Original Research Article

Investigating d-cycloserine as a potential pharmacological enhancer of an emotional bias learning procedure

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Abstract

The partial N-methyl-D-aspartate receptor agonist d-cycloserine may enhance psychological therapies. However, its exact mechanism of action is still being investigated. Cognitive bias modification techniques allow isolation of cognitive processes and thus investigation of how they may be affected by d-cycloserine. We used a cognitive bias modification paradigm targeting appraisals of a stressful event, Cognitive Bias Modification-Appraisal, to investigate whether d-cycloserine enhanced the modification of appraisal, and whether it caused greater reduction in indices of psychopathology. Participants received either 250 mg of d-cycloserine (n=19) or placebo (n=19). As a stressor task, participants recalled a negative life event, followed by positive Cognitive Bias Modification-Appraisal training. Before and after Cognitive Bias Modification-Appraisal, appraisals and indices of psychopathology related to the stressor were assessed. Cognitive Bias Modification-Appraisal successfully modified appraisals, but d-cycloserine did not affect appraisals post-training. There were no post-training group differences in frequency of intrusions. Interestingly, d-cycloserine led to a greater reduction in distress and impact on state mood from recalling the event, and lower distress post-training was associated with fewer intrusions. Therefore, d-cycloserine may affect emotional reactivity to recalling a negative event when combined with induction of a positive appraisal style, but via a mechanism other than enhanced learning of the appraisal style.

Keywords

d-Cycloserine, emotional learning, appraisal, emotional reactivity, cognitive bias modification

Pharmacological cognitive enhancers are promising candidates for improving the efficacy of cognitive behavioural treatment (CBT) for anxiety disorders (for a meta-analysis and review, see Bontempo et al., 2012; Hofmann et al., 2013; Mataix-Cols et al., 2017; Otto et al., 2016). One such potential enhancer is d-cycloserine (DCS). DCS targets N-methyl-D-aspartate receptors (NMDARs) by binding with their glycine binding sites, enhancing NMDAR-mediated activation. As a result, synaptic plasticity is increased, which is considered a key cellular mechanism involved in emotional, associative learning (e.g. Izquierdo et al., 2006; Sotres-Bayon et al., 2007). On the assumption that associative, emotional learning is the basis of change in CBT, a number of studies have investigated whether enhancement of neuroplasticity via DCS could have beneficial effects in a therapeutic context, that is, enhancing or accelerating CBT treatment effects. While some findings have been promising, for example, in social phobia (Guastella et al., 2008; Hofmann et al., 2006) or panic disorder (Otto et al., 2010), other studies failed to find a direct, enhancing effect of DCS on treatment outcome, for example in posttraumatic stress disorder (PTSD; de Kleine et al., 2012) or obsessive compulsive disorder (Kushner et al., 2007).

The reasons for these inconsistent findings are not yet well understood. Accordingly, the present study aimed to further advance our understanding of the mechanisms underlying the effects of DCS on emotional learning. To do this, we took an experimental medicine approach, using a controlled laboratory setting to investigate effects on analogue posttraumatic stress symptoms (i.e. experiences, such as intrusive memories of a distressing or stressful event, assumed to reflect a transient, milder version of PTSD symptoms, such as intrusive memories of trauma; see e.g. James et al., 2016). We used an emotional learning paradigm previously investigated in the context of analogue posttraumatic stress (Woud et al., 2012, 2013), namely Cognitive Bias Modification-Appraisal (CBM-App) training (for a review of CBM in PTSD, see Woud et al., 2017). CBM paradigms involve simple computerised training procedures during which participants are exposed to an experimentally established contingency between a disorder-relevant stimulus and a response, that is, participants are trained to respond in a systematically biased manner (Koster et al., 2009). In the context of CBM-App,

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participants are trained to adopt a positive or negative appraisal style, for example, towards an analogue stressful event. During training, participants are presented with a series of ambiguous, reappraisal-related scripts. Each script is followed by a word fragment participants are required to complete. Completing the fragment then produces an outcome which is consistent with a functional or dysfunctional appraisal of the script. Studies by Woud et al. showed that, compared to induction of a negative appraisal style, training a positive appraisal style induced more adaptive appraisals and reduced analogue posttraumatic stress symptoms, such as intrusions over a one-week period (for similar results, see e.g. Cheung and Bryant, 2017; Schartau et al., 2009). From a mechanisms perspective, the learning that takes place during CBM paradigms such as CBM-App can be conceptualised as emotional associative learning, and more specifically counter-conditioning (see for example Hertel and Mathews, 2011), in that a stimulus (ambiguous script) potentially signalling a negative outcome (dysfunctional appraisal) is repeatedly paired instead with a positive outcome (functional appraisal), leading to formation of new associations. As such, the action of DCS on NMDA receptors could be expected to enhance associative learning during CBM-App and thus effects of the training.

Investigating the effects of DCS on emotional learning by means of a single session learning paradigm provides at least three advantages. First, many psychological disorders are complex, and the 'learning' during standard treatments such as CBT may also be complex and multi-faceted. Thus, learning effects during treatment may be more difficult to establish. Hence, studying the effects of DCS by using a single, distressing event, and focusing on one dysfunctional process, that is, appraisals, might provide a more efficient means for assessing specific mechanistic processes than is possible with trials of complex interventions. Second, evidence suggests that the effects of DCS are most obvious with a small number of treatment sessions (Otto et al., 2016). Following this, a single learning session may have most potential to reveal DCS's effects. Third, according to Hofmann et al. (2013), learning needs to be established before effects of DCS can be expected, a premise that is not always given during treatment. Interpretation-based CBM procedures robustly revealed training-congruent changes in interpretation (Koster and Bernstein, 2015; Woud and Becker, 2014), making this paradigm a promising candidate. To the best of our knowledge, there is only one other study that examined the effects of DCS on a CBM procedure, namely the effects of attention training on trait anxiety (Behar et al., 2010). Results demonstrated that both the DCS and placebo group showed less attentional bias post-training. However, this effect was stronger in the DCS compared to the placebo group. Interestingly, DCS did not have an effect on (emotional) stress tasks.

