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

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ABSTRACT

Purpose: Long COVID brain fog is often disabling. Yet, no empirically-supported treatments exist. This study's objectives were to evaluate feasibility and efficacy, provisionally, of a new rehabilitation approach, Constraint-Induced Cognitive Therapy (CICT), for post-COVID-19 cognitive sequelae.

Design: Sixteen community-residents ≥ 3-months post-COVID-19 infection with mild cognitive impairment and dysfunction in instrumental activities of daily living (IADL) were enrolled. Participants were randomized to Immediate-CICT or treatment-as-usual (TAU) with crossover to CICT. CICT combined behavior change techniques modified from Constraint-Induced Movement Therapy with Speed of Processing Training, a computerized cognitive-training program. CICT was deemed feasible if (a) ≥80% of participants were adherent, (b) the same found treatment highly satisfying and at most moderately difficult, and (c) <2 study-related, serious adverse-events occurred. The primary outcome was IADL performance in daily life (Canadian Occupational Performance Measure). Employment status and brain fog (Mental Clutter Scale) were also assessed.

Results: Fourteen completed Immediate-CICT (*n*=7) or TAU (*n*=7); two withdrew from TAU before their second testing session. Completers were [*M* (S*D*)]: 10 (7) months post-COVID; 51 (13) years old; 10 females, 4 males; 1 African American, 13 European American. All the feasibility benchmarks were met. Immediate-CICT, relative to TAU, produced very large improvements in IADL performance (*M*=3.7 points, p<.001, *d*=2.6) and brain fog (*M*=-4 points, p<.001, *d*=-2.9). Four of five non-retired Immediate-CICT participants returned-to-work post-treatment; no TAU participants did, *p*=.048.

Conclusions: Those who received CICT adhered to the protocol and were highly satisfied with their outcomes. The findings warrant a large-scale RCT with an active-comparison group.

IMPACT

- Brain fog in adults with Long COVID is often associated with dysfunction in everyday activities and unemployment. Yet, there are no empirically supported treatments targeting cognition in this population. Findings from this small-scale, pilot randomized controlled trial (RCT) suggest that a novel intervention, i.e., Constraint-Induced Cognitive Therapy, is a feasible cognitive rehabilitation method in adults with Long COVID cognitive sequelae with promise of (a) improving performance of cognition-based tasks in daily life and (b) promoting return-to-work. Further studies with larger sample sizes are warranted.
- Speed of Processing Training (SOPT) has been shown to increase processing speed in older adults without neurological disorders but has not been applied to adults with brain fog due to Long COVID, in whom slowing of cognitive processing speed is common. The results of this pilot RCT suggest that SOPT, in conjunction with behavior change techniques, may increase cognitive processing speed in this brain-injured population.

KEYWORDS

Post-acute COVID-19 Syndrome, long COVID brain fog, cognitive rehabilitation, processing speed, employment

SUPPLEMENTAL MATERIALS

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INTRODUCTION

The worldwide spread of coronavirus disease 2019 (COVID-19) represents the largest pandemic since influenza B in 1935 (Wijdicks, 2008). Current estimates from the U.S. Centers for Disease Control and Prevention suggest that about 11% of those who contract COVID-19 develop chronic symptoms, i.e., “long COVID” or Post-Acute Sequelae of SARS-COV-2 (PASC) (Ford, 2023). The symptoms include “brain fog” and cognitive impairment, fatigue, anxiety, depression, and shortness of breath and other physical problems (Graham EL et al., 2021; Perrin et al., 2022). Increasing evidence suggests that CNS inflammation, along with microvascular and cellular damage, contribute to the neuropsychological symptoms (Boldrini et al., 2021).

Brain fog, which is the experience of confusion, forgetfulness, and sluggish thinking, and cognitive dysfunction are among the most common PASC symptoms (Graham EL et al., 2021; Hampshire A et al., 2021; Nouraeinejad, 2022). In a 56-country 2020 Internet survey (*N*=3,762), 85% of adults with PASC endorsed these two symptoms (Davis HE et al., 2021). In a U.S., nonprobability, population-based 2023 Internet survey (N=14,767), 57% of adults with PASC reported difficulty with at least one of the following: slowed thinking, decision-making, multi-tasking, memory, starting tasks, attention, and concentration (Jaywant et al., 2024). These perceptions are accompanied typically by mild impairments on neuropsychological tests of processing speed, executive function, memory encoding and recall, and phonemic and category fluency (Becker et al., 2021). Although the impairments detected by neuropsychological tests are mild, brain fog is disabling in many. Adults with PASC are less likely to have full-time jobs and more likely to be unemployed than before COVID-19 infection and report brain fog as the main cause of difficulties with work duties such as remembering routine tasks, learning new tasks, and communicating with others (Chasco et al., 2022; Perlis RH et al., 2023). Systematic reviews show that adults with PASC also have difficulties with performing everyday activities with important cognitive components, i.e., instrumental activities of daily living (IADL) (de

