SUPPLEMENT

Long COVID Brain Fog Treatment: An Early-phase Randomized Controlled Trial of Constraint-Induced Cognitive Therapy Signals Go

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METHODS

Feasibility

The INCA and CTAL were used to track engagement by participants in CICT. The POS was used to assess participants' acceptance of CICT. Each is described below.

Inventory of New Cognitive Activities

The INCA was developed by this lab to track resumption of or improvement in a wide range of functional, cognition-based, activities outside the treatment setting. In this structured interview, participants report (a) resumption of any activities not performed since stroke onset, i.e., new activities, and (b) meaningful improvement in any activities since their last INCA interview. To verify their reports, participants are asked to demonstrate or explain how the activities are done. The number of new activities is counted on each interview occasion and added to the cumulative total from the previous occasion; the same is done for improved activities. An example of a completed INCA is provided in **Figure s1**.

SUPPLEMENT continues on next page.

Inventory of New Cognitive Activities (INCA)

EXAMPLE SUMMARY	Key: ***I*** = **Significant Improvement** | ***N*** = **New ability since treatment started** | ✓ = **Start of new or improved ability** | ✓✓ **and (#) = Further improvement of ability** | **X = Task improvement has dropped off** | • = **No further improvement noted** |					
SID: XXXX	**Treatment Day #:**	**TD # 5**		**TD # 8**		**TD # 12**	
ACTIVITY		***I***	***N***	***I***	***N***	***I***	***N***
Preparing and cooking full meals			✓	✓✓		•	
Looking for different recipes online			✓	•		•	
Meditation			✓	•		•	
Making a purchase					✓	•	
Reading music		✓		•		•	
Socializing with friends		✓		•		✓✓	
General socializing with strangers			✓	✓✓		✓✓	
Organizing group activities			✓	•		•	
Ability to watch and focus on TV program		✓		•		•	
Handwriting				✓			
Piano playing		✓		•		✓✓	
Learning a new language (Spanish)			✓	•		•	
Reading			✓	•		•	
Responding to questions		✓		•		•	
Daily Total:		**5**	**7**	**1 (2)**	**1**	**0 (3)**	**0**
Treatment Total:				**6 (2)**	**8**	**6 (5)**	**8**

Figure s1. **Example of completed INCA data collection form.**

Cognitive Task Activity Log

The CTAL is a structured interview that was modeled after the Motor Activity Log (MAL) and the Verbal Activity Log (VAL), both of which have rigorous evidence of validity (Haddad et al., 2017; Uswatte et al., 2006; Uswatte et al., 2005). Participants are asked to rate their degree of independence (Independence Scale) and quality of their performance (Quality Scale) on 24 cognition-based activities. The questionnaire is scored on a five-point scale (0=activity not done at all, 5=completed activity normally). The total score is the average of the Independence and Quality scores. **Tables s1** and **s2** show individual items and scales for CTAL, respectively.

Table s1. Cognitive Task Activity Log (CTAL) Items

Item	Description
1	Start a conversation with a person outside the home
2	Remember the day of the week
3	Organize medications to take
4	Pay attention to a task with several steps
5	Use a smartphone or computer to access multiple websites
6	Make a purchase using cash or a credit card
7	Remember appointments or events
8	Detailed and correct responses to questions
9	Look up a phone number or cell phone contact
10	Calculate a tip in a restaurant
11	Manage day-to-day purchases without overspending or forgetting (e.g., groceries)
12	Remembering personal effects (e.g., keys, wallet, purse)
13	Navigate to a location beyond walking distance
14	Remember to take meds according to directions
15	Follow or understand the plot of a movie
16	Use a keypad (e.g., remote, microwave)
17	Prepare food that includes at least three ingredients
18	Read and understand written text (e.g., magazine, book, newspaper)
19	Writing or typing multi-word messages (e.g., email, letter, note)
20	Remember PIN number (e.g., SmartPhone, debit card, security code)
21	Remember passwords for multiple websites
22	Locate an item on a file system, physical or computer
23	Check accuracy of an account balance or billing statement (e.g., checking, saving, Greenphire)
24	Put away items (e.g., clothes, linen)