The aim of the present double-blind, placebo-controlled, randomised study was to examine the effects of DCS on affective appraisal and indices of psychopathology following a laboratory stressor. Therefore, one group of participants received a single dose of DCS (250 mg), while the other group received a placebo. As a stressor task, participants were instructed to recall a negative life event. This was followed by positive CBM-App training related to the event. We expected that DCS, compared to placebo, would facilitate emotional learning during the CBM-App training task. Specifically, we expected that participants who received DCS, compared to those who received placebo, would show less dysfunctional appraisals pre-post CBM-App training and at follow-up (assessed via the Encoding Recognition Task (ERT) and the Posttraumatic Cognitions Inventory (PTCI)). Further, we expected that participants receiving DCS, compared to those receiving placebo, would experience fewer intrusions and less intrusion distress post-training (i.e. in-session intrusion questionnaire) and at 24-hour follow-up (i.e. intrusion diary and intrusions subscale of the Impact of Event Scale-Revised (IES-R)). Changes in mood and event-distress were assessed pre-post recall of the negative life event and served as a manipulation check for the impact of recalling the event. Finally, correlational analyses were conducted to examine whether (changes in) appraisals were associated with (changes in) indices of psychopathology, immediately after training and over a 24-hour period.

Methods

Participants

Thirty-eight healthy participants (18 female, age range 18–35 years) enrolled in the study. Inclusion criteria were: no severe physical illness, no history of neurological or psychological disorder as assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-CV) (First et al., 1996), no first-degree family member with a history of a severe psychiatric disease, no central nervous system (CNS)-active medication or medication with cycloserine, ethionamide, or isoniazid during the last six weeks, a body mass index (BMI) between 18–30 kg/m^2, non- or light-smoking (<5 cigarettes a day), fluent English skills. Female participants were neither pregnant nor breast-feeding. All participants were included in the analysis. Demographic details and baseline measures included age, years of education, BMI, Beck Depression Inventory II (Beck et al., 1996), State Trait Anxiety Inventory-Trait/State (Spielberger et al., 1983), Eysenck Personality Questionnaire-Neuroticism (Eysenck and Eysenck, 1994); Trauma History Checklist (THC; Holmes et al., 2004); PTCI baseline (Foa et al., 1999), sex, type of employment, ethnicity, first language. The study was approved by the Oxford University Medical Sciences research ethics committee (approval number: MSD-IDREC-C3-2014-09), and participants provided written informed consent to take part in the study.

Recall negative life event

To provide a distressing event as a target for the CBM-App training, participants were asked to identify a negative life event (for a similar procedure, see Santa Maria et al., 2012). Before the first full recall of the negative life event, participants were given an information sheet to explain the task requirements. Participants were asked to identify an event that had happened in the past five years (if possible), which caused distress at the time that persisted to some degree to the time of experimental testing. Participants were asked to continue to keep the same event in mind throughout the course of their participation in the study. During the first recall, participants were asked bring to mind the most distressing moment of the event and to provide a brief, written description of that moment. Next, participants were instructed to imagine themselves in that moment for 30 s. Participants were asked to close their eyes and to imagine the moment as vividly as possible, as if they were

experiencing it again, with all images and emotions. Distress caused by recalling the event was indexed by a rating of distress in the present moment ('How distressing is this moment right now'), from 0 (not at all) to 10 (extremely). In addition, participants rated the moment's past distress and vividness, and how detailed their memory was, using an 11-point Likert rating ranging from 0 (not at all) to 10 (extremely) (see Supplementary Material). The second recall deviated only in one aspect from the first recall. That is, participants did not write a summary of the distressing moment but were provided with the summary they wrote during the first recall and were asked to read it silently to themselves.

CBM-App

The CBM-App training followed the same procedure as the positive training condition in previous studies (Woud et al., 2012, 2013), with the only difference being that the training was anchored to a negative life event rather than a film: participants were instructed to think back to their specified negative life-event when completing the training. The training task itself comprised processing a series of reappraisal-related scripts that appeared to participants as a sentence completion task. Each script ended with a word fragment such that the meaning of the script remained ambiguous. It was participant's task to finish each script by completing the word fragment. Word fragments were designed so that only one possible solution could complete the script's meaning. In this context, this meant that the completed word fragments produced an outcome consistent with a functional appraisal of the script. Scripts were based on items of the PTCI Self subscale (Foa et al., 1999). For example, 'trusting oneself to act appropriately in future' was adapted as follows: 'In a crisis, I predict my responses will be h-lpf-l' (resolved as 'helpful'). Thirty-two of the scripts were followed by a simple yes/no question to test ongoing comprehension (for the example above: 'Do you believe you will be able to respond in a useful way when there is a crisis?'). The training comprised 72 training and eight neutral filler scripts (presented in blocks of 10). Blocks were presented in the same order for each participant but the sentence order within each block was randomised. The trial procedure was as follows: The script first appeared on the screen without the word fragment. Participants were instructed to press the 'advance' key when they had read the script. After that, the text disappeared, revealing the word fragment. Participants then typed the first missing letter of the fragment as quickly as possible, and the completed correct word appeared on the screen. Next, either a comprehension question or a new script was presented.

