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Learn to forget: Does post-exposure administration of d-cycloserine enhance fear extinction in agoraphobia?

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ABSTRACT

The use of d-cycloserine (DCS) to augment exposure based therapy for anxiety disorders has shown mixed, although overall positive effects. Aim of the present study was to examine post-exposure administration of DCS in patients with agoraphobia with or without panic disorder. 73 patients with agoraphobia (with or without panic disorder) were treated with 12 sessions of cognitive behavioral therapy (CBT) including 3 exposures. Following successful exposure patients were given double blind either placebo or 50 mg of DCS. Primary outcome criterion was change in the *Panic and Agoraphobia Scale (PAS)* between CBT session t1, t4 (+ ~2 months), t10 (+ ~3 months) und t11 (+ ~4 months). During the course of CBT the patients' symptomatology decreased significantly as measured by primary and secondary outcome criteria, however, without an additional benefit for DCS treated patients. Exploratory sub-group analyses for severely ill patients and patients with high anxiety and strong habituation during exposure showed that DCS administration was associated with increased improvement during the 1-month follow-up period (t10 - t11) with medium to large effect sizes (range in effect size η_p^2 from .06 to .25). Our study results are consistent with recent research on DCS, indicating a beneficial augmentative effect for sub-groups of anxiety patients. The lack of an overall DCS effect for the whole patient sample might be explained by a dual mechanism in fear conditioning and extinction with different cognitive processes being involved during exposure depending on the degree of anxiety experienced by the patient.

1. Introduction

Cognitive behavioral therapy (CBT) is an effective treatment for agoraphobia ((NICE), 2011, 2013; Baldwin et al., 2014; Bandelow et al., 2015a; Bandelow et al., 2015b; Bandelow et al., 2008; Furukawa et al., 2007; Gould et al., 1995; Mitte, 2005; School of and Related Research, 2004). The central and probably most effective element of CBT for agoraphobia is repeated in-vivo exposure in the anxiety provoking situations. There is evidence indicating that exposure therapy alone might be equally effective compared to exposure therapy and cognitive therapy combined (Emmelkamp and Powers, 2009; Gloster et al., 2009; Ruhmland and Margraf, 2001; Sanchez-Meca et al., 2010). Despite its strengths, 30–50% of patients with agoraphobia fail to respond sufficiently to CBT (Aaronson et al., 2008; Furukawa et al., 2007) or discontinue therapy particularly due to the anxiety produced by exposure techniques (Hembree et al., 2003). Accordingly, there is a clear need for additional treatment strategies to enhance outcome of CBT for agoraphobia.

The development of d-cycloserine (DCS) - an antibiotic agent originally used in the treatment of tuberculosis - as an augmentation strategy for exposure based CBT is considered a promising strategy from translational research (Anderson and Insel, 2006). Besides its antibiotic properties, DCS also acts as a partial agonist of glutamatergic N-methyl-D-aspartate (NMDA) receptors found in the basolateral nucleus of the amygdala. Here, it influences synaptic plasticity and can lead to enhancement of emotional learning processes such as extinction of fear. Precisely, it is believed that DCS administration facilitates the consolidation of extinction learning rather than extinction learning per se as seen in animal studies where it was effective when administered before and up to 60 min after extinction training (Ledgerwood et al., 2004, 2005; Walker et al., 2002).

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Given the similarity between fear extinction in animals and learning processes during exposure therapy in patients with anxiety disorders, it was hypothesized that DCS might be a translational agent able to augment the efficacy of CBT in humans. In the first clinical trial investigating DCS as an augmentation strategy of CBT, patients with acrophobia showed significantly greater symptom reduction when treated with CBT combined with DCS compared to CBT plus Placebo (PBO) (Ressler et al., 2004). In the following, several placebo-controlled clinical trials reported positive results in the advantage of DCS augmentation of CBT in treating specific phobia, social phobia, obsessive-compulsive disorder and post-traumatic stress disorder (see Table 1). However, there have also been studies showing only small effect sizes or no effect at all for the augmentation of CBT with DCS, especially the more recent and larger-scale clinical trials (see Table 1).

Specifically regarding agoraphobia and panic disorder, there have been four studies up to date investigating DCS augmentation for patients with primarily panic disorder. In their pilot study testing 31 patients with panic disorder, Otto et al. (2010) found that DCS significantly improved outcomes on relevant clinical scales and that it was associated with more clinically significant change status compared to PBO. However, the authors were not able to replicate their findings in the following large-scale study testing 180 panic disorder patients (Otto et al., 2016). Despite this, their results did indicate a benefit with DCS early during CBT treatment. Our own research group conducted a clinical trial on DCS augmentation of group CBT treatment in 39 patients with panic disorder and agoraphobia (Siegmund et al., 2011). Similar to Otto et al. (2016) we found no overall augmentation effect of DCS. Instead, an acceleration of symptom reduction for the severely ill patients was observed. A very recent trial on 57 patients with panic disorder and agoraphobia (Hofmeijer-Sevink et al., 2017) found no augmentation effect of DCS, neither for administration before exposure sessions nor for administration directly after exposure.

The aspect of post-administration, i. e. taking DCS directly after exposure sessions, is of particular clinical relevance. The specific mode of action of DCS in the human brain carries the risk of possibly reinforcing „negative“ learning experiences in unsuccessful exposure sessions, i. e. the patient continues to experience anxiety, habituation does not take place and consequently fear of the specific situation is reconsolidated. Thus, using DCS in clinical practice would possibly not only make “good exposures” better but also “bad exposures” worse (Hofmann, 2016). Animal studies could show the reinforcing effect of DCS also for administration after extinction training or reexposure to fear contexts (Ledgerwood et al., 2003; Norberg et al., 2008; Parnas et al., 2005; Saitoh et al., 2017; Santini et al., 2001; Weber et al., 2007) suggesting the augmentation to occur primarily during the period of memory consolidation after exposure rather than during exposure itself. An advantage of post administration also for patients with anxiety disorders would be the possibility to use DCS more specifically and only in cases of positive learning experiences. Yet, until now, DCS studies with a post-exposure design failed to find a reinforcing effect of DCS on exposure therapy (Hofmeijer-Sevink et al., 2017; Mataix-Cols et al., 2014; Tart et al., 2013), with one exception: in the study by Hofmeijer-Sevink et al. (2017) post-exposure administration of DCS was significantly superior to pre-exposure administration but not to PBO at 3-month follow-up (FU).