Table s2. Cognitive Task Activity Log (CTAL) Quality and Independence scales

Score	Description
CTAL Quality Scale	
0	Activity not done at all (never)
1	Tried to do the activity, but was unable to complete it (very poor)
2	Sometimes completed the activity, but it was very slow or difficult (poor)
3	Routinely completed the whole activity, but it was slow or moderately difficult (fair)
4	Always completed the activity, but not as rapidly or easily as normal (almost normal)
5	Always completed the activity as well and as easily as normal (normal)
CTAL Independence Scale	
A. Prompt: Activity required prompting or reminder to start…	
0	All the time
1	Almost all the time
2	Most of the time
3	About half the time
4	Less than half the time
5	None of the time
B. Prompt: Activity requires assistance or supervision to complete…	
0	All the time
1	Almost all the time
2	Most of the time
3	About half the time
4	Less than half the time
5	None of the time

Note. Codes for recording “no” responses: (1) “I never do that activity, with or without help, because it is not relevant.” For example, a person does not have or use a smartphone or a computer. (assign N/A and drop the item in future administrations), (2) “Someone else did the activity for me.” (assign a “0”), and (3) “I sometimes do that activity but did not have the opportunity since the last time I answered these questions.” (carry-over last assigned number for that activity.)

If participants debate between two scores, they are allowed to choose a score in between (e.g., 3.5).

The CTAL Quality test score is the average of the 24 item scores.

The CTAL Independence scale is divided into two parts, A and B, that consist of two different questions. The CTAL Independence test score is calculated by taking the minimum of the question A and B scores for each item and then averaging these values. The CTAL Total test score is the average of the Independence and Quality test scores.

Participant Opinion Survey

The POS is a survey developed by this lab to assess participants' satisfaction with the treatment program. POS asks caregivers and patients to rate the treatment's difficulty, benefit, and satisfaction levels on a scale from 1 (not at all) to 7 (extremely) before and after the treatment (see **Table s3**).

Table s3. Participant Opinion Survey Items

Item	Description
	Participant Form
1	How difficult do you think your therapy program has been?
2	I believe that the therapy program has benefitted me.
3	How satisfied are you with your therapy program?
	Caregiver Form
1	I believe that the therapy program has benefitted the participant.

Note. For questions 1 and 3 in the participant form, a 7-point scale was used where 1 was "not at all" and 7 was "extremely". For question 2 in the participant form and question 1 in the caregiver form, response anchors were "strongly disagree" and "strongly agree" for 1 and 7, respectively.

Data Analysis

TAU Crossover to CICT

TAU group completed three baseline assessments prior to crossover to CICT; a fourth assessment was completed after CICT (see Figure 1). The third baseline assessment was chosen for comparison against post-treatment scores on all outcome measures as this accounted best for the cumulative practice effects of all baseline assessments. The small sample size (n = 4) precluded formal inferential statistical analysis. Instead, several descriptive statistics were calculated, i.e., the mean change from Baseline 3 to Post-treatment along with the corresponding *SD* and effect size index (d'). d' is the mean change divided by its *SD*; values ≥0.57 are considered large (Cohen, 1988). In addition, the number of participants with improvement greater than a minimal clinically important difference (MCID) was counted. Last, spaghetti plots were drawn.

RESULTS

Efficacy

Self-reports of Long COVID Symptoms

Results of Alternate Analysis of the Patient Health Questionnaire-9 (PHQ-9) Data

As noted in the **Data Analysis**, the PHQ-9 data were not distributed normally, which violated a requirement for standard analysis of covariance (ANCOVA). Hence, we conducted an ANCOVA test substituting ranks for raw scores. The latter detected a statistically significant advantage for Immediate-CICT over TAU; the test statistic and *p* value from this test are reported in the **Results**, along with the median post-treatment PHQ-9 score and corresponding inter-quartile range (IQR) in each group. At baseline, the median PHQ-9 score in the Immediate-CICT group was 15 (IQR = 8 – 21); the corresponding value in the TAU group was 12 (IQR = 10 – 15). To be transparent, we here report the standard ANCOVA test results, which were negative: *MD* = -5.1; *95% CI*, -10.7 - 0.4; $F(1,11) = .2$, $p = 0.07$; $d = -0.9$.