Appraisal assessment

Success of the training was assessed primarily via a two-phase ERT (Mathews and Mackintosh, 2000, for details, see Woud et al., 2012, 2013). During the encoding-phase, participants read 10 novel ambiguous scripts in random order. Scripts started with a title and remained ambiguous. Participants were asked to imagine themselves vividly in the described situation. In the recognition phase, the 10 encoding-phase titles were presented again, followed by a set of four related sentences. By means of a four-point Likert scale, participants rated how close in meaning each sentence was to the original script of that title. There were two target sentences, representing a possible positive and negative interpretation of the original script, and there were two foil sentences, representing a general positive and negative meaning that did not resolve the script's ambiguity. A bias index was calculated by subtracting the mean recognition rating for negative targets from that for positive targets, such that a positive score indicates a relative bias for endorsing positive over negative interpretations. There were two sets of scripts, the order of which was counterbalanced across participants.

As a further measure of change in appraisal, participants completed the PTCI (Foa et al., 1999). The PTCI is a self-report measure including 36 statements assessing appraisals surrounding distressing or traumatic experiences. It contains three subscales: negative cognitions about the self (21 items), negative cognitions about the world (seven items) and self-blame (five items). Each item is rated using a seven-point Likert scale ranging from one (totally disagree) to seven (totally agree). The instructions were modified in that participants were asked to think back of their own negative life event (as opposed to a trauma) when completing the PTCI.

Mood

Four mood states were assessed over the course of the study (happiness, depression, anger, anxiety, see Woud et al., 2012, 2013) using 11-point scales ranging from zero (not at all) to 10 (extremely). Scores across the four scales were averaged (happiness reverse-scored) to provide a single mood index.

Negative involuntary memory assessment

In-session intrusion questionnaire. The number and quality of intrusions related to the negative life event were assessed with an adapted version of the intrusion diary used by Woud et al. (2012, 2013). That is, the diary was presented as a questionnaire in order to assess intrusions during the session. On the questionnaire, intrusions were defined as 'any memory of the negative life event (or part of it) that appears apparently spontaneously in mind. Do not include any memories that you deliberately or consciously bring to mind'. Participants were also instructed that intrusions could be experienced as an image, verbal thought, or combination of both, and were asked to specify this for each intrusion they recorded. Further, participants were asked to record how distressing each intrusion was on a rating scale ranging from zero (not at all) to 100 (extremely) and to provide an overall vividness rating of their intrusions from zero (not all vivid) to 100 (extremely).

24-Hour intrusion diary. To assess intrusions that occurred during the 24 h after testing, participants were provided with an intrusion diary. This had the format of the in-session intrusion questionnaire used during the laboratory session, that is, intrusions were defined and the different types of intrusions were explained. Participants were instructed to record all intrusions immediately after they occurred (whenever possible). If participants had experienced no intrusions during any period they were also asked to make this explicit in the diary.

IES-R (Weiss and Marmar, 1997). The IES-R is a self-report measure including 22 items assessing current

intrusion, avoidance, and hyperarousal phenomena tied to a stress-inducing event. The instructions were adapted to reflect experiences during the past 24 h, linked to the negative life event (as opposed to the past week and a traumatic event), and the intrusion subscale was used as an additional measure of intrusive memories.

Procedure

Participants were randomly allocated to a single dose of DCS (250 mg) or a matching placebo capsule (major ingredient: microcrystalline cellulose) in a double-blind, placebo-controlled design. The dose of drug was chosen based on previous studies showing cognitive effects of DCS within a range of 50–500 mg (Klumpers et al., 2012; Onur et al., 2010). Participants fasted two hours before testing to limit gastrointestinal influences on drug pharmacokinetics, and they were tested three hours after drug administration, the time of estimated peak plasma levels (King Pharmaceutical product information). The drug manufacturer's (King's Pharmaceutical) product information suggests that plasma levels are reached within 3–4 h. However, other studies report peak levels to be reached within one hour (Patel et al., 2011; van Berckel et al., 1997). Considering that DCS is thought to have half-life properties of eight hours (King's Pharmaceutical product information) to 15 h (Patel et al., 2011), plasma levels were expected to be close to peak levels during testing.

Demographic details and baseline measures were collected prior to administration of drug or placebo, and subjective effects of perceived side-effects of the drug were taken at baseline, drug peak level, and at the end of the session. Prior to the experimental procedures relevant to this manuscript, participants worked on a tactile sensory learning task (unrelated to the current study – a paper reporting these data is submitted), to explore whether DCS affects this form of non-emotional learning relevant to recovery after stroke. Plastic dome gratings with varying groove widths were used for testing and training, and participants indicated whether a grating was presented horizontally or vertically on the glabrous surface of the distal finger pad. Before and after the CBM-App training task, participants completed the appraisal assessments (i.e. ERT and PTCI) and the negative memory recall, with the latter also including the distress ratings. Further, the occurrence of intrusive memories of the recalled event was recorded throughout the session via the in-session intrusion questionnaire. Prior to the administration of the questionnaire, participants sat quietly for two minutes, wearing a chest-strap heart-rate monitor for the purposes of an approved deception that a resting heart rate was being recorded (for a similar procedure, see Santa Maria et al., 2012). Mood was rated four times: pre-post first recall (pre CBM-App training), and pre-post second recall (post CBM-App training). At the end of the first session, participants received a diary to monitor their intrusions over the following 24 h, after which they returned to the laboratory to complete the follow-up (i.e. IES-R and PTCI). Figure 1 gives a diagrammatic overview of the procedure. The Supplementary Material describes some additional measures (i.e. side effects drug, demand effects, and diary compliance rating) and analyses, and includes a more detailed description of the procedure.

