 1–5) repeated-measures ANOVA on total scores of the LSAS obtained before each therapy session. In addition, we conducted a Drug (DCS, placebo) × Exposure Treatment Session (Sessions 2–5) repeated-measures ANOVA to determine whether there were differences between drug groups on the SPQ immediately after all four speech tasks. Finally, we tested the relationship between change in negative appraisals of the speech task and change in fear and avoidance in the real world and investigated whether DCS moderated this relationship. Moderation of these two variables, A (Change on SPQ) and C (LSAS Session 5), by a categorical variable B (Drug Group), was tested with regression in which A, B, and the product term AB were used to predict C (27,28). If AB is a significant predictor over and above A and B, then B is moderating A's effect on C.

Results

Participant Beliefs About Treatment

Participants assigned to both drug conditions reported no significant side effects. The *t* tests showed there was no difference between drug conditions at any time point in regard to guessing what treatment they were receiving [Largest $t(54)$ = .88, p = .38]. On average, 36.5% of DCS-assigned participants and 39.5% of placebo-assigned participants believed they had received DCS. Participants were asked about both their expectations and credibility for the treatment approach after the educational session (session 1). Participants' ratings on these scales were moderate–high and not significantly different between the two groups [Largest $t(54)$ = .46, p = .65].

Symptom Outcome

Table 1 shows the means and SDs of the four self-report outcome measures (SPAI, LSAS, BFNE, LIS) at pretreatment, post-treatment, and 1-month follow-up in the two groups. A Drug (DCS, placebo) × Time (Pre, Post, 1-month follow-up) repeated-measures MANOVA with all total scores from self-report outcome measures revealed a main effect of Time [$F(8,47)$ = 14.77, p < .001]. Examination of 95% confidence intervals for all measures showed that there was a reduction in self-reported SAD symptoms from pretreatment to immediately after treatment and this difference with pretreatment scores was maintained at follow-up. There was no main effect for Drug, [F < 1.0] on these measures but there was a significant Drug × Time interaction [$F(8,47)$ = 3.75, p = .002]. Examination of 95% confidence intervals for all measures, except the SPAI, showed that DCS-treated participants showed a greater reduction in SAD symptoms than placebo-treated participants from pretreatment to immediately after treat-
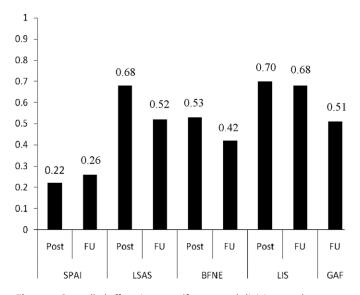
Table 1. Means and SDs for Self-Report and Clinician Ratings Across Assessments

	Pre	Post	Follow-Up
SPAI (range = 27–161)			
DCS	107.53 (19.89)	89.52 (22.63)	83.63 (29.04)
Placebo	112.13 (25.95)	99.30 (27.26)	94.92 (31.41)
LSAS (range = 12–140)			
DCS	78.75 (20.58)	52.86 (20.24)	52.89 (19.71)
Placebo	77.21 (25.18)	66.68 (21.84)	63.07 (22.89)
BFNE (range = 21–60)			
DCS	52.00 (6.56)	44.68 (8.81)	43.36 (11.11)
Placebo	52.68 (7.54)	49.32 (6.57)	47.50 (7.18)
LIS (range = 4–46)			
DCS	32.18 (9.16)	25.43 (8.97)	21.04 (9.91)
Placebo	31.64 (6.07)	30.75 (8.38)	26.75 (10.73)
GAF (range = 40–80)			
DCS	56.25 (6.36)		63.57 (9.33)
Placebo	55.71 (7.29)		58.92 (8.84)

SPAI, Social Phobia Anxiety Inventory (Total Score); DCS, D-cycloserine; LSAS, Leibowitz Social Anxiety Scale (Total Score); BFNE, Brief Fear of Negative Evaluation Scale; LIS, Life Interference Scale; GAF, Global Assessment of Functioning (Clinician Rated).