Oliveira Almeida K et al., 2023). Yet, there are no interventions in this population with evidence of ameliorating cognitive dysfunction from a randomized controlled trial (RCT) (Mathern et al.; Whitaker-Hardin et al., 2025).

Constraint-Induced Cognitive Therapy (CICT) is a new rehabilitation method that our laboratory has applied to stroke survivors with mild-to-moderate cognitive impairment with promising results (Uswatte et al., 2024). CICT combines two interventions: Speed of Processing Training (SOPT) and a modified version of the Transfer Package of Constraint-Induced Movement Therapy (CIMT) focused on cognition (Ball K et al., 2002; Ball K et al., 2007; Taub E et al., 1993; Taub et al., 2006; Wolf SL et al., 2006). For both interventions, efficacy is supported by multiple, single-site, randomized controlled trials (RCT) and several large multisite RCTs (SOPT, CIMT) (Ball K et al., 2002; Ball K et al., 2007; Taub E et al., 1993; Taub et al., 2006; Wolf SL et al., 2006). SOPT is computerized cognitive training that requires users to identify and locate targets on a monitor; cognitive load is increased as the user progresses by, for example, adding distractors (Ball K et al., 2007). Results from the largest-to-date RCT of cognitive interventions in community-dwelling older adults indicate that SOPT produces long-lasting benefits on in-lab tests of (a) cognitive processing speed and (b) IADL performance (Ball K et al., 2002; Edwards et al., 2002; Edwards et al., 2005; Rebok GW et al., 2014). Benefits are also present in improved driving in the real world (Ball et al., 2010). However, SOPT's impact on other cognition-based IADL outside of the lab is mixed (Uswatte et al., 2024). The Transfer Package contains behavior change techniques designed to transfer gains from the treatment setting to daily life (Gauthier et al., 2008; Taub et al., 2013). **Figure 1** sketches the mechanisms by which we think CICT operates.

Insert Figure 1 here

The large improvements observed in our stroke pilot, along with the overlap in stroke and PASC neuropathology and cognitive symptoms, including reduced cognitive processing speed, prompted us to test CICT in post-COVID adults with persistent brain fog accompanied by mild cognitive impairment and IADL dysfunction (Jaywant et al., 2021; Mahon et al., 2020; Nannoni et al., 2021; Uswatte et al., 2024). The pilot RCT described herein aims to evaluate the feasibility and efficacy, on a preliminary basis, of CICT for rehabilitating everyday cognitive function in this population. This study also explored the effects of CICT on in-lab tests of cognitive ability and self-reports of brain fog, fatigue, depressive and anxiety symptoms, which frequently accompany cognitive impairment in adults with Long COVID (Graham EL et al., 2021; Perrin et al., 2022).

METHODS

Study Design

Participants in this pilot RCT with an unblinded, open-label, parallel arm, partial-crossover design, were randomized in blocks of two by the project coordinator to receive CICT immediately or any treatment-as-usual (TAU) from healthcare providers. TAU participants were crossed over to CICT three months afterwards (see **Figure 2**). Random assignment was performed using a computer-generated random-numbers table, which the project data manager set up. In addition to assessing feasibility, outcomes were evaluated, on a preliminary basis, in three domains: (1) everyday cognitive activity performance, (2) participant-reported Long COVID symptoms, and (3) in-lab cognitive ability. The primary endpoint, which was in the first domain, was pre- to post-treatment change on the Canadian Occupational Performance Measure Performance Scale (see **Measures**). For Immediate-CICT participants, testing occurred before and after treatment. For TAU participants, testing occurred on parallel occasions (Baseline 1 & 2) during the TAU period and before and after crossover to CICT. The assessment battery (see **Outcomes**) at each testing occasion was the same. All the testing and

treatment took place in a clinical research facility at the University of Alabama at Birmingham (UAB), an urban academic medical center.

