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ARTICLE

Optimizing behavior therapy for youth with Tourette's disorder

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Tourette's Disorder (TD) is characterized by tics that cause distress and impairment. While treatment guidelines recommend behavior therapy as a first-line intervention, patients with TD may exhibit limited therapeutic response. Given the need to improve treatment outcomes, this study examined the efficacy of augmenting behavior therapy with D-cycloserine (DCS) to reduce tic severity in a placebo-controlled quick-win/fast-fail trial. Twenty youth with TD completed a baseline assessment to characterize tic severity, premonitory urges, medical history, and psychiatric comorbidity. Youth were randomly assigned to receive a single session of habit reversal training (HRT) augmented by either 50 mg of DCS or placebo. Two bothersome tics on the Hopkins Motor/Vocal Tic Scale (HM/VTS) were targeted for treatment during HRT. One week after the HRT session, youth completed a posttreatment assessment to evaluate change in the severity of bothersome tics. All assessments were completed by independent evaluators masked to treatment group. There was a Treatment Group by Time Interaction in favor of DCS-augmented HRT ($p < 0.01$), controlling for baseline tic severity, tic medication, and attention deficit hyperactivity disorder. Follow-up comparisons revealed small group differences at the treatment visit ($d = 0.27$), with the DCS group exhibiting slightly greater severity for targeted tics. There was a large group difference at posttreatment, in which the DCS group exhibited lower severity for targeted tics ($d = 1.30$, $p < 0.001$) relative to the placebo group. Findings demonstrate the preliminary enhancement of tic severity reductions by augmenting HRT with DCS compared with placebo augmentation.

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INTRODUCTION

Tourette's Disorder and persistent tic disorders (collectively referred to as TD) are neuropsychiatric conditions characterized by recurrent motor and/or vocal tics. For many patients with TD, the severity of tics causes impairment and contributes to a poor quality of life [1]. Behavior therapy has shown considerable efficacy for reducing tic severity [2], which has led to its recommendation as a first-line treatment across professional organizations [3, 4]. However, evidence suggests that only 50% of youth with TD exhibit a positive treatment response and many treatment responders continue to experience bothersome tics [5]. Thus, it is critical to investigate strategies that improve therapeutic outcomes from behavior therapy for patients with TD.

Behavioral therapies like habit reversal training (HRT) and comprehensive behavioral intervention for tics recognize the neurological origin of tics, but highlight that tic expression is influenced by internal and external factors [6]. Prominently, many patients with TD experience aversive premonitory urges that are temporarily relieved by the expression of tics. Consequently, this urge-tic association becomes negatively reinforced and strengthened due to the reduction of premonitory urge distress. This model receives empirical support from experimental studies [7], tic suppression studies [8], and provides evidence that tic expression is influenced via associative learning and reward learning processes.

In behavior therapy, treatment emphasizes building awareness to early tic warning signs like premonitory urges (awareness training) and implementing competing responses contingent upon identified early tic warning signs (competing response training), which prevents tic expression and its associated urge relief. These therapeutic exercises facilitate the formation of a new learned association (urge-competing response) to both inhibit the initial tic association (urge-tic response) and discontinue the negative reinforcement cycle between tic expression and urge reduction. Therefore, treatment strategies that strengthen the formation of new learned associations (i.e., urge-competing response) may make behavioral therapies more effective at inhibiting the urge-tic association and reduce the severity of tics.

One approach to strengthen associative learning during treatment involves pairing therapeutic skills with cognitive enhancers. Translational research suggests that cognitive enhancers like D-cycloserine (DCS) strengthen newly learned associations in animal studies [9, 10] and show promise to improve treatment outcomes when combined with cognitive behavioral therapy (CBT) [10–12]. While prior studies have focused on enhancing therapeutic outcomes in anxiety disorders, post-traumatic stress disorder, and obsessive-compulsive disorder (OCD) [10–12], the combination of DCS and behavior therapy may efficiently strengthen the formation of therapeutic associations (urge-

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competing response) to inhibit initial associations (urge-tic associations) to reduce the severity of tics.

We examined the efficacy of augmenting behavior therapy with DCS in a randomized controlled quick-win/fast-fail trial for youth with TD. Given the focus on individual tic associations, our a priori outcome was the reduction in tic severity for bothersome tics targeted in behavior therapy. We also explore reductions in tic severity for all bothersome tics, and reductions in premonitory urge severity.