ment and this effect was maintained at follow-up (Table 1). When the analysis was restricted to those participants who completed treatment (DCS = 27, placebo = 23), the Drug × Time interaction remained significant and in the same direction [$F(8,41) = 3.07$, $p = .008$]. Effect sizes on all measures (.42–.70) except the SPAI (.22–.26) were in the moderate range (Figure 1)—analysis on SPAI sub-scales show effects sizes indicating DCS improvement in comparison with placebo [Social Phobia Subscale: Post ES = .42; follow-up ES = .45; Agoraphobia Subscale: Post ES = .48; follow-up ES = .52]; the SPAI total or difference score reflects the subtraction of the Agoraphobia sub-scale score from the Social Phobia sub-scale score; this subtraction lowered the overall effect size. Table 1 also shows the means and SDs for GAF ratings made from clinical interviews

Figure 1. Controlled effect sizes on self-report and clinician-rated outcome measures for D-cycloserine- over placebo-medicated treatment groups. FU, follow-up; SPAI, Social Phobia and Anxiety Inventory; LSAS, Liebowitz Social Anxiety Scale; BFNE, Brief Fear of Negative Evaluation Scale; LIS, Life Interference Scale; GAF, Global Assessment of Functioning.
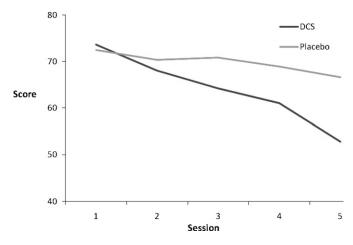

Figure 2. Total scores on the Liebowitz Social Anxiety Scale for each drug group before each treatment session. DCS, D-cycloserine.

conducted pretreatment and at 1-month follow-up. A Drug (DCS, placebo) × Time (Pre, 1-month follow-up) repeated-measures ANOVA comparing pretreatment with follow-up clinician-rated GAF scores revealed a main effect for Time [$F(1,54) = 31.42$, $p < .001$], no main effect for Drug [$F(1,54) = 1.79$, $p = .19$], and a significant Drug × Time interaction [$F(1,54) = 4.78$, $p = .03$]. Treatment improved clinician ratings of general life functioning, and these improvements were greater in the DCS-treated group in comparison with the placebo-treated group. The effect size was in the moderate range (Figure 1).

Weekly Symptom Tracking

A Drug (DCS, placebo) × Treatment Session (Sessions 1–5) repeated-measures ANOVA on LSAS total symptom scores indicated a main effect of Treatment Session [$F(4,51) = 8.73$, $p < .001$]. As expected, anxiety symptoms scores decreased over the five treatment sessions. There was no main effect of Drug [$F(1,54) = 1.45$, $p = .23$], but there was a significant Drug × Treatment Session interaction [$F(4,51) = 3.00$, $p = .02$]. As can be seen in Figure 2, DCS-treated participants reported a greater reduction across treatment sessions than placebo-treated participants (results on both fear and avoidance sub-scales of the LSAS were similar). Follow-up t tests, with a Bonferroni adjustment, confirmed that the difference between drug conditions was significant only at the fifth-session assessment point [$t(54) = 2.54$, $p = .01$].

A Drug (OT, placebo) × Exposure Treatment Session (Sessions 2–5) repeated-measures ANOVA conducted on the SPQ indicated a main effect for Session [$F(3,52) = 10.23$, $p < .001$]. As expected, participants' appraisals of their speech performance improved as sessions progressed. There was no main effect of Drug [$F < 1.0$] or an interaction effect between Session and Drug [$F < 1.0$]. To address our hypothesis that participants receiving DCS would show a stronger association between appraisals of their speech performance and subsequent anxiety reduction, change scores were created by subtracting the score reported in session 5 from the score reported in session 2; for the SPQ, lower scores indicated greater perceived improvements; for the LSAS, higher scores meant greater reductions in social anxiety. In the DCS group, significant negative correlations were found between change scores on the LSAS and the SPQ ($r = -.38$, $p = .04$), but this was not significant in the placebo condition ($r = -.08$, $p = .73$). This suggests that the more participants assigned to DCS believed that their performance had improved across the treat-

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Table 2. Degree Speech Performance and Drug Group Predicts Social Fear and Avoidance at Session 5

	LSAS—Session 5		
	R	B	ΔR^2
B1			
LSAS Pre-Treatment	.75[a]	.76[a]	
B2			
Ch Speech Perf (centered)	−.12	−.17[b]	
Drug	−.32[b]	−.35[a]	
B3			
Ch Speech Perf Drug	−.09	−.18[b]	
R^2		.69	
F		$F(4,51) = 31.81, p < .001.$	

B, Standardized beta-weight; LSAS, Leibowitz Social Anxiety Scale; Ch Speech Perf, Change in Speech Performance Ratings (Sessions 5–2); Drug, D-cycloserine, 1 and placebo, −1; R, bivariate correlations.
[a]$p < .001$.
[b]$p < .05$.

ment sessions, the greater their reduction in general social fear and avoidance symptoms. In contrast, there was no relationship between these variables in the placebo group.