Design and statistical approach

The present study used a between-subjects design, which included two groups: DCS and placebo. Repeated-measures analysis of variance (ANOVA) was conducted to examine changes in appraisal, distress, and mood from pre- to post-training and pre-post recall of the negative life event, respectively. Time×Group interactions indicate the outcomes of interest. If significant, paired sample *t*-tests were conducted to decompose the interaction. Outcomes at follow-up were compared via between-groups *t*-tests or non-parametric equivalents in the case of severely skewed distributions or lack of homogeneity between groups. Correlational analyses used Kendall tau indices. Demographic and baseline data and means and standard deviations of all outcome measures are presented in Tables 1 and 2, respectively. The Supplementary Material provides additional analyses such as questionnaire subscales.

Results

Baseline data

There were no statistically significant differences between the groups prior to the CBM training (all *p*s>0.05), except that in the DCS group fewer participants were of Caucasian ethnicity (p=0.046, Fisher's exact test).

Appraisal assessment

Pre-post CBM-App, ERT. The CBM training successfully modified participants' appraisal in the intended direction on the ERT from pre- to post-training (Time: $F_{1,33}$=48.64, p<0.001, η^2=0.60), but this effect did not differ between groups (Group×Time: $F_{1,33}$=0.046, p=0.83, η^2=0.001). Due to missing data of one participant of the placebo group the n for both ERTs is n=18.

Pre-post CBM-App, PTCI. Results of the PTCI mirrored those of the ERT. That is, participants reported less dysfunctional appraisals post-training (Time: $F_{1,36}$=21.36, p<0.001, η^2=0.37), but this was not qualified by group (Group×Time: $F_{1,36}$=0.86, p=0.36, η^2=0.023).

Follow-up, PTCI. There was no difference between the two groups in scores on the PTCI at follow-up t(35)=1.11, p=0.28

Manipulation checks recall negative life event pre-post CBM-App

Effects on distress. Participants' distress on recalling the event decreased from pre- to post-training (Time: $F_{1,36}$=8.94, p=0.005, η^2=0.2), and this decrease differed between groups (Group×Time: $F_{1,36}$=4.78, p=0.035, η^2=0.12). Follow-up *t*-tests showed that there was a decrease in ratings of distress in the DCS group (t(18)=3.75, p=0.001, d=0.81), but not in the placebo group (t(18)=0.56, p=0.59, d=0.09) (see Figure 2).

Effects on mood. Participants' mood response to recalling the event (i.e. change in state mood from pre- to post-recall,