METHODS

Participants

Twenty youth were enrolled in the parallel group randomized controlled trial. To participate youth had to be: 8–17 years old; have TD or a Persistent Motor Tic Disorder; a total tic severity score ≥14 on the Yale Global Tic Severity Scale (YGTSS; or ≥10 for youth with only motor or vocal tics); and medication free or taking a stable dose of psychiatric medication for at least 6 weeks. Youth were excluded from participation if they had any of the following: a medical condition contraindicated for DCS; a lifetime diagnosis of schizophrenia, bipolar disorder, psychosis, or autism spectrum disorder; greater than four sessions of behavior therapy; or were taking an antipsychotic medication. Participants were predominantly male, White, and exhibited moderate tic severity on the YGTSS (see Table 1). Most youth had a diagnosis of TD, and 35% were taking an alpha-agonist. Co-occurring psychiatric conditions included ADHD, anxiety disorders, and oppositional defiant disorder (see Table 1).

Measures

Yale Global Tic Severity Scale (YGTSS) [13]. The YGTSS is a clinician-administered scale that measures global tic severity. It has excellent psychometric properties of reliability and validity [13–15].

Hopkins Motor Vocal Tic Scale (HM/VTS) [16]. Participants nominated up to five motor and five vocal bothersome tics at baseline and these tics were reassessed at the treatment and posttreatment visits. Clinicians rated the severity of bothersome tics on a five-point scale: (0) none, (1) mild, (2) moderate, (3) moderate–severe, and (4) severe. Ratings incorporated the frequency, forcefulness, interference, and distress of each tic. The HM/VTS has demonstrated good reliability, validity, and treatment sensitivity to behavior therapy [16, 17].

Individualized Premonitory Urge for Tics Scale (I-PUTS) [18]. The I-PUTS is a clinician-administered measure that assesses the frequency and intensity of premonitory urges for individual tics. After identifying the presence of an urge for each tic, raters inquire about the frequency (1 = "Urge occurs 0–25% of the time" to 4 = "Urge occurs 75–100% of the time") and intensity (1 = "Minimal Intensity" to 4 = "Strong intensity") of each endorsed urge on a four-point scale. Items are summed to create a total urge frequency (I-PUTS Frequency) and intensity (I-PUTS Intensity) score [18].

Session summary sheet. Therapists completed a session summary sheet that included information about the fidelity of HRT delivered for the two tics that were targeted for treatment on the HM/VTS. Following the instruction of HRT skills, therapists were asked to rate participants' ability to implement the identified competing response contingent upon early tic detection (e.g., premonitory urge, early tic movements) for each tic on a Likert-type scale that ranged from poor (1) to excellent (7). Therapists also assigned formal practice of HRT skills following the therapy session, and

Table 1. Demographic and Clinical Characteristics at Baseline for Participants ($N = 20$).

	All Participants ($N = 20$)	DCS Group ($n = 9$)	Placebo Group ($n = 11$)		
	N (%)	*N* (%)	*N* (%)	χ^2	*p* value
% White	11 (55%)	6 (67%)	5 (45%)	0.90	0.34
% Male	17 (85%)	9 (100%)	8 (73%)	2.89	0.09
% On tic medication (clonidine, guanfacine)	7 (35%)	5 (56%)	2 (18%)	3.04	0.08
% On other psychiatric medication[a]	5 (25%)	4 (44%)	1 (9%)	3.30	0.07
Tic disorder diagnosis[b]					
Tourette's disorder	16 (80%)	8 (89%)	8 (73%)	0.81	0.37
Persistent motor tic disorder	4 (20%)	1 (11%)	3 (27%)		
Co-occurring psychiatric conditions[b]					
Attention deficit hyperactivity disorder	6 (30%)	4 (44%)	2 (18%)	1.63	0.20
Any anxiety disorder	5 (25%)	2 (22%)	3 (27%)	0.07	0.80
Oppositional defiant disorder	2 (10%)	2 (22%)	0 (0%)	2.72	0.10
	Mean (SD)	Mean (SD)	Mean (SD)	*t*	
Age	10.90 (1.83)	11.33 (1.87)	10.55 (1.81)	0.95	0.35
Total Targeted Tic Score on the HM/VTS	4.95 (1.22)	5.00 (1.12)	4.90 (1.37)	0.17	0.87
Overall Bothersome Total Tic Score on the HM/VTS	11.95 (4.60)	13.89 (5.69)	10.20 (2.53)	1.79	0.10
YGTSS Total Tic Score	19.90 (5.16)	21.89 (6.05)	18.27 (3.85)	1.63	0.12
YGTSS Impairment Score	22.50 (7.16)	21.11 (7.41)	23.64 (7.10)	0.78	0.45
I-PUTS frequency of premonitory urges	7.84 (8.43)	9.63 (7.21)	6.55 (9.33)	0.78	0.45
I-PUTS intensity of premonitory urges	6.95 (8.34)	9.13 (7.10)	5.36 (9.12)	0.97	0.35