Taken together, many empirical studies suggest that DCS enhances the effect of CBT in anxiety disorders. Nevertheless, there are also clinical trials indicating no augmentation effect of DCS, especially the later and well powered trials (Burkner et al., 2017; Mataix-Cols et al., 2017). The most recent reviews and meta-analyses that attempted to sum up all results from clinical trials with anxiety patients found no or only little superiority of CBT combined with DCS compared to PBO (Burkner et al., 2017; Mataix-Cols et al., 2017; Ori et al., 2015) contrasting earlier meta-analyses that clearly indicated an augmentation effect of DCS (Bontempo et al., 2012; Norberg et al., 2008).

Given this heterogeneity of empirical evidence in DCS research, recent studies often included exploratory sub-group analyses with the aim of clarifying the specific working mechanism of DCS. The results point to possible moderators of the DCS effect like severity of illness (de Kleine et al., 2012; Siegmund et al., 2011), habituation, success of exposure or between-session anxiety (Litz et al., 2012; Rothbaum et al., 2014; Smits et al., 2013b, 2013c), personality traits (de Kleine et al., 2014; Smits et al., 2013a), antidepressants (Andersson et al., 2015; Rodebaugh et al., 2013), adaptive learning (Guastella et al., 2008) or

Table 1
Overview of clinical trials for anxiety disorders.

Reference	Anxiety disorder	DCS > PBO[a]	DCS ≤ PBO[b]
Ressler et al. (2004)	Acrophobia	X	
Gutner et al. (2012)	Spider phobia	X	
Nave et al. (2012)	Snake phobia	X	
Guastella et al. (2008)	Social anxiety disorder	X	
Hofmann et al. (2006)	Social anxiety disorder	X	
Hofmann et al. (2013a)	Social anxiety disorder	X	
Rodebaugh et al. (2013)	Social anxiety disorder	X	
Otto et al. (2010)	Panic disorder	X	
de Kleine et al. (2012)	Post-traumatic stress disorder	X	
Difede et al. (2014)	Post-traumatic stress disorder	X	
Farrell et al. (2013)	Obsessive-compulsive disorder	X	
Kushner et al. (2007)	Obsessive-compulsive disorder	X	
Storch et al. (2010)	Obsessive-compulsive disorder	X	
Wilhelm et al. (2008)	Obsessive-compulsive disorder	X	
Tart et al. (2013)	Acrophobia		X
Hofmeijer-Sevink et al. (2017)	Panic disorder with agoraphobia		X
Otto et al. (2016)	Panic disorder		X
Siegmund et al. (2011)	Panic disorder with agoraphobia		X
Heresco-Levy et al. (2002)	Post-traumatic stress disorder		X
Litz et al. (2012)	Post-traumatic stress disorder		X
Rothbaum et al. (2014)	Post-traumatic stress disorder		X
Scheeringa and Weems (2014)	Post-traumatic stress disorder		X
Andersson et al. (2015)	Obsessive-compulsive disorder		X
Mataix-Cols et al. (2014)	Obsessive-compulsive disorder		X
Storch et al. (2007)	Obsessive-compulsive disorder		X
Storch et al. (2016)	Obsessive-compulsive disorder		X

[a] D-cycloserine significantly superior to placebo.
[b] D-cycloserine not significantly superior to placebo.

homework compliance (Olatunji et al., 2015). A possible explanation could be that DCS is especially effective in patients who experience a high degree of anxiety during exposure and/or habituation and profit from psychotherapy primarily by amygdala-mediated processes involving NMDA-receptors (~habituation). In contrast, DCS might be less effective in only slightly anxious patients who profit from psychotherapy by means of higher order cognitive processes (~cognitive restructuring) (Grillon, 2009).

The present study aimed to investigate the effect of DCS administration after exposure sessions in patients with agoraphobia with or without panic disorder. We hypothesized that DCS augmentation of exposure based CBT would enhance treatment outcome relative to augmentation with PBO. Following the results of our first DCS study as well as other current findings in DCS research we furthermore intended to analyze sub-groups of agoraphobic patients. Referring to the assumptions of Grillon (2009), we aimed to apply exploratory sub-group analyses to a) severely ill patients, b) patients with high anxiety and c) strong habituation during exposure. We expected a stronger DCS effect in the three sub-groups of agoraphobic patients.

2. Material and methods

The present study was funded by the Federal Ministry of Education and Research (BMBF) ('Panik-Netz'; 01 GV 0612). Ethical approval was obtained on 27.06.2011 at the State Office of Health and Social Affairs Berlin (LaGeSo) (Eudra-CT: 2011-001398-19). Two participating centers were involved:

- Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité-Universitätsmedizin Berlin.
- Center of Psychotherapy at the Department of Psychology, Humboldt-Universität zu Berlin.

The study is registered at *ClinicalTrials.gov* (NCT01928823) and was monitored before start of recruitment, during treatment and after completion of study by independent monitors.

2.1. Participants

Interested patients were screened by phone and, if eligible, were invited for written informed consent and diagnostic examination (including a physical examination and comprehensive laboratory check). Patients were included in the study if they fulfilled Good Clinical Practice (GCP) conformal inclusion and exclusion criteria and met the diagnosis of agoraphobia with or without panic disorder according to ICD-10 (F40.00, F40.01). Diagnoses were made on the basis of clinical exploration as well as the *SCID-I Screening* (Wittchen et al., 1997) and the coordinated use of *IDCL-checklists* (Hiller et al., 1995). Severity of disease measured by the *Clinical Global Impression scale (CGI)* (Guy et al., 1976) had to be a minimum of 4 - 'moderately ill'. Medications were unchanged during the 4 weeks before enrollment and were to remain stable throughout treatment. Including 4 drop-outs, a total of 73 male and female agoraphobic patients aged between 22 and 67 years were recruited and randomized (‚intention-to-treat-sample'). Accordingly, there were complete data sets for 69 patients available (‚completer-sample'). For details concerning the recruitment of patients see Fig. 1.