To test whether DCS was moderating the relation between SPQ and the LSAS, we ran a regression (27,28) to predict the Session 5 LSAS score with pretreatment LSAS scores in block 1, Drug (DCS = 1, placebo = −1) and change on the SPQ in block 2, and the interaction between Drug and Change on the SPQ in block three (Table 2). The model predicted 69% of the variance [$F(4,51) = 31.81, p < .001$]. Lower Pre-LSAS scores, being assigned to the DCS group, and reporting improvement between sessions 2 and 5 on the SPQ were all positively associated with lower LSAS scores at the final treatment session. More importantly, after controlling for these factors, the interaction between change on the SPQ and Drug was significant. This suggests DCS moderated improvement such that the relationship between improvement on the SPQ and anxiety reduction was stronger in the DCS group in comparison with placebo.

Discussion

The present study was a double-blind placebo-controlled trial of DCS to augment ET with SAD and had a sample twice as large as any previous studies. The ET reduced SAD symptoms regardless of whether participants received DCS or placebo. However, the results of this trial also showed that DCS enhanced ET treatment further, as indicated by a range of SAD symptom measures, including social fear, avoidance, dysfunctional cognitions, life impairment from SAD, and clinician ratings of the quality of general life functioning.

Effect sizes on most outcome measures (i.e., LSAS, BFNE, LIS, and GAF but not the SPAI [see note on SPAI in Results: Symptom Outcome section]) were in the moderate range. In comparison with the previous SAD study (5), our data replicates closely what was found on the LSAS: moderate effect sizes showing greater improvement in the DCS group compared with placebo at post-treatment assessment, with effects maintained at 1-month follow-up. In contrast, our treatment outcomes on the SPAI were moderate and substantially smaller than the large effect size reported previously (5).

Weekly tracking measures indicated that DCS facilitated the reduction of social fear and avoidance gradually. Significant differences between DCS and placebo drug groups emerged at

the fifth-session assessment point, which was after the third DCS exposure-treatment session. In combination with the findings of Kushner *et al.* (6), these results suggest that using DCS acutely as an adjunct with three or four ET sessions provides the best opportunity to show DCS enhancement on anxiety treatment. It should be noted that effects of DCS might be detected at an earlier session if a larger sample was employed. Results also showed that participants were not able to identify whether they had received DCS, because the number of participants who believed they had taken DCS was low and there was no difference between drug groups. This might suggest that participants might be more likely to attribute therapeutic gain to the therapy process itself rather than to any acute effect from the medication.

Animal research has shown that DCS consolidates fear-extinction learning (1). Attempts to identify the mechanisms of how DCS enhances loss of fear in humans have provided few insights (7,8). This study provides the first preliminary evidence that the amount of adaptive learning between exposure treatment sessions was associated with DCS effects in humans. For participants given DCS, a relationship was found between improvements from session 2 to 5 on appraisals about participants' speech performance and reported improvements in social fear and avoidance symptoms in the real-world. Thus, the present data extend current knowledge of the effect of DCS by suggesting that anxiety reductions are associated with adaptive learning that one can perform in front of a group successfully and that this learning might be facilitated by DCS's action as a partial agonist at the NMDA receptor (29,30). It is interesting to note that DCS did not directly increase the amount of learning that took place within each exposure session, as indicated by self-ratings of speech performance. This finding is not inconsistent with the animal literature that shows that DCS does not enhance within-session extinction (1). Our data suggest that DCS facilitates the generalization of learning that occurs during within-session extinction and thus is more likely to lead to broader and more durable reductions of SAD symptoms. Finally, our findings do not provide evidence of causality. Future research might wish to manipulate the degree of learning that occurs in each exposure session to better evaluate the causal role of DCS on learning and subsequent anxiety reduction.

Overall, this trial confirms and extends previous demonstrations that DCS enhances ET for anxiety disorders in humans. This research adds further support to a radical new approach to the treatment of anxiety disorders by enhancing the adaptive learning that occurs in therapy via medication. Research is now required across various anxiety disorders in non-specialist community-based clinics to better determine the potential impact of DCS on lowering the burden of disease from anxiety disorders.

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