DCS D-cycloserine, *YGTSS* Yale Global Tic Severity Scale.
[a]Psychiatric medications included the following: Strattera, Celexa, Zoloft, Remeron, Fluoxetine.
[b]Psychiatric diagnoses were determined by using the Anxiety Disorders Interview Schedule-Child and Parent Report. Any anxiety disorder included the following conditions: social anxiety disorder, generalized anxiety disorder, specific phobia.

collected parent report of the formal practice time completed over the intervening week between the treatment session and posttreatment visit.

Procedures

Study procedures were approved by the local institutional review board, and the trial was registered on ClinicalTrials.gov prior to initiating enrollment (NCT02582515). The study took place at the University of California Los Angeles from October 2015 to August 2017. Study enrollment was anticipated to be 20 participants during the recruitment period. This would provide adequate power (power = 0.80) to detect medium-sized effects, but would have less power to detect smaller effects. After obtaining consent, participants completed a baseline assessment to characterize medical history, psychiatric diagnoses, global tic severity (YGTSS), bothersome tic severity (HM/VTS), and urge severity (I-PUTS). One week later, participants completed the treatment visit. During this visit, bothersome tics severity (HM/VTS) and premonitory urge severity (I-PUTS) were reassessed. Next, participants were randomly assigned to receive 50 mg of DCS or placebo which was taken immediately. The randomization sequence was created using a random number generator with a 1:1 allocation, and only the research assistant and study pharmacist were aware of participants' randomization assignment. Afterward, participants received psychoeducation about TD and the neurobehavioral treatment model underlying behavior therapy. Following procedures comparable with other DCS studies [19], HRT procedures were initiated 1 h after ingesting DCS/placebo. Two bothersome tics on the HM/VTS were targeted for treatment during this 1-hour HRT session. Therapists' rated the participants' ability to implement HRT skills for the two bothersome tics targeted for treatment on the session summary sheet. One week after the treatment visit, participants returned for the posttreatment assessment to determine the occurrence of any adverse events using a standardized form, inquire about the amount of time spent formally practicing HRT skills, and evaluate reductions in bothersome tic severity (HM/VTS) and premonitory urge severity (I-PUTS). Participants, parents, therapists, and independent evaluators who administered study assessments (i.e., YGTSS, HM/VTS, and I-PUTS) were all masked to treatment assignment.

Analytic plan

T-tests and chi-square tests were performed to evaluate baseline group differences between the DCS and placebo groups. Next, participants' abilities to implement HRT skills for targeted tics and amount of time spent formally practicing HRT skills were compared between treatment groups. The primary outcome was the change in tic severity for the two bothersome tics nominated for treatment on the HM/VTS (range: 0–8). In addition, we evaluated the change in tic severity for all bothersome tics nominated on the HM/VTS (range: 0–40). Finally, we explored whether group differences emerged for urge frequency and urge intensity on the I-PUTS. The tic severity ratings for bothersome tics (HM/VTS) and premonitory urges (I-PUTS) were examined using a fixed-effects repeated-measures analysis that controlled for baseline tic severity, co-occurring ADHD and alpha-agonist medication, which have been found to influence tic severity outcomes in behavior therapy [2, 20]. The Greenhouse–Geisser correction for sphericity was applied. Our model included one between-group factor (DCS versus placebo), tic severity, co-occurring ADHD and tic medication were entered as covariates, and the repeated measure was time (treatment and posttreatment).

RESULTS

Baseline characteristics

Table 1 presents baseline characteristics for the DCS and placebo groups. There were no differences between groups on demographic or clinical characteristics. One participant in the placebo group dropped out prior to the treatment visit (5% attrition, see Fig. 1), which is comparable with prior behavior therapy studies of youth with TD [5].