Insert Figure 2 here

Participants

Adults ≥3 months from their initial COVID-19 infection of any severity with brain fog symptoms were recruited from the UAB post-COVID clinic. In addition, a few candidates made contact after press reports about the lab's work. Inclusion criteria included some impairment in IADL per a Cognitive Task Activity Log score ≤3.5 (see **SUPPLEMENT**) and mild to moderate cognitive impairment. Mild cognitive impairment was defined by a score between 18 to 26 on the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005); moderate cognitive impairment was defined by a MoCA score between 10 to 17. Participants had to be community residents, have reliable transportation, be medically stable, and have adequate sight and hearing to complete testing. Individuals with pre-existing cognitive impairment, such as those with dementia, traumatic brain injury and stroke, were excluded, as were those with severe depression or frailty. Enrollment, which occurred from January 2021 to August 2022, was performed by the screeners.

Interventions

Constraint-Induced Cognitive Therapy (CICT)

Thirty-six hours of training were scheduled over 2 to 7 weeks depending on participants' needs, e.g., to manage fatigue or match the schedule of the family member transporting them to treatment. (**Table 1**). Each training session included SOPT (approximately 20%), in-lab training on IADL (35%), the Transfer Package (30%), and rest periods (15%). **Figure 3** diagrams a typical training session. Each treatment component is described below. **Figure 1** provides a conceptual model of how the components work together to improve performance of cognition-

based everyday activities by participants. Participants were not permitted to get any therapy for their Long COVID cognitive symptoms outside the study during the CICT treatment period.

Insert Table 1 here

Insert Figure 3 here

The *SOPT* software required that participants rapidly detect, identify, discriminate, and locate targets on a monitor in successive exercises, each more difficult than the previous one. On the first exercise, participants were asked to identify a target at the center of the monitor. On the second exercise, participants were asked to identify a central target and locate another target in the periphery. On the third exercise, distractors were added to the visual display. In addition, the target display time was decreased on each exercise as participants improve (Ball K et al., 2002; Ball K et al., 2007; Edwards et al., 2005).

In-lab IADL Training, along with the Transfer Package, was designed to bridge SOPT to performance of IADL outside the lab. After identifying challenging tasks in concert with the trainer, participants received training on the IADL following shaping principles. This involved approaching a behavioral objective in small steps with training chunked into brief, readily quantifiable, trials and provision of frequent positive reinforcement with no comment on errors (Skinner, 1938, 1968; Taub E et al., 1994). Performance time was recorded and shared with participants after each trial. Examples of tasks from the bank built by this laboratory were generating a shopping list, making an appointment calendar, and drafting a work email. New shaping tasks were designed when necessary to meet participants' needs and preferences. Task practice, which employs continuous, less easily quantifiable, tasks, was also used (Taub E et al., 1993; Wolf SL et al., 2006).

The *Transfer Package* here was a close analog for cognitive tasks of the Motor Transfer Package used in the studies described in the **Introduction**. The Transfer Package arranged contingencies of reinforcement with the objective of increasing the frequency with which participants engaged in IADL outside the treatment setting. The elements of the Transfer Package, e.g., goal-setting and self-monitoring, are commonly used to increase engagement in and adherence to the treatment protocol in behavioral therapies that target substance abuse and medication adherence (Bowers et al., 1987; Friedman, 1998; O'Farrell TJ, 1998). **Table 2** lists the Transfer Package elements and describes them at length (Gauthier et al., 2008; Taub et al., 2013).

Treatment-as-Usual

In the post-COVID clinic from which most of the participants were referred, all patients were seen by a neurologist by who ordered rule-out of secondary causes of cognitive changes, such as vitamin deficiency, hypothyroidism, sleep apnea and other sleep disorders. The patients were also evaluated for significant mood disorder and referred to psychiatry if appropriate. Evaluation of dysautonomia was performed if patients had other symptoms like postural dizziness and tachycardia in addition to cognitive changes. MRI scans of the brain were ordered if patients had focal neurologic symptoms or if there was clinical concern for a progressive neurodegenerative disorder. Neuropsychological testing was requested when symptoms persisted after correction of any identified secondary causes. This approach was common at post-COVID clinics at major medical centers across the U.S.A. during the enrollment period of this trial (Graham et al., 2022). An even more select group of clinics, in addition, offered cognitive rehabilitation and stress management training, including psychoeducation on sleep, nutrition, and relaxation methods (Graham et al., 2022; Rodriguez, 2023). However, outside of the small numbers with access to these specialty clinics, most with persistent post-COVID brain fog did not receive any treatment for their cognitive symptoms.