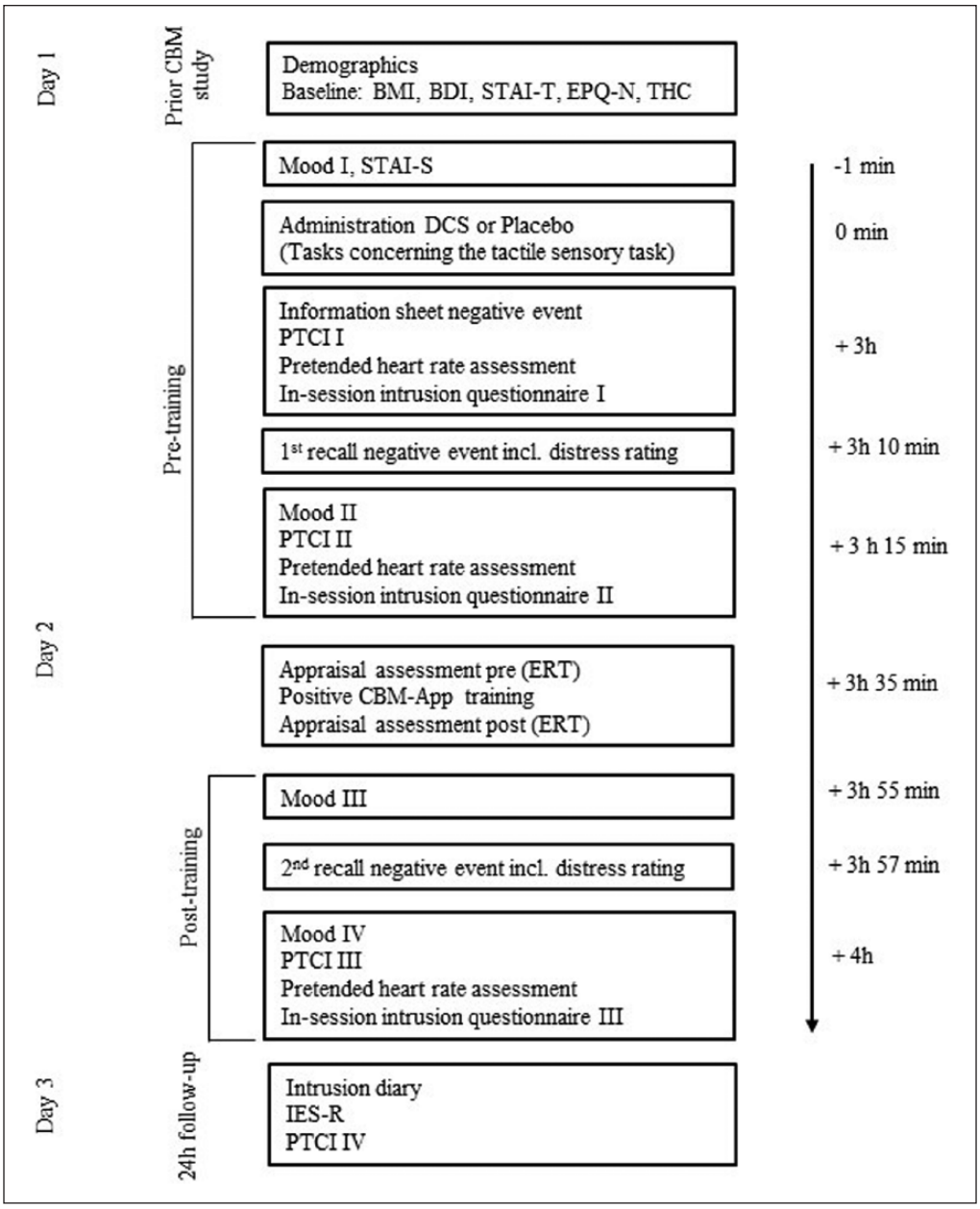

Figure 1. Flowchart of experimental procedure. Times in the right hand column represent time since administration of placebo/d-cycloserine (DCS). BDI: Beck Depression Inventory; BMI: body mass index; CBM-App: Cognitive Bias Modification-Appraisal; DCS: d-cycloserine; EPQ-N: Eysenck Personality Questionnaire – Neuroticism; ERT: Encoding Recognition Task; IES-R: Impact of Event Scale-Revised; PTCI: Posttraumatic Cognitions Inventory baseline; STAI-T/STAI-S: State Trait Anxiety Inventory-Trait/State; THC: Trauma History Checklist.

indicated by the Time factor in the analyses) changed from pre- to post-training, and this change differed per group (Time×Pre-/Post-training×Group: $F_{1,36}$=5.04, p=0.031, η^2=0.12.). This three-way interaction was decomposed by two additional ANOVAs per group, both revealing a significant Time (i.e. Pre- to Post-recall)×Pre-/Post-training interaction (DCS: $F_{1,18}$=23.67, p>0.001, η^2=0.57; Placebo: $F_{1,18}$=11.31, p=0.003, η^2=0.39). Paired sample t-tests comparing the pre-training mood changes (i.e. Mood I vs Mood II) further showed that both groups' mood became more negative after the first recall of the negative event (DCS: t(18)=4.33, p<0.001, d=3.79; Placebo: t(18)=2.87, p=0.01, d=0.64). When comparing the post-training mood changes (Mood III vs Mood IV), results showed that the mood of the DCS group became better (t(18)=2.42, p=0.03, d=0.45). However, there was no such change in the placebo group (t(18)=0.8, p=0.44) (see Figure 2).

CBM-App effects on intrusive memories

In-session intrusion questionnaire. Participants reported fewer intrusive memories in the two minutes after the negative

Table 1. Group characteristics and baseline measures.

	DCS (n=19, females=9) Mean (SD)	Placebo (n=19, females=9) Mean (SD)
Age	24.21 (5.00)	22.37 (3.53)
Years of education	16.42 (3.45)	16.63 (2.71)
BMI	22.97 (3.35)	22.16 (2.04)
BDI	1.74 (1.76)	3.47 (4.65)
STAI-T	31.84 (6.60)	34.16 (7.98)
STAI-S	27.63 (4.41)	31.58 (10.21)
EPQ-Neuroticism	6.16 (4.11)	8.74 (4.43)
THC	0.79 (0.85)	0.68 (1.06)
PTCI I	77.16 (25.87)	75.11 (30.95)
Intrusions I	1.26 (1.33)	1.11 (1.10)
	n (%)	n (%)
Sex: female	9 (47.4)	9 (47.4)
Employment		
Student	16 (84.2)	13 (68.4)
Unemployed	0 (0)	1 (5.3)
Employed	3 (15.8)	5 (26.3)
Ethnicity: Caucasian	19 (100)	14 (73.7)
First language English	16 (84.2)	18 (94.7)

BDI: Beck Depression Inventory; BMI: body mass index; DCS: d-cycloserine; EPQ-Neuroticism: Eysenck Personality Questionnaire – Neuroticism; Intrusions: Intrusion questionnaire lab session; PTCI: Posttraumatic Cognitions Inventory; SD: standard deviation; STAI-T/STAI-S: State Trait Anxiety Inventory-Trait/State; THC: Trauma History Checklist.
For BDI see Beck et al., 1996; for EPQ-Neuroticism see Eysenck and Eysenck, 1994; for PTCI see Foa et al., 1999; for STAI-T/STAI-S see Spielberger et al., 1983; for THC see Holmes et al., 2004.

memory recall post- compared to pre-training (Time: $F_{1,36}$=23.06, p<0.001, η^2=0.39). However, this reduction did not differ between the groups (Time×Group: $F_{1,36}$=0.22, p=0.65). Due to the small number of intrusions, we did not analyse the data for intrusion distress and vividness.

24-hour diary. There was no difference between groups in number of intrusive memories recorded in the 24-hour diary (U=146, Z=0.81, p=0.46.).

Intrusion subscale IES-R. There was no difference between groups on the IES-R intrusion subscale at follow-up, U=141, Z=0.93, p=0.37.

Correlational analyses

First, we examined whether changes in appraisals (ERT and PTCI) were associated with changes in indices of psychopathology (number of intrusions, distress after recall) from pre- to post-training. Contrary to expectations, none of these correlations were significant (all ps>0.05). Second, we examined whether distress experienced after the second recall was associated with indices of psychopathology 24 h later (i.e. PTCI, diary intrusions, IES-R intrusion subscale). Distress associated with recalling the event post-training correlated with diary intrusions (τ=0.37, p<0.01) and the IES-R intrusion subscale (τ=0.52, p<0.01), showing that a lower level of distress after the second (post-training) recall was associated with fewer intrusions over the subsequent 24 h.