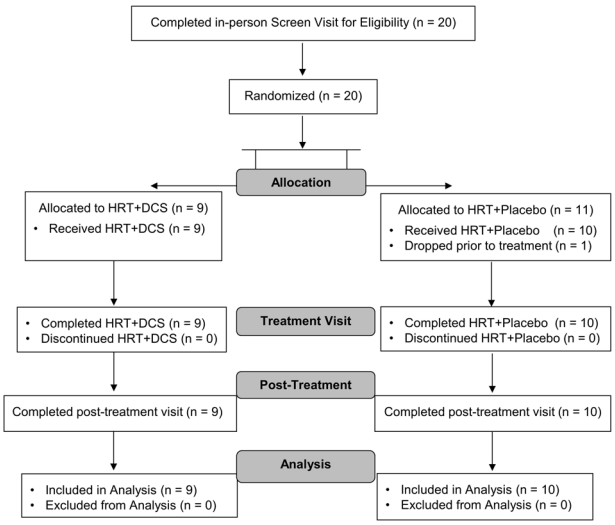

Fig. 1 CONSORT diagram of participant flow through the trial. HRT habit reversal training; DCS D-cycloserine.

Implementation of HRT

Participants demonstrated good abilities to implement competing responses contingent upon early tic detection for tics targeted in the HRT session ($M = 5.18$, $SD = 0.99$) and reported some practice of HRT skills between the treatment and posttreatment visit ($M_{minutes} = 117.36$, $SD_{minutes} = 63.05$). There was no significant difference between treatment groups on HRT implementation abilities for tics targeted in treatment ($t = 0.16$, $p = 0.88$, $d = 0.07$) or amount of time dedicated to formal HRT practice between the treatment and posttreatment visits ($t = 0.46$, $p = 0.66$, $d = 0.25$).

Tic severity reductions for tics targeted in behavior therapy

There was a significant Treatment Group by Time Interaction for tics targeted in behavior therapy (see Table 2). Follow-up comparisons revealed small differences between groups at the treatment visit, but large differences at the posttreatment visit in favor of the DCS group ($d = 1.28$, see Table 3 and Fig. 2).

Tic severity reductions for all bothersome tics

The Treatment Group by Time Interaction for all bothersome tics did not reach statistical significance ($p = 0.07$, see Table 2), but displayed a similar pattern to the targeted tic analyses. Specifically, small groups differences were identified at the treatment visit, with larger group differences found at the posttreatment visit in favor of the DCS group ($d = 0.88$, see Table 3).

Premonitory urge frequency and intensity

The Treatment Group by Time interaction was significant for premonitory urge frequency. Follow-up comparisons revealed small group differences at the treatment visit, but large differences at posttreatment in favor of the DCS group ($d = 1.07$, see Table 3). Meanwhile, the Treatment Group by Time interaction for urge intensity was not statistically significant ($p = 0.13$, Table 2), but is qualified by a main effect for treatment group that shows group level differences across time points ($p = 0.02$). While there was a moderate-to-large difference between treatment groups at the treatment visit ($d = 0.76$), the DCS group exhibited a decline in urge intensity by the posttreatment visit whereas the placebo group did not (see Table 3). This resulted in a large group

Table 2. Repeated-measures fixed-effects model for change in tics severity and premonitory urge severity.

	Targeted tics		All bothersome tics		I-PUTS frequency		I-PUTS intensity	
	F	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Treatment group	2.71	0.122	1.53	0.24	1.44	0.25	7.36	0.02
Baseline severity	21.43	<0.001	66.27	<0.001	129.30	<0.001	199.23	<0.001
ADHD	0.002	0.97	0.36	0.56	0.50	0.49	0.12	0.73
Tic medication	3.98	0.07	3.24	0.09	0.001	0.98	2.60	0.13
Time	0.95	0.35	1.45	0.25	1.69	0.22	0.25	0.62
Time × baseline severity	4.49	0.05	2.60	0.13	2.22	0.16	2.28	0.16
Time × ADHD diagnosis	0.04	0.85	0.11	0.74	0.03	0.87	1.71	0.21
Time × tic medication	15.55	<0.001	2.61	0.13	3.43	0.09	0.00	0.99
Time × treatment group	13.83	0.002	3.99	0.07	7.34	0.02	2.60	0.13

Presented model estimates control for ADHD diagnosis and tic medication presence at baseline.