Feasibility

Adherence to and acceptance of CICT by participants were measured. Adherence was quantified by the number of treatment hours and homework tasks completed. Acceptance was assessed using an in-house survey, i.e., the Participant Opinion Survey (POS), which was completed by both the participant and a family caregiver, when available. The POS features 7-point scales that quantify satisfaction with, perception of benefit from, and difficulty of the intervention. This survey POS is described further in the **SUPPLEMENT**. Safety was monitored by logging adverse events in consultation with the project Medical Director (VWM). Benchmarks for these feasibility metrics are set in the **Data Analysis** section.

Several additional aspects of feasibility were assessed for which benchmarks were not set. Engagement in CICT was indexed by (a) the number of everyday activities resumed after starting treatment, which was measured with an in-house behavior log, the Inventory of New Cognitive Activities (INCA, see **SUPPLEMENT**), and (b) changes in how independently and how well everyday tasks were performed, which were measured with an in-house, structured, patient-centered interview, the Cognitive Task Activity Log (CTAL, see **SUPPLEMENT**) (Uswatte et al., 2024). Plus, we quantified the enrollment rate (total enrolled/enrollment period in months), recruitment rate (number enrolled/number screened), and drop-out rate (number of drop-outs/number randomized).

Outcomes

Performance of Everyday Activities

Canadian Occupational Performance Measure (COPM). This validated, widely-used, patient-centered, transdiagnostic, structured interview has been used to measure changes in self-rated occupational performance (e.g., self-care, productivity, and leisure) over time (Carswell et al., 2004; Cup et al., 2003). Here, five, self-selected activities with important cognitive components were rated on performance quality (Performance scale; 1=not able, 10=able to do it extremely well) and satisfaction (Satisfaction scale; 1=not at all, 10=extremely). A minimal clinically important difference (MCID) is 2 on each of these 10-point scales (Ohno et

al., 2021).

Employment status. Employment status was assessed at three points, (1) before COVID onset, (2) after COVID onset, (3) after CICT. Participants were assigned into one of the following categories: employed, unemployed, and retired. Participants also reported where they worked and whether they were able to fulfill their duties.

Self-reports of Long COVID Symptoms

Mental Clutter Scale (MCS). This 8-item self-report scale assesses the severity of brain fog symptoms. Respondents rate how frequently they experience 8 symptoms (e.g., fuzzy-headedness, cluttered thinking) using a 10-point scale (1=not at all, 10=all the time) (Leavitt & Katz, 2011).

Fatigue Assessment Scale (FAS). This self-report scale quantifies how frequently respondents experience ten fatigue symptoms with a 5-point scale (1=never, 5=always) (Michielsen et al., 2003). The FAS MCID is 4 (de Kleijn et al., 2011).

The *Patient Health Questionnaire-9(Kroenke et al., 2010)* (PHQ-9, max=27, MCID=5) assesses depressive symptom frequency (Löwe et al., 2004); the *General Anxiety Disorder-7*, (GAD-7, max=21, MCID=4) assesses anxiety symptom frequency (Spitzer et al., 2006; Toussaint A, 2020). Both are standard transdiagnostic measures (Kroenke et al., 2010; Löwe et al., 2004; Spitzer et al., 2006; Toussaint A, 2020).

In-lab Tests of Cognitive Ability

Symbol Digit Modalities Test -Oral Version: The *SDMT* is a standard, transdiagnostic measure of information processing speed (Costa et al., 2017; Jaywant et al., 2018). Participants are shown an array of abstract symbols along with a key pairing each unique symbol with a number from 1-9; participants are asked to say the number for each symbol in the array. The score is the number of symbols coded correctly in 90 seconds (max=110; MCID=8) (Weinstock et al., 2022).

Montreal Cognitive Assessment (MoCA). This standard, transdiagnostic, cognitive

screen assesses a broad array of cognitive functions (max=30, MCID=2) (Nasreddine et al., 2005).