2.2. Study design

For a detailed overview of study design see Fig. 2.

Patients were treated with 12 sessions (t (ime point)1 – t12) of individual CBT including 3 in-vivo exposure sessions (t7 – t9). Therapists followed a psychotherapy treatment manual (Pyrkosch et al., 2011) which was based on established and validated CBT treatment manuals (Gloster et al., 2009; Lang et al., 2012; Margraf and Schneider, 1990). It included standard CBT techniques such as psychoeducation, cognitive restructuring, in-vivo exposure and relapse prevention. All treating therapists were clinical psychologists experienced in CBT and underwent special training in exposure therapy based on the described manual. They received weekly supervision from senior psychotherapists specialized in the field of agoraphobia and exposure therapy. Therapy sessions were videotaped and therapist adherence was assessed by the use of session content checklists that corresponded to the treatment manual. 50% of all available therapy videos were randomly selected and two independent and trained raters filled in the corresponding checklists (inter-rater reliability was $\alpha = 0.84$).

In session t7 to t9 therapist-assisted exposures according to the 'flooding' principle took place. Patients and therapists selected real life situations which intended to provoke maximum anxiety. Additionally, the situations should be important and relevant for the patients' everyday life (e. g. catching the bus, taking the lift, shopping in a supermarket). Together with the therapist, patients confronted their anxiety at the chosen place where they remained until anxiety decreased by itself. Therapists supported the patients to endure the anxiety experienced and to not engage in any avoidance or safety behavior. They furthermore recorded subjective anxiety ratings from 0 - 'no anxiety' to 10 - 'maximal anxiety' on standardized exposure protocols. On the base of these evaluations the following parameters could be extracted: *anxiety at the start of exposure*; *maximum anxiety during exposure*; *anxiety at the end of exposure*; and *habituation*, i. e. the difference between maximum anxiety and anxiety at the end of exposure.

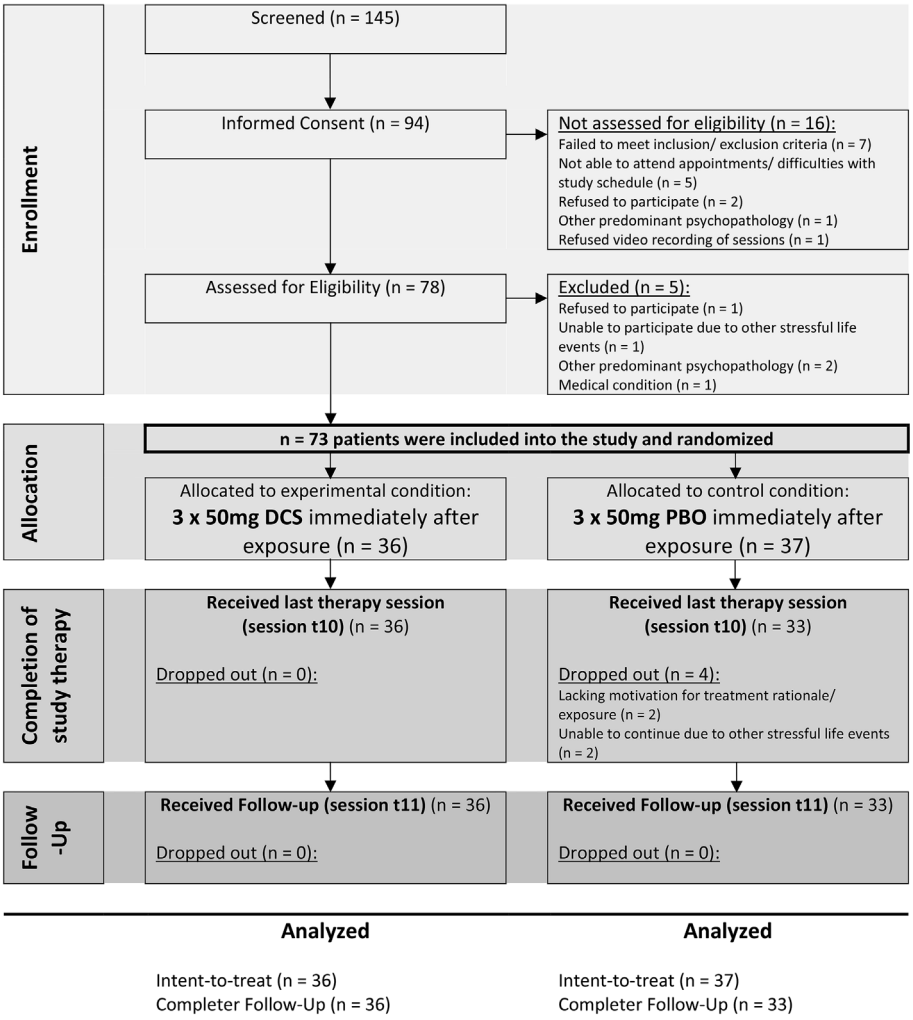
When patients subjectively reported no or only minimal anxiety and ratings had decreased to at least 3, the exposure session was considered successful and terminated. After a short break the same confrontation was repeated. Accordingly, patients underwent 3 exposure sessions with two rounds respectively. Within 30 min after the second round of exposure patients were given double blind and randomized either PBO or 50 mg of DCS by oral administration. 50 mg of DCS is a commonly used dosage in DCS studies with anxiety patients as clinical trials (e. g. Ressler et al., 2004) and meta-analyses (e. g. Mataix-Cols et al., 2017) could not show better efficacy with higher dosages. Study medication and the randomization list were generated by the Charité Pharmacy, Campus Virchow, with the aid of the software *Randomization* (version 01/08/2008) and using the method of randomly permuted blocks of pairs. The randomization list remained in the Charité Pharmacy until completion of data collection, thus assuring for blindness of patients, therapists and all study personal regarding the patients' study condition. Potential side effects of the study drug were elicited by protocol-guided questioning and monitored from therapy session t7 on.