Discussion

The current study investigated whether administration of DCS would facilitate learning during an emotional, associative learning task (CBM-App). We expected that administration of DCS, compared to placebo, would be associated with less dysfunctional appraisals and fewer stress symptoms. Results showed that overall, appraisals were less dysfunctional following CBM-App (as shown by changes on the ERT and PTCI from pre- to post-CBM-App). Contrary to our expectations, there was no greater decrease in dysfunctional appraisals in the DCS group compared to the placebo group. Additionally, the two groups did not differ on appraisals at follow-up (measured by the PTCI). We further did not find the expected group difference on any of the three intrusion measures, that is, the in-session intrusion questionnaire administered during the laboratory session, the 24-hour diary, or the intrusions subscale of the IES-R. However, participants in the DCS group showed reduced emotional reactivity to recalling a negative life event, as indexed by both a measure of distress and change in state mood. Finally, correlational analyses showed that less distress after the recall was associated with fewer intrusive memories about the negative event over a 24-hour period.

There are at least three possible explanations as to why we did not find differential effects of DCS on our CBM learning paradigm. First, it is possible that this reflects a ceiling effect due to general effectiveness of the CBM training. Participants in both groups showed more positive appraisals post-training, suggesting that the training task in itself was sufficient for successful learning and there was not much scope for DCS to further enhance it. Second, the ERT may not have been sensitive enough to capture

Table 2. Scores on outcome measures pre-post Cognitive Bias Modification-Appraisal (CBM-App) training.

	DCS (*n*=19) Mean (SD)	Placebo (*n*=19) Mean (SD)	All (*n*=38) Mean (SD)
Appraisal			
ERT			
Pre-training: ERT I[a]	0.13 (1.04)	–0.04 (0.77)	0.4 (0.91)
Post-training: ERT II	1.31 (0.93)	1.07 (0.69)	1.20 (0.82)
PTCI			
Pre-training: PTCI II	77.84 (25.32)	73.53 (35.82)	75.68 (30.67)
Post-training: PTCI III	66.05 (22.53)	65.68 (32.76)	65.87 (27.73)
Ratings recall			
Distress on recall			
Pre-training	4.26 (2.00)	3.88 (2.54)	4.07 (2.26)
Post-training	2.74 (1.76)	3.65 (2.68)	3.19 (2.28)
Negative mood[b]			
Pre-training			
Mood I	4.74 (2.08)	7.83 (5.89)	6.28 (4.63)
Mood II	12.63 (7.34)	11.59 (7.98)	12.11 (7.58)
Post-training			
Mood III	7.90 (5.90)	9.12 (6.96)	8.51 (6.39)
Mood IV	5.26 (3.51)	8.15 (5.93)	6.71 (5.02)
Intrusions			
Pre-training: Intrusions II	1.26 (1.1)	1.16 (1.54)	1.21 (1.32)
Post-training: Intrusions III	0.37 (0.6)	0.42 (0.77)	0.39 (0.68)
Follow-up			
Diary intrusions	1.00 (1.25)	2.11 (3.8)	1.54 (2.82)
IES-R intrusions	0.45 (0.45)	0.73 (0.76)	0.62 (0.57)
PTCI IV	63.79 (20.37)	56.33 (20.51)	60.16 (20.51)

ERT: Encoding Recognition Task; IES-R intrusions: Impact of Events Scale-Revised intrusion subscale; Intrusions: Intrusion questionnaire lab session; PTCI: Posttraumatic Cognitions Inventory.
For IES-R see Weiss and Marmar, 1997; for PTCI see Foa et al., 1999.
[a]Due to missing data of one participant of the placebo group the *n* for both ERTs is *n*=18.
[b]Values represent the means of the sum scores.

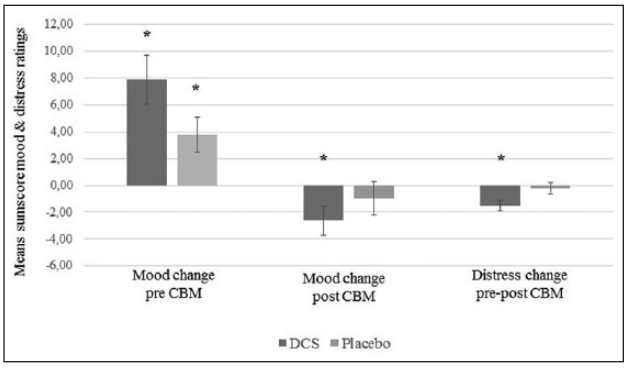

Figure 2. Mean difference scores mood and distress pre-post cognitive bias modification (CBM). Mood change pre-CBM: Mood II/Mood after 1st recall – Mood I/Mood before 1st recall; Mood changes post-CBM: Mood IV/Mood after 2nd recall – Mood III/Mood before 2nd recall; Distress change: Distress post CBM-App – Distress pre CBM-App. Error bars represent standard deviations. DCS: d-cycloserine.

any effects DCS may have had on learning. These suggestions are consistent with other studies showing that DCS does not have an effect on overall learning, but instead leads to differences in more subtle measures of trial-by-trial responding (Scholl et al., 2014, and for similar results, see e.g. Rothbaum et al., 2014). A third potential explanation is that DCS may in fact not have robustly demonstrable effects on emotional learning, or even non-emotional learning (e.g. Butler et al., 2015; Cherry et al., 2014; Günthner et al., 2016). However, there are many (subtle) factors that have to be taken into account when studying the effects of DCS (Hofmann et al., 2015), including factors such as drug dose, timing, and participants' medication status, or the functional properties of the intervention itself. Hence, it may be that there are definable circumstances in which robust effects of DCS on (emotional) learning could be found.