Trainer and Tester Training

The intervention was delivered by a psychology doctoral student or the study coordinator, who has a bachelor's degree in kinesiology and > 20 years of experience delivering CIMT, with assistance from undergraduate students majoring in psychology. The interventionists were trained and supervised by the individuals who developed CICT. The testing and screening were conducted by a psychology doctoral student, an undergraduate majoring in neuroscience, and a recent graduate with a major in kinesiology and minor in psychology. The interventionists were not permitted to conduct treatment until deemed ready by the study principal investigator (PI) or the study coordinator; the testers were not permitted to conduct testing until deemed ready by the PI and the licensed neuropsychologist or rehabilitation psychologist on the study team. We highlight that the lead interventionist and lead tester had developed mastery in their respective domains prior to the start of this study by virtue of conducting a case series in which CICT was applied to adults after stroke with chronic cognitive impairment (Uswatte et al., 2024). The expertise of the supervisors spanned neuroscience, behavioral psychology, cognitive training, neuropsychology, rehabilitation psychology, test development, and the design and conduct of clinical trials.

Data Analysis

Power calculations were not performed to determine a sample size sufficient to reliably detect statistically significant changes for this pilot. Its primary purpose was to evaluate CICT's feasibility, which was done by calculating whether ≥80% of participants met the following benchmarks: (1) completed ≥80% of treatment hours prescribed, (2) completed ≥70% of homework assigned, (3) found CICT highly satisfying (≥6 on relevant POS item), (4) found CICT highly beneficial (≥6 on relevant POS item), and (5) found CICT to be at most moderately

difficult (≤5 on relevant POS item). A sixth benchmark was ≤2 study-related, serious adverse-events.

CICT's efficacy was evaluated on a preliminary basis by using analysis of covariance (ANCOVA). Separate models, which adjusted for baseline scores, were used to compare scores after CICT and TAU on each of the outcomes except employment. Effect sizes were described using Cohen's *d*; values ≥0.8 are large (Cohen, 1988). Non-parametric ANCOVAs were used to analyze the COPM Satisfaction, MoCA, SDMT, FAS, and PHQ-9 data because they deviated from normality per review of Q-Q plots, outliers, and Shapiro-Wilk test statistics. For these non-parametric models, ranks were substituted for raw scores. Raw-score statistics are reported for the COPM Satisfaction scale, MoCA, and FAS because the non-parametric and parametric models produced similar results. Dissimilar results were observed for the PHQ-9 and SDMT; hence, rank-based and raw-score statistics are reported in the **Results** and **SUPPLEMENT**, respectively. Fisher's Exact Test was used to compare employment status after CICT vs TAU. Analyses of changes in the TAU group after crossover to CICT are described in the **SUPPLEMENT**. All data are reported only on a completers basis because the completers analyses were conservative; all the drop-out occurred in the TAU group (see below) (Armijo-Olivo et al., 2024; Sheiner & Rubin, 1995). We did not correct for multiple comparisons because our focus was on the feasibility endpoints. However, all nine outcomes showed an advantage for the same group; the probability of that occurring by chance was only 0.2%. All analyses were performed using IBM SPSS.

Transparency and Openness

The study was approved by the Institutional Review Board at the University of Alabama at Birmingham (IRB-300002814); all participants gave written informed consent. The study's design was pre-registered; see clinicaltrials.gov/study/NCT04644172. The study write-up follows the Consolidated Standards of Reporting Trials (CONSORT) RCT checklist. All data exclusions

and manipulations are reported. The study materials, de-identified data, and analytic code are available by emailing the corresponding author.

RESULTS

Participant Characteristics

Figure 2 depicts participants' flow through the study. Seven were assigned to Immediate-CICT; nine to TAU. Two assigned to TAU withdrew before Baseline 2 testing: one lost interest in the study, the other had transportation problems. They have been excluded from all the analyses. An additional three TAU participants dropped out prior to crossover to CICT because of medical problems (*n*=2) or loss of interest (*n*=1); they have been excluded from the feasibility calculations below and crossover descriptive statistics in the **SUPPLEMENT**. Due to scheduling issues, one of these participants did not complete the COPM, MCS, and SDMT at Baseline 1; hence, he was excluded from the efficacy analyses of these measures. **Table 1** lists participants' demographics. There were no significant differences at baseline between Immediate-CICT and TAU participants' age, PASC chronicity, gender, education, and unemployment; neither were there on the outcomes.