In-lab Tests of Cognitive Ability

Results of Alternate Analysis of the Symbol Digit Modalities Test (SMDT) Data

As noted in the **Data Analysis**, the SDMT data were not distributed normally, which violated a requirement for standard analysis of covariance (ANCOVA). Hence, we conducted an ANCOVA test substituting ranks for raw scores. The latter detected a statistically significant advantage for Immediate-CICT over TAU; the test statistic and *p* value from this test are reported in the **Results**, along with the median post-treatment SMDT score and corresponding IQR in each group. To be transparent, we here report the standard ANCOVA test results, which were negative: SDMT *MD* = 7.8; *95% CI*, -2.1 to 17.8; $F(1,10) = 3.1$, $p = 0.11$; $d=0.6$.

Crossover CICT Results

As noted, four TAU participants completed Baseline 3 testing and received CICT. **Table s4** shows mean pre- to post-CICT changes and corresponding effect sizes for these participants**. Figures s2-s9** display participant-level data for each outcome measure.

In the TAU group, outcome measure values were relatively stable across the three baseline assessments. The treatment response for TAU participants crossed over to CICT generally mirrored the findings from Immediate-CICT participants. After crossover to CICT, very large gains in performance of cognition-based activities in daily life were observed, along with very large improvements in brain fog and general cognitive ability. Large reductions were observed in fatigue and depressive and anxiety symptoms. Moderate gains were observed in cognitive processing speed. Three of four participants had clinically meaningful gains in performance of cognition-based activities in daily life and general cognitive ability. Two of the four had clinically meaningful gains in anxiety symptoms. All four TAU participants who were crossed over to CICT were unemployed before treatment. Afterwards, two of the four returned to work.

Table s4. Mean (*SD*) Test Scores of TAU Participants Before and After Crossover to CICT

Outcome	Baseline 3	Post-treatment	Change	Effect size (*d*′)	Improvement ≥ MCID[a]
COPM Performance scale, points, range 1-10	4.6 (2.3)	6.4 (2.2)	1.9 (1.2)	1.5	75%
COPM Satisfaction scale, points, range 1-10	3.1 (1.6)	5.9 (2.4)	2.8 (1.0)	2.8	75%
MCS, points, range 1-10	6.9 (1.6)	4.1 (1.1)	-2.8 (2.4)	-1.2	N/A
FAS, points, range 1-50	30 (11.2)	26 (11.5)	-4 (4.8)	-0.8	25%
PHQ-9, points, 0-27	11.8 (7.6)	8 (7.4)	-3.8 (4.3)	-0.9	25%
GAD-7, points, range 0-21	9.0 (5.4)	7.0 (4.1)	-2.0 (3.4)	-0.6	50%
SDMT raw scores, points, range 0-110	46 (14.8)	50.3 (9.5)	4.3 (8.5)	0.5	25%
MoCA, points, range 0-30	25.3 (2.6)	27.8 (2.1)	2.5 (1.3)	1.9	75%

Abbreviations: COPM, Canadian Occupational Performance Measure; MCS, Mental Clutter Scale; FAS, Fatigue Assessment Scale; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; SDMT, Symbol Digit Modalities Test; MoCA, Montreal Cognitive Assessment.

[a] This is the number of participants with improvement above the threshold for an MCID expressed as a percentage of the number of participants for whom data is available. No validated MCID is available for the MCS.