In the present study, change in appraisals was used as an index for the effect of DCS on learning. Although there was no evidence for an effect of DCS on appraisals, other measures did suggest differential effects: In the DCS but not in the placebo group, participants' distress following the recall of the negative life event decreased from pre- to post-training. Further, the DCS group's mood improved after the second recall, compared to the mood of the placebo group. To summarise, the DCS group showed reduced emotional reactivity, compared to the placebo group. Given the fact that these findings are secondary, they should be interpreted with caution. Nevertheless, we suggest some potential explanations: One possibility is that following the training, participants in the DCS

group appraised their negative life event in a more adaptive manner than the placebo group, which in turn made them less vulnerable to the effects of the recall. However, at this stage it is difficult to know whether these effects are in fact a result of the drug enhancing a subtle beneficial effect of the CBM training on appraisal, or via a direct effect that would also have been found in the absence of the CBM-App training. For example, it may be that the reduction in memory distress post-training is an effect of exposure to the memory pre-training, and it is this exposure-learning that DCS enhanced (Hofmann et al., 2013), or that DCS just had a direct effect on mood.

A limitation of the current study is the degree to which the recall task was able to elicit strong emotional reactions and analogue posttraumatic-stress symptoms among participants: Despite the significant worsening in negative mood in both groups after the first recall, participants' mood was still generally positive. Further, the number of intrusions pre-training were small. As such, future studies may need to optimise such analogue trauma manipulations in order to obtain robust effects on stress parameters. A second, related, limitation is that the sample was not selected on the basis of pre-training stress symptoms (although we note that Santa Maria et al., 2012 also did not use such a selection). Both these issues may have limited our ability to observe beneficial effects of DCS-enhanced learning. The administration of the study procedures after administration of DCS or placebo precluded the use of a potentially more powerful and standardised experimental trauma analogue such as a distressing film (James et al., 2016), as DCS may have influenced initial processing and consolidation of the negative event itself. Thus, in this first study we relied on negative memories already experienced by participants. However, future studies could benefit from either using a standardised analogue trauma such as a film prior to DCS administration, or a selected sample of individuals recruited on the basis of having experienced a highly distressing event of which they experience intrusive memories. Follow-up investigations should also include a DCS-only group in order to assess whether potential benefits of DCS were in fact via enhancing the effects of CBM-App or were instead a direct effect independent of the training. Finally, the study had a relatively short time-frame, and so we do not yet know whether our findings can be attributed to a suboptimal combination of dose and time of administration (Hofmann et al., 2015).

In the present study, by combining a pharmacological enhancer (DCS) with an emotional bias learning paradigm (CBM-App), we aimed to contribute to the growing literature recognising the potential benefits of combining psychological and pharmacological approaches in developing more effective treatments for mental health problems (e.g. Moss et al., 2016; Reinecke and Harmer, 2014). Our results showed that DCS did not have an effect on our measure of learning, that is, appraisals of a negative life event. However, DCS reduced participants' emotional reactivity in response to recalling a negative life event after participants had completed the learning task. This suggests either that DCS had a direct effect on reducing the emotional response to a negative memory after a minimal reactivation, or that it enhanced the application of the learning (a more positive appraisal style) to the negative memory. These hypotheses provide interesting avenues for future research aiming to enhance psychological therapy outcomes via pharmacological agents.

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References

Beck AT, Steer RA and Brown GK (1996) *Beck Depression Inventory: II Manual*, 2nd edn. San Antonio, TX: The Psychological Corporation.

Behar E, McHugh RK, Peckham A, et al. (2010) D-cycloserine for the augmentation of an attentional training intervention for trait anxiety. *J Anxiety Disord* 24: 440–445.

Bontempo A, Panza KE and Bloch MH (2012) D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders: A meta-analysis. *J Clin Psychiatry* 73: 533–537.

Butler AJ, Kallos J, Housley SN, et al. (2015) Randomized, placebo-controlled, double-blind pilot study of D-cycloserine in chronic stroke. *Rehabil Res Pract* 2015: 534239.

Cherry KM, Lenze EJ and Lang CE (2014) Combining d-cycloserine with motor training does not result in improved general motor learning in neurologically intact people or in people with stroke. *J Neurophysiol* 111: 2516–2524.

Cheung J and Bryant RA (2017) The impact of appraisals on intrusive memories. *J Behav Ther Exp Psychiatry* 54: 108–111.

de Kleine RA, Hendriks GJ, Kusters WJ, et al. (2012) A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. *Biol Psychiatry* 71: 962–968.

Eysenck HJ and Eysenck SBG (1994) *Manual for the Eysenck Personality Questionnaire (EPQ R Adult)*. San Diego: Educational Industrial Testing Service.

First MB, Spitzer RL, Gibbon M, et al. (1996) *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, D.C.: American Psychiatric Press, Inc.

Foa EB, Ehlers A, Clark DM, et al. (1999) The posttraumatic cognitions inventory (PTCI): Development and validation. *Psychol Assess* 11: 303–314.

Guastella AJ, Richardson R, Lovibond PF, et al. (2008) A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. *Biol Psychiatry* 63: 544–549.

Günthner J, Scholl J, Favaron E, et al. (2016) The NMDA receptor partial agonist d-cycloserine does not enhance motor learning. *J Psychopharmacol* 30: 994–999.

Hertel PT and Mathews A (2011) Cognitive bias modification past perspectives, current findings, and future applications. *Perspect Psychol Sci* 6: 521–536.