Feasibility

Adherence to and Engagement in CICT

All Immediate- and Crossover-CICT participants but one adhered to the requirement to complete ≥29 hours of CICT (mean [SD]= 33.8 [3.7]; **Table 1**); one Crossover-CICT participant did only 26.5 hours because of scheduling conflicts. All but one met the threshold for adhering to the homework (80% [17.5%]); one Immediate-CICT participant completed only 37% of her assignments.

Participants were highly engaged in CICT. According to the INCA, Immediate-CICT participants resumed, on average, 14 cognition-based activities (*SD* = 6.7, range = 7-26; **Figure 4A**) after starting therapy that participants had ceased post-COVID; the corresponding value for Crossover-CICT participants was 8 (*SD* = 2.9, range = 5-11; **Figure 4B)**. In addition, according

to the INCA, Immediate-CICT participants improved their performance of 85 cognition-based activities (*SD* = 72.9, range = 17-192; **Figure 4C**) after starting therapy; the corresponding value for Crossover-CICT participants was 23 (*SD* = 25.8, range = 6-61; **Figure 4D**). As noted, the CTAL measures how well and independently participants perform 24 cognition-based activities outside of the treatment setting; the Total score ranges from 0 (activity not done at all) to 5 (activity completed normally). At the beginning of treatment, the mean Total in the Immediate-CICT group was 3.2 (*SD* = 0.5, range = 2.4-3.9); at the end of treatment the mean Total in this group was 4.4 (*SD* = 0.5, range 3.8-4.8), which is close to normal (**Figure 5A**). Corresponding values at the beginning and end of treatment in the Crossover-CICT group were 2.9 (*SD* = 1.1, range = 1.3-3.6) and 4 (*SD* = 0.7, range = 3.0-4.5), respectively (**Figure 5B**). In both the Immediate- and Crossover-CICT groups, a ceiling effect restricted the observation of improvement on the CTAL; about half the participants in each group achieved scores above 4 midway through therapy.

Insert Figure 4 here

Insert Figure 5 here

Acceptance of CICT

Six Immediate-CICT participants met the thresholds on the POS for satisfaction with CICT (7 [0] points) and perceived benefit from CICT (6.8 [0.4] points). POS data were missing from one but her family caregiver perceived benefit that was high (6 out of 7). Five other participants' family caregivers also perceived high benefit (6.5 [0.5]). One participant did not have a family caregiver. Immediate-CICT participants reported that CICT was only moderately difficult (3.6 [2.04] points). POS data were only available for two Crossover-CICT participants, raising the possibility that their responses were unrepresentative. We report that data here for the purpose of transparency. Both Crossover-CICT participants reported that they were highly

satisfied after treatment; their scores on this metric were 6 and 7 of 7. One perceived extremely high benefit (7 of 7); the other perceived modest benefit (5). One reported that the intervention was a little bit difficult (2 of 7); the other reported that it was extremely difficult (7). Of interest, the latter was extremely satisfied and perceived extremely high benefit after treatment..

Recruitment, Drop-out, Safety, and Extra-trial Interventions

The study enrolled 0.8 participants per month. The recruitment rate was 21%; 16 enrolled out of 75 screened. Out of the latter number, 35% were excluded because of cognition or IADL function within-normal-limits. Another 17% were not interested, which often results because an individual does not have significant dysfunction. Participation in the trial did not fit with the schedule of 9%; difficulty getting to the research facility excluded 7%. Only one had cognition or IADL function that was too impaired. **Figure 2** has a complete breakdown of the factors that excluded candidates.

The drop-out rate in the RCT phase of the study was 12.5%; two of nine randomized to TAU dropped out after Baseline 1 testing. The drop-out rate while awaiting crossover was 43%; three of the seven remaining in the TAU group after Baseline 2 testing dropped out before crossover to CICT (see **Figure 2**). Reasons for drop-out by these individuals are described in the **Participant Characteristics** section. None assigned to Immediate-CICT or who started Crossover-CICT dropped out.

There were no study-related adverse events. No participants reported receipt of therapy for their Long COVID cognitive symptoms from healthcare providers in the community or from other studies during the CICT or TAU conditions.