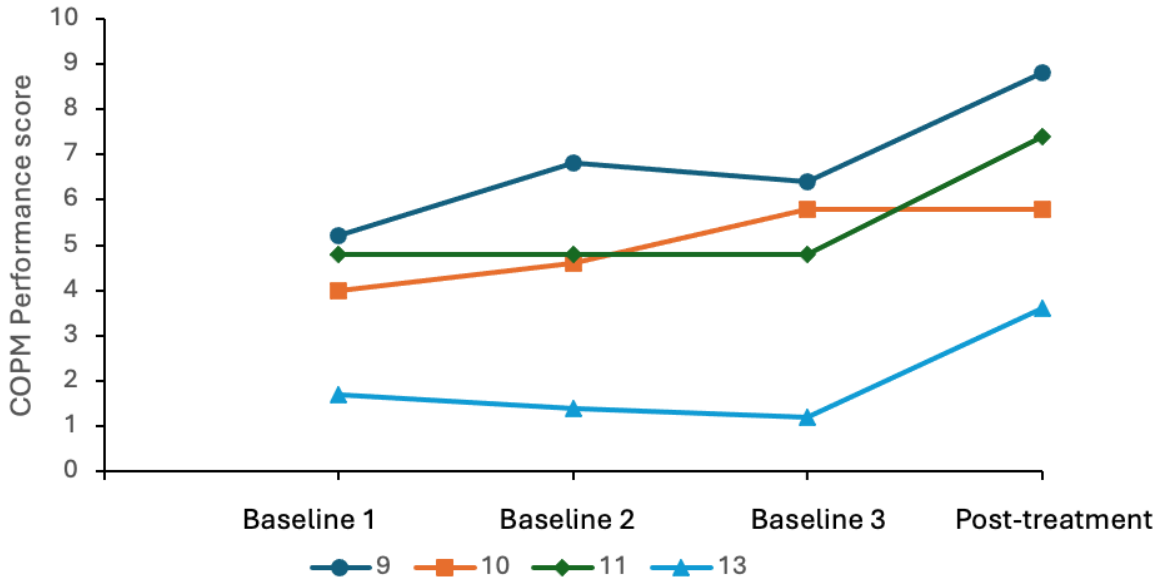

Figure s2. Canadian Occupational Performance Measure (COPM) Performance Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All but one showed improvement after crossover to CICT.

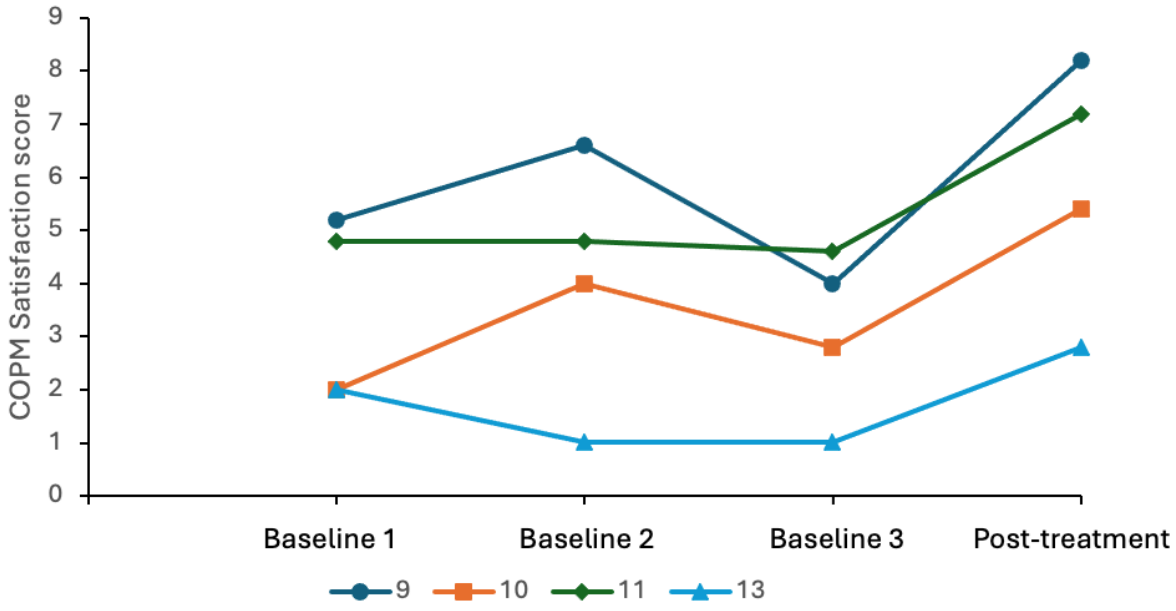

Figure s3. Canadian Occupational Performance Measure (COPM) Satisfaction Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All showed improvement after crossover to CICT.