Hofmann SG, Meuret AE, Smits JA, et al. (2006) Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Arch Gen Psychiatry* 63: 298–304.

Hofmann SG, Otto MW, Pollack MH, et al. (2015) D-cycloserine augmentation of cognitive behavioral therapy for anxiety disorders: An update. *Curr Psychiatry Rep* 17: 1–5.

Hofmann SG, Wu JQ and Boettcher H (2013) D-Cycloserine as an augmentation strategy for cognitive behavioral therapy of anxiety disorders. *Biol Mood Anxiety Disord* 3: 11.

Holmes EA, Brewin CR and Hennessy RG (2004) Trauma films, information processing, and intrusive memory development. *J Exp Psychol* 133: 3–22.

Izquierdo I, Bevilaqua LRM, Rossato JI, et al. (2006) Different molecular cascades in different sites of the brain control memory consolidation. *Trends Neurosci* 29: 496–505.

James EL, Lau-Zhu A, Clark IA, et al. (2016) The trauma film paradigm as an experimental psychopathology model of psychological trauma: Intrusive memories and beyond. *Clin Psychol Rev* 47: 106–142.

Klumpers F, Denys D, Kenemans JL, et al. (2012) Testing the effects of Δ9-THC and D-cycloserine on extinction of conditioned fear in humans. *J Psychopharmacol* 26: 471–478.

Koster EH and Bernstein A (2015) Introduction to the special issue on cognitive bias modification: Taking a step back to move forward? *J Behav Ther Exp Psychiatry* 49: 1–4.

Koster EH, Fox E and MacLeod C (2009) Introduction to the special section on cognitive bias modification in emotional disorders. *J Abnorm Psychol* 118: 1–4.

Kushner MG, Kim SW, Donahue C, et al. (2007) D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biol Psychiatry* 62: 835–838.

Mataix-Cols D, de la Cruz LF, Monzani B, et al. (2017) D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders: A systematic review and meta-analysis of individual participant data. *JAMA Psychiatry* 74: 501–510.

Mathews A and Mackintosh B (2000) Induced emotional interpretation bias and anxiety. *J Abnorm Psychol* 109: 602–615.

Moss A, Curran HV, Bloomfield MAP, et al. (2016) Bringing together pharmacological and psychological approaches to mental health research. *Lancet Psychiatry* 3: 700–702.

Onur OA, Schlaepfer TE, Kukolja J, et al. (2010) The N-methyl-D-aspartate receptor co-agonist D-cycloserine facilitates declarative learning and hippocampal activity in humans. *Biol Psychiatry* 67: 1205–1211.

Otto MW, Kredlow MA, Smits JJ, et al. (2016) Enhancement of psychosocial treatment with D-cycloserine: Models, moderators, and future directions. *Biol Psychiatry* 80: 274–283.

Otto MW, Tolin DF, Simon NM, et al. (2010) Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biol Psychiatry* 67: 365–370.

Patel DS, Sharma N, Patel MC, et al. (2011) Development and validation of a selective and sensitive LC-MS/MS method for determination of cycloserine in human plasma: Application to bioequivalence study. *J Chromatogr B* 879: 2265–2273.

Reinecke A and Harmer C (2015) A cognitive-neuropsychological account of treatment action in anxiety: Can we improve clinical efficacy? *Psychopathol Rev* 3: 77–109.

Rothbaum BO, Price M, Jovanovic T, et al. (2014) A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. *Am J Psychiatry* 171: 640–648.

Santa Maria A, Reichert F, Hummel SB, et al. (2012) Effects of rumination on intrusive memories: Does processing mode matter? *J Behav Ther Exp Psychiatry* 43: 901–909.

Schartau PE, Dalgleish T and Dunn BD (2009) Seeing the bigger picture: Training in perspective broadening reduces self-reported affect and psychophysiological response to distressing films and autobiographical memories. *J Abnorm Psychol* 118: 15–27.

Scholl J, Günthner J, Kolling N, et al. (2014) A role beyond learning for NMDA receptors in reward-based decision-making a pharmacological study using D-cycloserine. *Neuropsychopharmacology* 39: 2900–2909.

Sotres-Bayon F, Bush DE and LeDoux JE (2007) Acquisition of fear extinction requires activation of NR2B-containing NMDA receptors in the lateral amygdala. *Neuropsychopharmacology* 32: 1929–1940.

Spielberger CD, Gorsuch RL, Lushene R, et al. (1983) *Manual for State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

van Berckel BN, Lipsch C, Timp S, et al. (1997) Behavioral and neuroendocrine effects of the partial NMDA agonist D-cycloserine in healthy subjects. *Neuropsychopharmacology* 16: 317–324.

Weiss DS and Marmar CR (1997) The impact of event scale: Revised. In: Wilson JP and Keane TM (eds) *Assessing Psychological Trauma and PTSD: A Handbook for Practitioners*. New York: Guilford Press, pp. 399–411.

Woud ML and Becker ES (2014) Editorial for the special issue on cognitive bias modification techniques: An introduction to a time traveller's tale. *Cogn Ther Res* 38: 1–6.

Woud ML, Holmes EA, Postma P, et al. (2012) Ameliorating intrusive memories of distressing experiences using computerized reappraisal training. *Emotion* 12: 778–784.

Woud ML, Postma P, Holmes EA, et al. (2013) Reducing analogue trauma symptoms by computerized reappraisal training: Considering a cognitive prophlaxis? *J Behav Ther Exp Psychiatry* 44: 312–315.

Woud ML, Verwoerd JRL and Krans J (2017) Modification of cognitive biases related to posttraumatic stress: A systematic review and research agenda. *Clin Psychol Rev* 54: 81–95.