2.3. Assessments

Primary outcome criterion in the present trial was change in the sum score of the *Panic and Agoraphobia Scale (PAS)* (Bandelow, 1995) between session t1, t4 (+~2 months), t10 (+~3 months) and t11 (+~4 months). The *PAS* is a reliable, valid and internationally used scale for the determination of severity of disease in patients with agoraphobia and/or panic disorder (Bandelow, 1995). In many therapy studies also its sensitivity for measuring change or improvement of symptomatology was demonstrated (Bandelow, 1995). For the present trial, the *PAS* was used in the self-rated and observer-rated (by therapist) version.

Besides the specific agoraphobic symptomatology, further symptoms typically related to agoraphobia (anxiety, depression, reduced mobility etc.) were also assessed by the use of the following psychometric scales:

- *Agoraphobic Cognitions Questionnaire (ACQ)* (Chambless et al., 1984; Ehlers and Margraf, 2001). The *ACQ* consists of 14 items measuring the patients central phobic cognitions, e. g. "I am going to pass out". It may be scored as a total scale or according to its two subscales (*loss of control* and *physical concerns*).
- *Body Sensations Questionnaire (BSQ)* (Chambless et al., 1984; Ehlers



Abbreviations: DCS = D-Cycloserine, PBO = Placebo.

Fig. 1. Flow chart of recruitment.

and Margraf, 2001). The *BSQ*, consisting of 17 items, is a valid an reliable instrument to assess the patients phobic fear of bodily symptoms such as “heart beat” or “dizziness”.

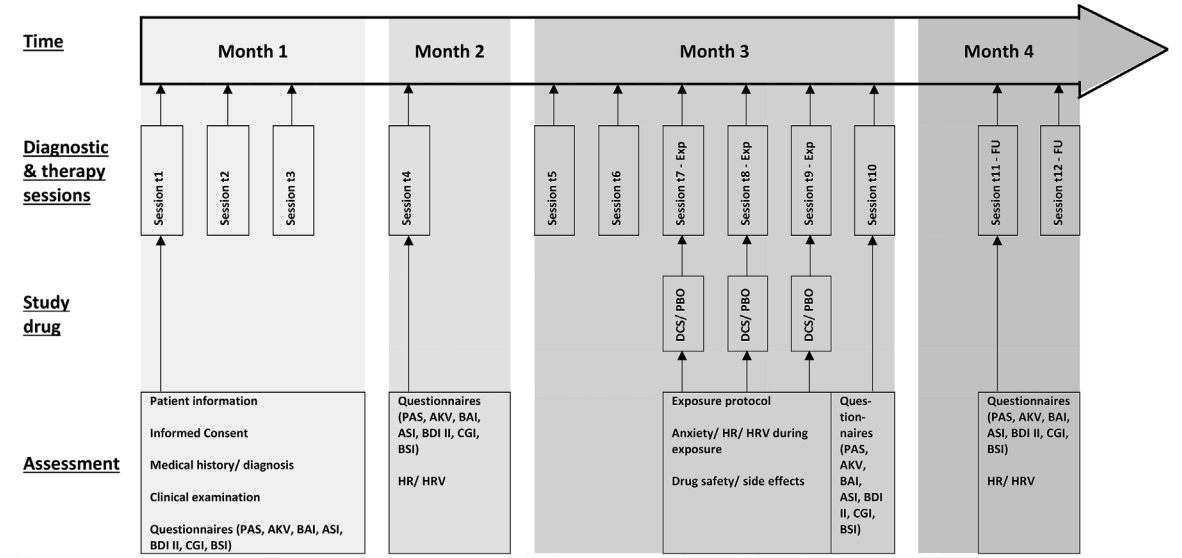
- *Mobility Inventory (MI)* (Chambless et al., 1985; Ehlers and Margraf, 2001). In the *MI* 26 situations are rated for avoidance by the patients both when they are alone (subscale *MI alone*) or when they are accompanied (subscale *MI accompanied*).
- *Anxiety Sensitivity Index (ASI)* (Reiss et al., 1986). The 16-item *ASI* measures the patients' fear of anxiety-related sensations and the evaluation about their harmful consequences. The *ASI* was shown to also display good sensitivity to change over the course of treatment (Rifkin et al., 2015).
- *Beck Anxiety Inventory (BAI)* (Beck et al., 1988; Beck and Steer, 1993). The *BAI*, containing 21 items, is a valid and reliable inventory for measuring common symptoms of clinical anxiety, e. g. numbness or sweating.
- *Beck Depression Inventory II (BDI II)* (Beck et al., 1996). As for the high overlap between anxiety and depression we considered it important to also assess depressive symptoms in our patient sample with the help of the most commonly used inventory *BDI II*.
- *Brief Symptom Inventory (BSI)* (Derogatis, 2001; Franke, 2000). We decided to apply the *BSI* in order to also have a measure for general psychopathological symptoms pertaining to different disorder-specific domains.
- *Clinical Global Impression (CGI)* (Guy et al., 1976). The *CGI* is a very easy to apply clinician rated scale measuring global severity of illness. Although short it is one of the most widely used brief assessment tools in psychiatry.

2.4. Statistical analyses

Validated data were entered twice in a SPSS (IBM SPSS Statistics 24) data base (*double data entry/verification*). Regarding primary and secondary outcome criteria there were very few missing data: Altogether 1,10%. Single missing values were therefore replaced by the mean of the respective subsample. With regard to the 4 drop outs the imputation technique *expectation maximization (EM)* was applied. On the grounds of this data preprocessing, statistical analyses were conducted for the intention-to-treat-sample.

Besides χ^2 and *t*-test analyses for differences in the baseline values, we employed for all outcome criteria repeated measures ANOVAS with one between-subject factor (group: DCS, PBO) and one within-subject factor (time: t1, t4, t10 and t11). Sphericity was analyzed by Mauchley testing and degrees of freedom were adjusted by Greenhouse-Geisser correction if $p < 0.05$. Effect sizes were reported as partial eta-squared (η_p^2). Tests were employed two-tailed and statistical significance was accepted if $p < 0.05$.