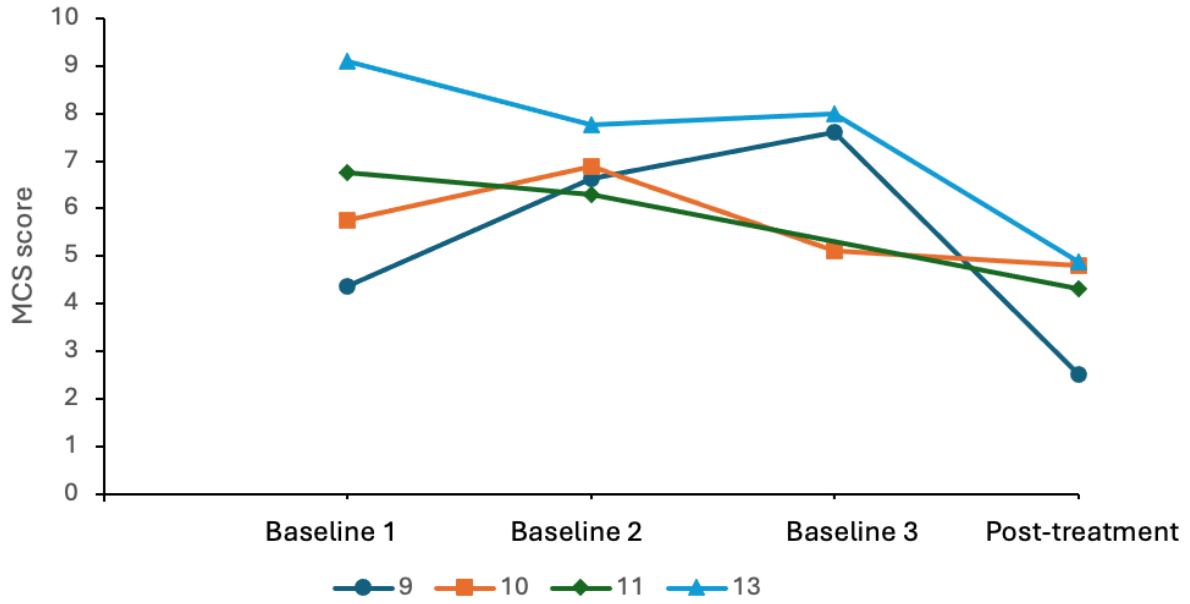

Figure s4. Mental Clutter Scale (MCS) Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All showed improvement after crossover to CICT.