Table 3. Tic severity estimates for treatment × time interaction on the HM/VTS and I-PUTS.

	DCS group		Placebo group		
	Mean	SE	Mean	SE	Effect size[a]
Average bothersome tics targeted in treatment on HM/VTS					
Treatment	5.01	0.20	4.93	0.19	0.14
Post-treatment	2.41	0.39	3.83	0.37	1.28
Average of all bothersome tics on HM/VTS					
Treatment	11.30	0.37	11.23	0.35	0.07
Post-treatment	6.82	0.74	8.66	0.70	0.88
Frequency of premonitory urges					
Treatment	8.64	1.02	8.69	0.90	0.02
Post-treatment	5.99	1.10	9.21	0.97	1.07
Intensity of premonitory urges					
Treatment	7.00	0.81	8.70	0.72	0.76
Post-treatment	5.03	1.01	9.08	0.89	1.47

Fixed-effects model estimates are presented controlling for ADHD diagnosis and tic medication presence at baseline.
HM/VTS Hopkins Motor/Vocal Tic Scale, *I-PUTS* Individualized Premonitory Urge to Tic Scale.
[a]Between-group effect sizes were calculated for each time point using standard error.

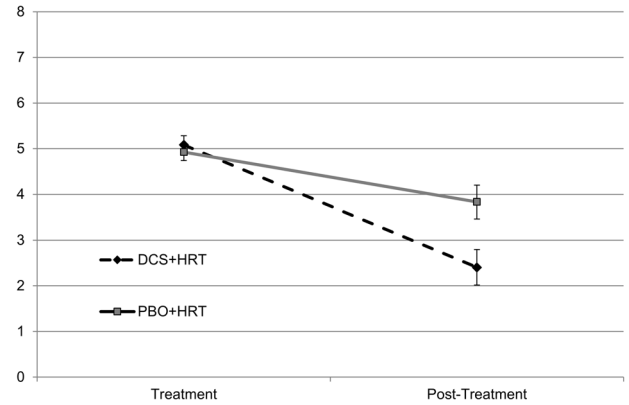

Fig. 2 Treatment by Time Interaction for Tics Targeted in Habit Reversal Training on the Hopkins Motor/Vocal Tic Scale, controlling for baseline tic severity on the HM/VTS, co-occurring ADHD and tic medication status. The DCS+HRT (black) and PBO+HRT (grey) had comparable tic severity for the two bothersome tics at the start of the treatment visit, the DCS+HRT group (black) exhibited greater improvement one week later in comparison to the PBO +HRT group (grey).

difference at the posttreatment visit ($d = 1.47$), which was nearly twice the difference observed at the treatment visit.

Adverse effects

Three participants in the DCS group reported adverse effects in the past week, which appeared unrelated to DCS. These included drowsiness ($n = 1$), difficulty falling asleep ($n = 1$), and a sore throat ($n = 1$). No adverse events reported in the placebo group.

DISCUSSION

This study provides initial evidence that augmenting HRT with DCS produces greater severity reductions for tics targeted in treatment, compared with augmentation with placebo. A similar pattern was observed for all bothersome tics, but did not achieve statistical significance.

While findings highlight the possibility for enhancing tic severity reductions, this trial only used a single session of HRT. Therefore, a larger multi-session clinical trial is critical to determine the optimum number of DCS-augmented behavior therapy sessions and evaluate the durability of its therapeutic effect. While early pilot studies demonstrated similar promising effects for DCS augmentation in related conditions like OCD [21], later definitive trials did not find these effects [22]. However, there are some notable distinctions between these two conditions in regards to the efficacy of evidence-based treatments. Specifically, therapeutic outcomes are fairly large for exposure-based CBT with or without DCS [22, 23]. As a result, there is limited room to enhance current treatment outcomes to achieve clinical and/or statistical significance. In comparison, only 50% of youth with TD exhibit a positive treatment response and many treatment responders continue to experience bothersome tics [5, 17]. Indeed, as a treatment response in TD is associated with a 25–35% reduction in tic severity [24, 25], there is clear room to detect and enhance therapeutic outcomes.