Regarding the sub-group analyses we divided the patient sample



Abbreviations: Exp = Exposure, FU = Follow Up, DCS = D-Cycloserine, PBO = Placebo, PAS = Panic and Agoraphobia Scale, ACQ = Agoraphobic Cognitions Questionnaire, BSQ = Body Sensations Questionnaire, MI = Mobility Inventory, ASI = Anxiety Sensitivity Index, BAI = Beck Anxiety Inventory, BDI II = Beck Depression Inventory II, BSI = Brief Symptom Inventory, CGI = Clinical Global Impression, HR = Heart Rate, HRV = Heart Rate Variability

Fig. 2. Overview of study design.

into two groups by means of median splits on the following variables: the severely ill patient group was extracted on base of the *PAS* observer-rated sum scores in session t1. For the patient group with high anxiety during exposures the parameter *maximum anxiety during exposure* was selected and averaged over all three exposures. Likewise, to generate the patient group with strong habituation during exposure the parameter *habituation* was taken and averaged over the three exposures. The advantage of median split – in contrast to an a priori fixed score – is the creation of two groups of comparable size independent of the severity of illness of the specific patient sample in the specific institution. For the three sub-groups of patients the same repeated measures ANOVAS as described above were employed.

3. Results

3.1. Treatment integrity

Therapist adherence with the treatment manual was tested on the grounds of therapy videos and session content checklists: in 96,6% therapist adherence was rated as “moderate” to “high”. Mean therapist adherence was *M(SD)* = 6.09 (0.84) indicating „good therapist adherence”.

All patients received 3 doses of pill administrations. In two cases exposure was considered unsuccessful and therefore the patients received no medication (to avoid reinforcement of negative learning experiences). In order to assure for the same degree of successful exposures for all patients the respective exposures were repeated and consequently all study drugs could be administered. Concerning the tolerability of DCS, there were no serious adverse events or instances of emergency unblinding.

3.2. Sample characteristics

Descriptive variables of the patient sample and baseline values in the different outcome parameters are shown in Table 2.

Despite randomization a significant age difference between the two treatment groups was observed with the PBO group being significantly older. Accordingly, they also displayed a significantly longer duration of illness. All other demographic variables were distributed equally between the two groups. Baseline values in the clinical scales showed no statistical differences except for the *CGI* with the DCS group being rated more severely ill than the PBO group.

3.3. Primary outcome criterion - PAS

Observer-rated version: repeated-measures ANOVA for the observer-rated version of the *PAS* showed a significant main effect for ‚time‘ (*PAS* sum score from 23.36 (t1) to 7.14 (t11), $F_{2.42,171.97} = 158.68$, $p < .001$) but no significant main effect for ‚group' ($p = .22$) and neither a significant interaction ($p = .72$) (see Fig. 3).

Self-rated version: repeated-measures ANOVA for the self-rated version of the *PAS* showed a significant main effect for ‚time‘ (*PAS* sum score from 19.93 (t1) to 7.96 (t11), $F_{2.51,178.20} = 87.28$, $p < .001$) but no significant main effect for ‚group' ($p = .50$) and neither a significant interaction ($p = .61$) (see Fig. 3).

Considering the variables *age* and *duration of disease* as covariates in the model (in order to rule out confounding) yielded the same pattern of results.

The lack of significant group × time interactions indicates that both the DCS and PBO group experienced comparable improvement of symptomatology over time.

3.4. Secondary outcome criteria

A similar pattern of effects emerged with the secondary outcome criteria: repeated-measures ANOVAs showed significant main effects for ‚time‘ but no significant main effects for ‚group' and neither significant interactions, except for the *ACQ* and *CGI* (see Table 3). The significant interaction between time and group in the *ACQ* mean score was due to the period between t1 and t4 ($F_{1,71} = 8.44$, $p = .005$; compared to t4 – t10: $F_{1,71} = 1.14$, $p = .29$; and t10 – t11: $F_{1,71} = 2.13$, $p = .15$) with the DCS group decreasing and the PBO group increasing in the *ACQ* mean score. Since this period was before administration of the study drug the interaction cannot be explained by a DCS augmentation effect. As for the *CGI*, the DCS group already displayed a more severe symptomatology at the beginning of the study (see Table 2) and this difference between the two groups remained stable until the end of treatment.

Table 2
Descriptive statistics and baseline values.

	DCS ($N = 36$) $M(SD)/N$	PBO ($N = 37$) $M(SD)/N$	t/Chi^2	df	p
Age	34.11 (10.37)	40.86 (12.94)	2.46	71	.02*
Duration of disease (months)	49.91 (53.97)	122.25 (111.59)	3.62	50.98	.001**
Sex					
Male	14	11	0.68	1	.41
Female	22	26			
Study center					
Charité	18	18	0.01	1	.91
Humboldt University	18	19			
Diagnosis					
F40.00	10	10	0.01	1	.94
F40.01	26	27			
Axis I comorbidities					
None	24	25	0.01	1	.94
≥ One	12	12			
Axis II personality disorders					
None	29	26	1.04	1	.31
≥ One	7	11			
Ongoing psychopharmacotherapy					
No	24	18	2.43	1	.12
Yes	12	19			
Family status					
Single	16	16	0.01	1	.92
Stable relationship	20	21			
Living situation					
Alone	14	8	2.58	1	.12
With family/friends	22	29			
Education					
No high school diploma	13	11	0.34	1	.56
High school diploma or higher	23	26			
Occupational status [a]					
None	8	7	5.29	2	.07
Part time or other	15	7			
Full time	13	22			
PAS observer-rated sum score	24.74 (8.96)	22.03 (7.77)	−1.38	71	.17
PAS self-rated sum score	20.68 (10.31)	19.20 (9.69)	−0.63	71	.53
ACQ mean	2.11 (0.44)	2.01 (0.55)	−0.87	71	.38
BSQ mean	2.67 (0.74)	2.68 (0.83)	0.07	71	.95
MI alone mean	2.69 (0.99)	2.56 (0.84)	−0.60	71	.55
MI accompanied mean	2.10 (0.79)	1.88 (0.61)	−1.33	71	.19
ASI sum score	27.55 (10.32)	28.13 (9.17)	0.25	71	.80
BAI sum score	21.44 (12.24)	21.25 (12.21)	−0.07	71	.95
BDI II sum score	12.03 (8.62)	10.94 (8.76)	−0.54	71	.59
BSI sum score	39.71 (26.00)	35.58 (26.58)	−0.67	71	.50
CGI	5.31 (0.62)	4.89 (0.61)	−2.86	71	.006**