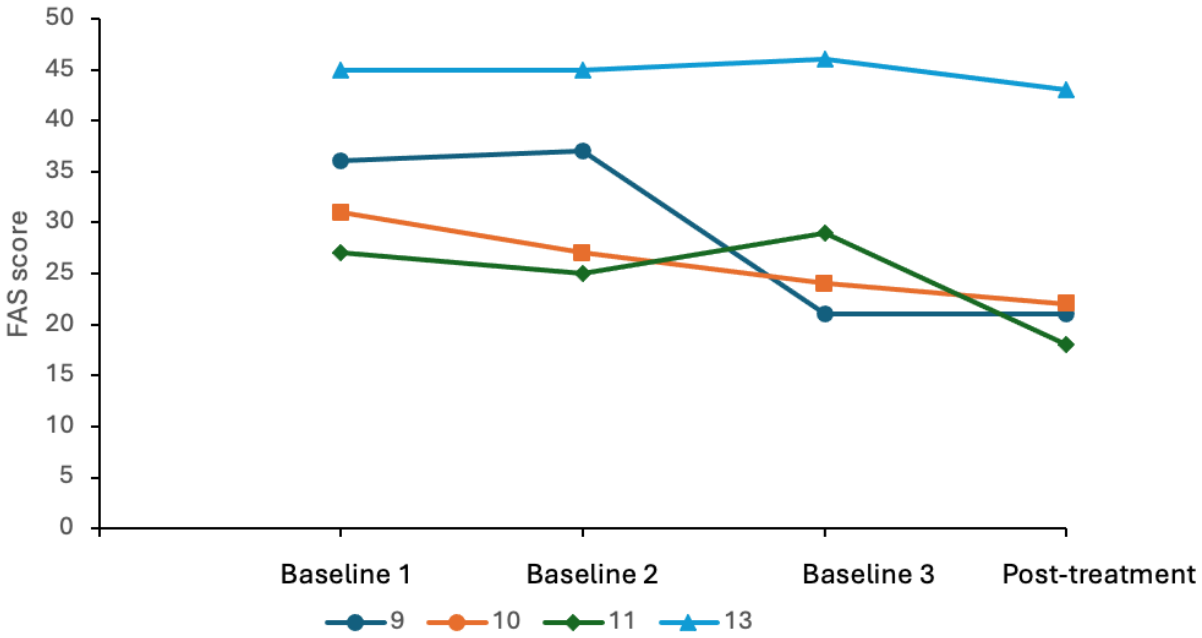

Figure s5. Fatigue Symptom Severity (FAS) Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to CICT. All but one showed improvement after crossover to CICT.

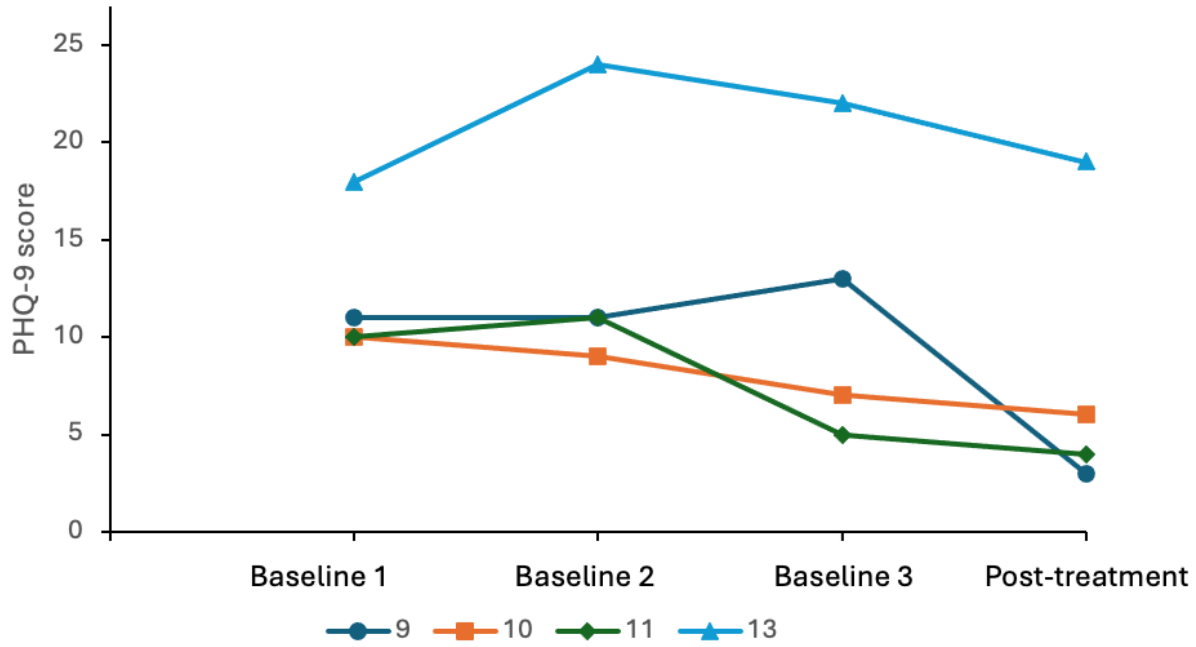

Figure s6. The Patient Health Questionnaire-9 (PHQ-9) Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All showed improvement after crossover to CICT.