The mechanism by which tic severity was reduced in this study is an important consideration. Evidence suggests that DCS does not broadly enhance motor learning [26] nor do glutamatergic modulators like DCS directly reduce tic severity [27]. In behavior therapy, patients develop new compensatory association (e.g.,

urge-competing response) to inhibit prior associations that maintain tic expression (e.g., urge-tic). It is likely that the compensatory associations learned in HRT are strenghtened when developed in the presence of DCS compared with placebo. This type of associative learning in which one association inhibits another association—extinction learning—would result in the greater inhibition of tic expression and reductions in tic severity, which was observed in this study. However, the related process of reversal learning may also play a role. Broadly, reversal learning is the ability to actively suppress reward-related responding to disengage an ongoing behavior and adapt to a new reward contingency. In behavior therapy, participants learn to disengage from expressing tics that alleviate premonitory urges (i.e., disengage from an ongoing behavior) and implement a new compensatory behavior to inhibit tic expression that is subsequently positively reinforced (i.e., adapting to a new reward contingency). Indeed, evidence from preclinical studies suggest that DCS may enhance both extinction learning and reversal learning processes [10, 28, 29].

While the specific mechanism requires further research, the learned associations acquired in HRT serve to disrupt the negative reinforcement cycle that maintains tic expression. In doing so, the frequency and intensity of premonitory urges becomes diminished over time and the cycle maintaining tic expression discontinued. This is supported by observations that the DCS group exhibited greater reductions in urge frequency relative to those in the placebo group, with a similar pattern observed for urge intensity that did not achieve statistical significance due to group level differences. A multi-session clinical trial can test the mechanisms (e.g., extinction learning, reversal learning) that are enhanced by DCS during behavior therapy and result in reduced tic severity and premonitory urge severity.

While this quick-win/fast-fail trial has several strengths (e.g., quadruple blinded study), a few limitations are present. First, youth on antipsychotic medications were excluded from participation. Antipsychotic and alpha-agonist medications are common pharmacological interventions to reduce tic severity [3]. However, concurrent antipsychotic medications were excluded to minimize potential confounds, as prior studies have shown that DCS has some interactive effects when administered alongside antipsychotic medications in adults [30, 31]. No such interactive effects were identified for alpha-agonists, which were permitted for inclusion to improve the generalizability of findings to clinical care. Future research should include youth on antipsychotic medications and incorporate medication status into randomization assignment. Second, this trial only utilized a single session of HRT and administered DCS 1 h prior to HRT procedures. Future research should test these promising findings in a multi-session HRT protocol and consider two key aspects of DCS dosing. Specifically, recent evidence shows that the therapeutic effects of DCS level off after about nine dose administrations and participants who received DCS doses more than 60 min before initiating treatment procedures exhibited greater therapeutic effects compared with DCS dose administrations 60 min or earlier [19]. Therefore, when designing and implementing a multi-session clinical trial, it will be important to have treatment be completed in fewer than nine sessions and administer DCS at an optimal time prior to initiating HRT. Third, we utilized the HM/VTS as the primary outcome measure. Although making conceptual sense due to the focus of HRT skills on specific bothersome tics, the scale has received minimal psychometric examination in comparison with gold standard scales like the YGTSS [13]. Furthermore, we did not include direct observation protocols of tic severity. Future research should examine changes in tic severity utilizing a multimodal assessment approach that includes bothersome tics (HM/VTS), global tic severity (YGTSS), and even tic observation protocols in a multi-session clinical trial. Finally, the sample is predominantly male and White. However, this is comparable with other clinical trials of behavior therapy for youth with TD [5].

In summary, augmentation of behavior therapy with DCS reduced tic severity to a greater degree compared with placebo augmentation and was well-tolerated. The evaluation of DCS in a multi-session behavioral treatment trial is needed to determine the precise mechanism (e.g., associative learning, reward learning) and duration of augmentation over multiple sessions to optimize behavior therapy outcomes for patients with TD.

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AUTHOR CONTRIBUTIONS

JFMG, JTMC, and JP contributed to the design of the study. JFMG, NG, KR, JKYE, EJR, JTMC, and JP contributed to the acquisition, analysis, and/or interpretation of the data for the work. JFMG, JTMC, and JP composed the initial draft of the work, and NG, KR, JKYE, and EJR contributed revisions and important intellectual content to the work. All authors approved the version of the paper, and agree to be accountable for all aspects of the work to ensure that any questions related to the accuracy or integrity are appropriately investigated and resolved.

ADDITIONAL INFORMATION

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