* = $p < .05$, ** = $p < .01$, *** = $p < .001$.
Abbreviations: DCS = D-Cycloserine, PBO = Placebo, PAS = Panic and Agoraphobia Scale, ACQ = Agoraphobic Cognitions Questionnaire, BSQ = Body Sensations Questionnaire, MI = Mobility Inventory, ASI = Anxiety Sensitivity Index, BAI = Beck Anxiety Inventory, BDI II = Beck Depression Inventory II, BSI = Brief Symptom Inventory, CGI = Clinical Global Impression.
[a] *PBO N = 36, 1 missing value.*

3.5. Sub-group analyses

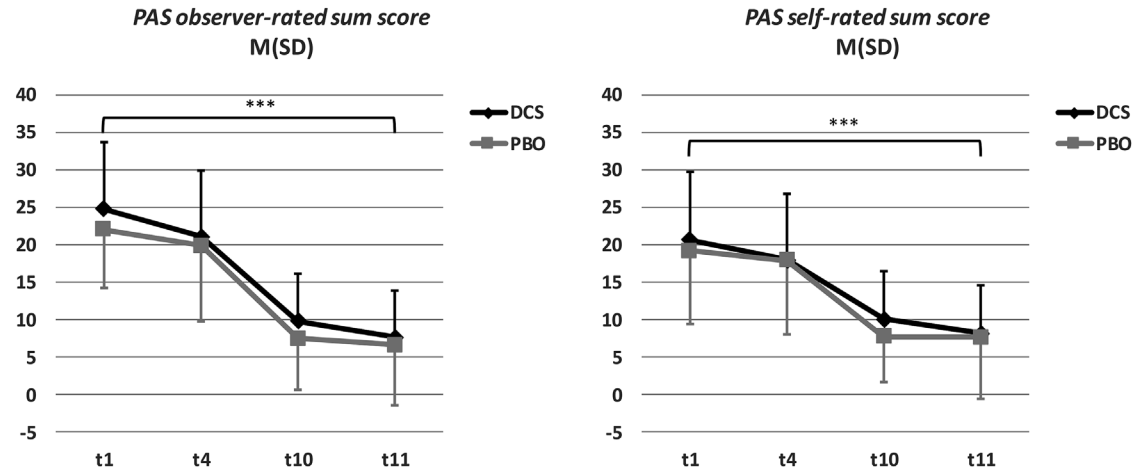
When entering the three sub-groups (severely ill patients, patients with high anxiety during exposure, patients with strong habituation during exposure) in our model, repeated measures ANOVAS indicated nonsignificant trends for several clinical scales. Closer inspection of the data revealed that a differential change in symptomatology only took place during the 1-month follow-up (FU) period. While the DCS and PBO group showed comparable decreases in symptomatology during the therapy period, DCS treated patients improved more between t10 and t11.

Table 4 shows p-values for the interaction between group (DCS vs. PBO) and time (t10, t11) in all three sub-groups (for reasons of clarity main effects are not listed). For several clinical scales the interaction effect is significant. Regarding the other scales the same pattern could be observed without reaching significance. As the analyzed samples were small, we considered the effect size partial eta-squared η_p^2, too, indicating a medium to large effect in many clinical scales even when significance level could not be reached.

Fig. 4 illustrates examples of the significant interaction in the FU period for three different clinical scales and in all three different sub-groups.

4. Discussion

This randomized, double-blind, placebo-controlled augmentation trial investigated post-exposure administration of DCS in a large sample of patients with agoraphobia with or without panic disorder. Our results indicated that patients in the DCS as well as the PBO group improved significantly regarding their agoraphobic symptomatology throughout the course of CBT. However, DCS did not lead to greater improvement than PBO. This finding contrasts several other clinical trials that did show an augmentation effect for DCS (Table 1), also for patients with panic disorder with or without agoraphobia (Otto et al., 2010). On the other hand, our study results are in line with comparable DCS studies on post-exposure administration (Hofmeijer-Sevink et al., 2017; Mataix-Cols et al., 2014; Tart et al., 2013) which also failed to find a superior effect of DCS compared to PBO. This raises the question



Abbreviations: DCS = D-Cycloserine, PBO = Placebo, PAS = Panic and Agoraphobia Scale.
* = significant (p<.05)
** = very significant (p<.01)
*** = highly significant (p<.001)

Fig. 3. PAS sum scores.

Table 3
Repeated measures ANOVAS for secondary outcome criteria.

Clinical scales	Effects	*F*	*df*	*p*
ACQ mean	Time[a]	88.59	2.51,178.06	< .001***
	Group[b]	0.09	1,71	.76
	Time x Group	3.22	2.51,178.06	.03*
BSQ mean	Time[a]	58.33	2.03,143.78	< .001***
	Group[b]	0.51	1,71	.48
	Time x Group	0.82	2.03,143.78	.44
MI alone mean	Time[a]	119.96	1.70,120.42	< .001***
	Group[b]	0.19	1,71	.67
	Time x Group	1.05	1.70,120.42	.34
MI accompanied mean	Time[a]	68.06	2.05,145.37	< .001***
	Group[b]	1.04	1,71	.31
	Time x Group	0.75	2.05,145.37	.48
ASI sum score	Time[a]	112.43	2.04,144.94	< .001***
	Group[b]	0.10	1,71	.75
	Time x Group	1.36	2.04,144.94	.26
BAI sum score	Time[a]	50.63	2.48,176.25	< .001***
	Group[b]	0.001	1,71	.98
	Time x Group	0.39	2.48,176.25	.72
BDI II sum score	Time[a]	56.10	2.23,158.54	< .001***
	Group[b]	0.28	1,71	.60
	Time x Group	0.17	2.23,158.54	.86
BSI sum score	Time[a]	66.36	2.08,147.83	< .001***
	Group[b]	0.28	1,71	.60
	Time x Group	0.48	2.08,147.83	.63
CGI	Time[a]	257.93	2.38,169.06	< .001***
	Group[b]	9.90	1,71	.002**
	Time x Group	1.38	2.38,169.06	.26