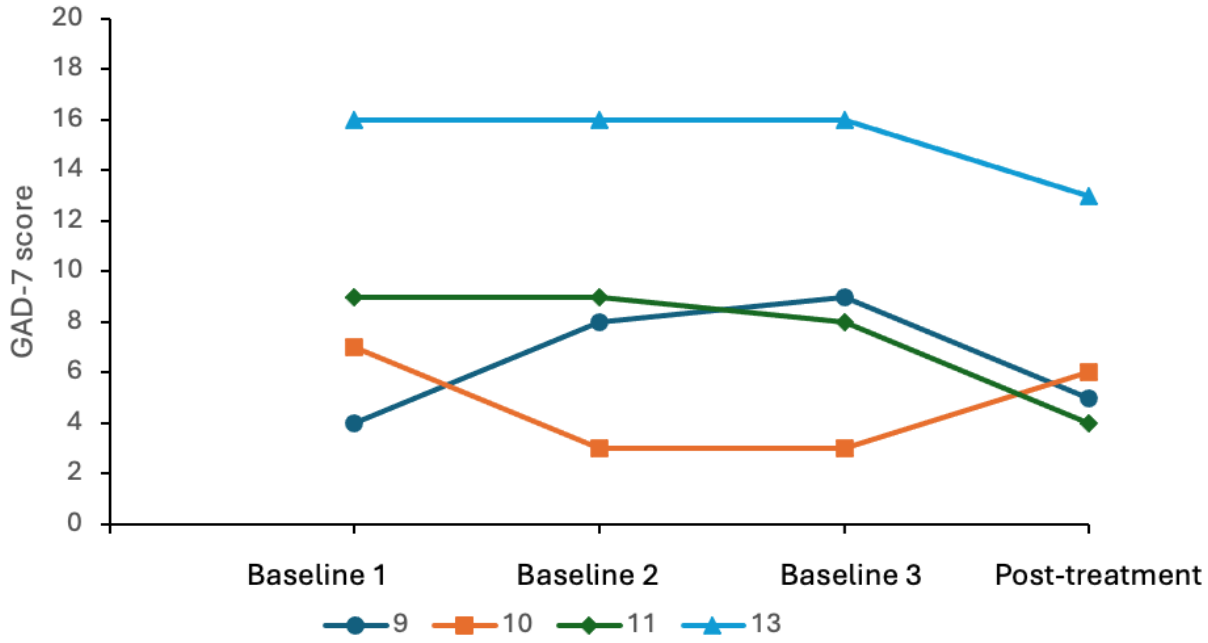

Figure s7. Generalized Anxiety Disorder-7 Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All but one showed improvement after crossover to CICT.