Abbreviations: DCS = D-Cycloserine, PBO = Placebo, PAS = Panic and Agoraphobia Scale, ACQ = Agoraphobic Cognitions Questionnaire, BSQ = Body Sensations Questionnaire, MI = Mobility Inventory, ASI = Anxiety Sensitivity Index, BAI = Beck Anxiety Inventory, BDI II = Beck Depression Inventory II, BSI = Brief Symptom Inventory, CGI = Clinical Global Impression.
* = p < .05, ** = p < .01, *** = p < .001.
[a] Factor time: t1, t4 (+ ~ 2 months), t10 (+ ~ 3 months) and t11 (+ ~ 4 months).
[b] Factor group: DCS (N = 36) vs. PBO (N = 37).

of whether post-exposure administration of DCS may not have the same potential to augment CBT like pre-exposure administration, despite the positive findings in animal studies (Ledgerwood et al., 2003; Norberg et al., 2008; Parnas et al., 2005; Saitoh et al., 2017; Santini et al., 2001; Weber et al., 2007).

A possible reason could be a delayed onset of action. Animal studies used DCS subcutaneously resulting in peak plasma levels within 15 min. In contrast, when administered orally in humans, DCS leads to maximum serum concentration after 90–120 min. It is possible that post-session oral administration of DCS fails to arrive at the significant site of action in a time course necessary for therapeutic effect. This could be a logical explanation for the negative findings regarding post-exposure administration of DCS in patients with anxiety disorders. Nevertheless, the most recent and comprehensive meta-analysis on DCS augmentation (Mataix-Cols et al., 2017) did not find a statistically significant difference between pre- and post-exposure administration of DCS across all existing clinical trials. Furthermore, Hofmeijer-Sevink et al. (2017) obtained the intriguing finding that post-exposure administration of DCS in patients with panic disorder and agoraphobia was even associated with better outcome in the FU period compared to pre-exposure administration (but not to PBO). Taken together, more empirical evidence and especially post-exposure DCS studies are required to further clarify a possible inferiority of post-exposure administration.

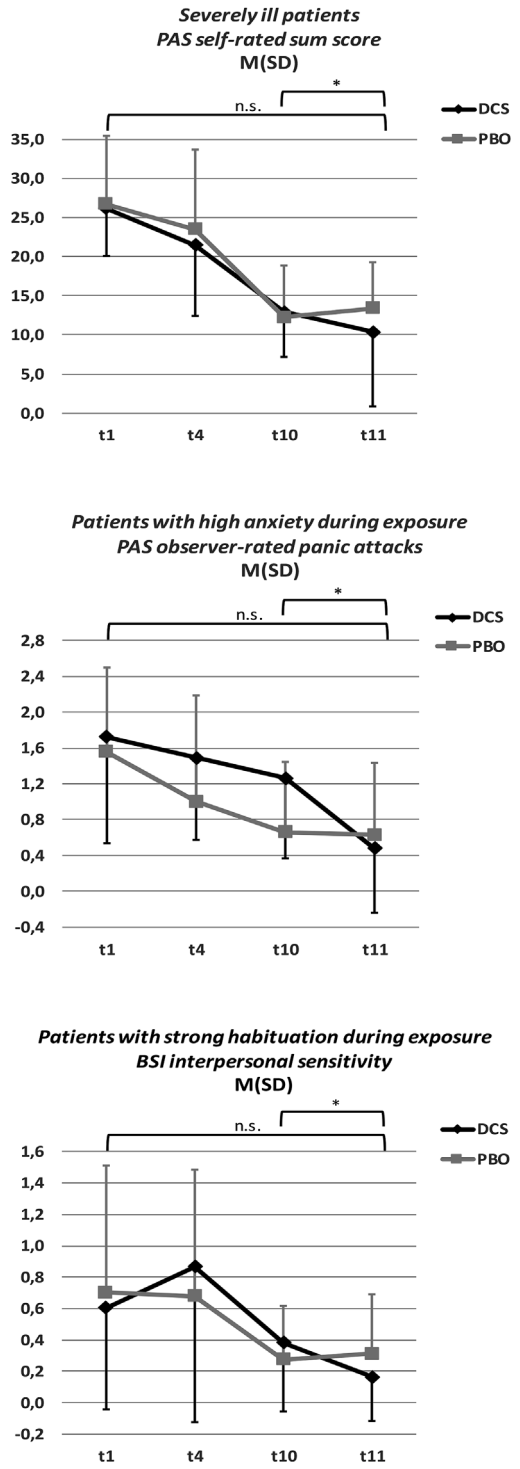
Although our study did not show a general DCS effect, exploratory sub-group analyses revealed that DCS might be beneficial for certain agoraphobic patients. As for their exploratory nature these results can only be interpreted with caution and rather serve as indicators for future research. Nevertheless, we did find an interesting pattern throughout several outcome measures in severely ill patients as well as in patients with high anxiety or strong habituation during exposures. Our data suggest that these patient samples improved more during the 1-month FU period when before DCS had been administered during therapy compared to PBO. This was true for clinical scales measuring panic and agoraphobic symptomatology but also for associated variables such as anxiety sensitivity, general psychopathology, social insecurity, depression, or psychotizism.

This interesting finding from sub-group analyses could be explained by a dual mechanism in fear conditioning and extinction as proposed by Grillon (2009). Phylogenetically older neural structures detect and react rapidly to danger cues, which is a low-level automatic process (Squire and Zola, 1996). Conditioning in humans, however, also relies on high-level cognitive learning processes involving relational learning, conscious thoughts, evaluations, and anticipation (Dawson and Furedy,

Table 4
Interaction effect time x group for different sub-groups.