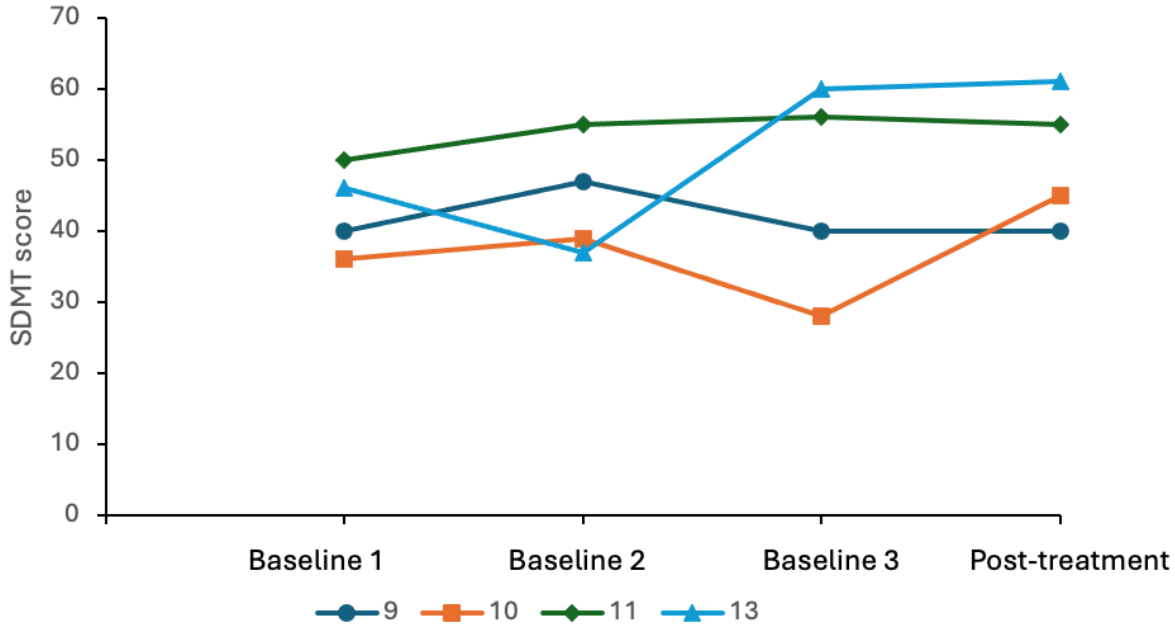

Figure s8. Symbol Digit Modalities Test (SDMT) Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). Half showed improvement after crossover to CICT.

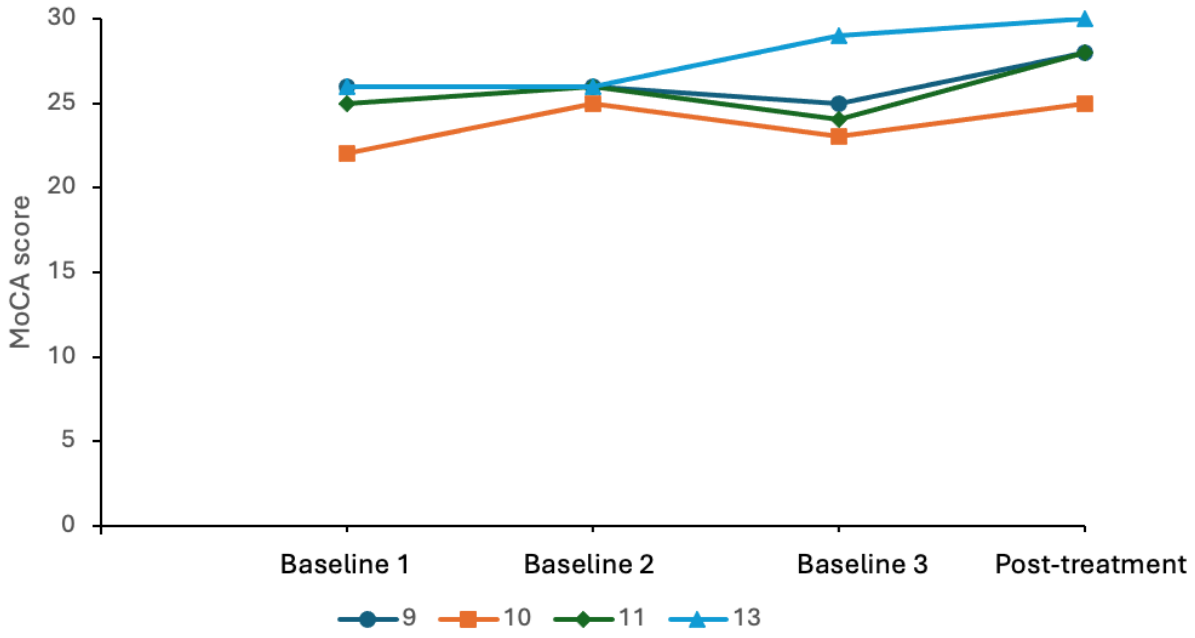

Figure s9. Montreal Cognitive Assessment Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All showed improvement after crossover to CICT.

REFERENCES

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