Clinical scales	Effect	Severely ill patients (N = 36)		Patients with high anxiety during exposure (N = 38)		Patients with strong habituation during exposure (N = 38)	
		p	η_p^2	p	η_p^2	p	η_p^2
PAS observer-rated sum score	Time[a] x Group[b]	.14	.06*	.05	.10*	.047*	.11*
- subscale panic attacks	Time[a] x Group[b]	.045*	.11*	.02*	.15**	.04*	.12*
PAS self-rated sum score	Time[a] x Group[b]	.045*	.11*	.11	.07*	.08	.09*
- subscale panic attacks	Time[a] x Group[b]	.04*	.12*	.06	.10*	.06	.10*
ACQ mean	Time[a] x Group[b]	.20	.05	.10	.07*	.15	.06*
- subscale loss of control	Time[a] x Group[b]	.07	.10*	.09	.08*	.16	.06*
BSQ mean	Time[a] x Group[b]	.34	.03	.13	.06*	.39	.02
MI alone mean	Time[a] x Group[b]	.57	.01	.71	< .01	.94	< .01
MI accompanied mean	Time[a] x Group[b]	.68	.01	.76	< .01	.87	< .01
ASI sum score	Time[a] x Group[b]	.049*	.11*	.27	.03	.52	.01
BAI sum score	Time[a] x Group[b]	.30	.03	.55	.01	.07	.09*
BDI II sum score	Time[a] x Group[b]	.21	.05	.49	.01	.96	< .01
BSI sum score	Time[a] x Group[b]	.03*	.13*	.14	.06*	.16	.05
- subscale social insecurity	Time[a] x Group[b]	< .01**	.19**	< .01**	.22**	< .01**	.25**
- subscale depression	Time[a] x Group[b]	< .01**	.25**	.04*	.11*	.11	.07*
- subscale hostility	Time[a] x Group[b]	.05	.11*	.06	.10*	.11	.07*
- subscale psychotizism	Time[a] x Group[b]	.04*	.12*	.24	.04	.45	.02
CGI	Time[a] x Group[b]	.54	.01	.28	.03	.26	.04

Abbreviations: DCS = D-Cycloserine, PBO = Placebo, PAS = Panic and Agoraphobia Scale, ACQ = Agoraphobic Cognitions Questionnaire, BSQ = Body Sensations Questionnaire, MI = Mobility Inventory, ASI = Anxiety Sensitivity Index, BAI = Beck Anxiety Inventory, BDI II = Beck Depression Inventory II, BSI = Brief Symptom Inventory, CGI = Clinical Global Impression.
$p < .05$: significant*, $p < .01$: very significant**, $p < .001$: highly significant***.
$\eta_p^2 = .01$: small effect, $\eta_p^2 = .06$: medium effect*, $\eta_p^2 = .14$: large effect**.
[a] Factor time: follow-up period: t10 and t11.
[b] Factor group: DCS vs. PBO.



Abbreviations: DCS = D-Cycloserine, PBO = Placebo, PAS = Panic and Agoraphobia Scale, BSI = Brief Symptom Inventory.
* = significant (p<.05)
** = very significant (p<.01)
*** = highly significant (p<.001)

Fig. 4. Interaction effects in follow-up period for different sub-groups.

1976; Lovibond and Shanks, 2002). DCS could be especially effective in subgroups of patients who display more psychopathology, experience stronger fear in exposure and profit from psychotherapy primarily by amygdala-mediated processes involving NMDA-receptors (~habituation). In contrast, slightly anxious patients are often surprised about the lack of fear during exposure. They usually profit from psychotherapy by means of higher order cognitive processes like the insight about their exaggerated anticipatory anxiety (~cognitive restructuring) (Grillon, 2009). Current studies showing no or only little effects of DCS augmentation in slightly ill patients as well as patients with less anxiety or habituation during exposure support this hypothesis (de Kleine et al., 2012; Hofmann et al., 2013b; Litz et al., 2012; Rodrigues et al., 2014; Rothbaum et al., 2014; Siegmund et al., 2011; Smits et al., 2013b, 2013c). Moreover, neither subclinical nor healthy populations profited from DCS augmentation (D'Souza et al., 2000; Guastella et al., 2007a; Guastella et al., 2007b; Otto et al., 2009). Precisely, it could be postulated: the stronger and more pathological the anxiety, the more lower-order cognitive learning processes were involved at acquisition of fear and are targeted by exposure, and the higher is the effect of DCS.

Moreover, the finding of the exploratory differential DCS effect was only apparent in the FU period. Even more intriguing, also Hofmeijer-Sevink et al. (2017) found post-exposure administration of DCS to be superior only during the 3-month FU period. This could further consolidate the notion that DCS potentially enhances learning processes even with a temporal distance to its actual intake. DCS might not only facilitate the consolidation of extinction learning but also deter rapid reacquisition of fear. During the 1-month FU period our patients were most likely repeatedly confronted with anxiety provoking stimuli without the support of weekly sessions with their therapists. DCS administration might have led to more resistant consolidation of new functional behavior rendering those patients less vulnerable to relapse phenomena, such as return of anxiety and avoidance, compared to PBO.

There are animal studies on drug-cue extinction where DCS administration slowed down the reacquisition of drug conditioned place preference (Groblewski et al., 2009; Nic Dhonnchadha et al., 2010). Also, Ebrahimi et al. (2017) found in their fMRI study that DCS-augmented extinction attenuated amygdala activation during recall of the extinguished cue. It could be shown on a neuronal level that DCS administration compared to PBO reduced the reactivation effect. Translated to a clinical context this could point to a protective aspect of DCS augmentation. By enhancing the consolidation of extinction learning and attenuating amygdala activation when re-confronted with anxiety provoking stimuli DCS could possibly reinforce patients in their new functional behavior and decrease risk of relapse to old avoidance strategies - an interesting hypothesis which deserves further investigation.

This study is not without limitations. There was no long-term FU period beyond 1 month, limiting the results in terms of understanding the durability of treatment effects and possible benefits of DCS on longer term functioning. A second limitation concerns the DCS effect in the FU period which originated from exploratory post hoc analyses in small patient samples. The observed interactions in the three subgroups of patients may have been caused by other confounding unmeasured variables. Accordingly, these results are not generalizable and can merely serve as indicators for future research.

5. Conclusions

Most importantly, the present study failed to find an overall augmentative effect of DCS when administered after exposure sessions to agoraphobic patients. This is consistent with emerging research suggesting that DCS may be beneficial only under specific conditions or for certain sub-groups of patients. The lack of a DCS effect for the whole patient sample might be explained by a dual mechanism in fear conditioning and extinction with different cognitive processes being involved during exposures depending on the degree of anxiety experienced by the patient. Future research should therefore focus on further clarifying the specific and differential working mechanism of DCS.

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