Efficacy

Performance of Everyday Activities

A very large advantage in favor of Immediate-CICT over TAU was observed after treatment on the primary outcome: COPM Performance scale mean difference (*MD*)=3.7 points; *95% CI*, 2.5-4.9; $F(1,10)=51$, $p<.001$; $d=2.6$ (**Figure 6**) (Chandler et al., 2019). A very large

advantage in favor of CICT was also observed on the COPM Satisfaction Scale, *MD* = 4.0 points; *95% CI*, 2.4 to 5.6; $F(1,9) = 22.8$, $p < 0.001$, $d = 2.6$. The advantage for CICT over TAU on this scale was larger for participants with low baseline scores than for those with high baseline scores, $F(1,9) = 22.8$, $p < 0.001$ (**Figure 7)**. The results reported for the Satisfaction scale were from an ANOVA model using raw scores; results from a parallel ANOVA model substituting ranks for raw scores were similar, $F(1, 9) = 5.64$ $p = 0.04$. An analysis of variance (ANOVA) model with an interaction term (Group x Baseline 1) rather than an analysis of covariance (ANCOVA) model was employed here because homogeneity of variance was not present. Post-crossover COPM changes in TAU participants, along with post-crossover changes on all the other outcomes, are described in the **SUPPLEMENT**.

Insert Figure 6 here

Insert Figure 7 here

A distinct advantage in favor of Immediate-CICT over TAU was observed in return-to-work, $p=0.048$ (**Figure 8**). In both groups, two had retired prior to COVID-19 onset. Out of the remaining five Immediate-CICT participants, four had to give up their job after COVID-19 onset, and one switched to remote-work, fulfilling only a limited duty set. After Immediate-CICT, four of five were able to resume work with a full duty set. None were able to work before or after TAU.

Insert Figure 8 here

<u>Self-reports of Long COVID Symptoms</u>

Immediate-CICT, compared to TAU, resulted in very large reductions in brain fog symptoms (MCS *MD*=-4 points; *95% CI*, -5.3 to -2.6.; $F[1,10]=43$, $p<0.001$; $d=-3.1$; **Figure 9**) and fatigue (FAS *MD*=-10.9 points; *95% CI*, -17.4 to -4.4; $F[1,10]=7.6$, $p=0.02$; $d=-1.8$). For the latter, the advantage of CICT over TAU was larger for participants with high baseline scores

than for participants with low scores, $F(1, 10) = 11.9$, $p = 0.006$ (**Figure 10**)**.** A large benefit from Immediate-CICT, relative to TAU, was observed for depressive symptoms, $F(1,11)=7.5$, $p=.019$ (**Figure 11A)**. The median post-treatment PHQ-9 score in the Immediate-CICT group after treatment was 6, inter-quartile range (IQR)=5-7; the corresponding value in the TAU group was 10.0, IQR=7-11. Although an advantage was observed for Immediate-CICT over TAU after treatment in anxiety symptoms, the difference was not statistically significant: GAD-7 *MD*=-3.3 points; *95% CI*, -7.3 to 0.6; $F(1,11)=3.4$, $p=0.09$; $d=-0.8$ (**Figure 11B)**.

Insert Figure 9 here

Insert Figure 10 here

Insert Figure 11 here

In-lab Tests of Cognitive Ability

A moderate benefit from Immediate-CICT, relative to TAU, was observed for cognitive processing speed, $F(1,10)=5.4$, $p=0.042$ (**Figure 12)**. In the Immediate CICT group, the median baseline SDMT score was 47 points, IQR=30-49; the corresponding value at post-treatment was 51, IQR=29-56. In the TAU group, the median baseline SDMT score was 43, IQR = 36-50; the corresponding value at post-treatment was 39, IQR=37-49. The relative improvement in the Immediate-CICT group, i.e., pre- to- post-treatment change in the median in the Immediate-CICT group minus that in the TAU group, was 8 points, which was equal to the MCID on the SDMT. In other terms, 43% had a clinically meaningful improvement, i.e., greater than or equal to the MCID, in the Immediate CICT group, while none did in the TAU group. No advantage for Immediate-CICT over TAU was seen for general cognitive ability: MoCA *MD*=0.3 points; *95% CI*, -3.1-3.7; $F(1,11)=0.04$, $p=0.84$; $d=0.1$.

Insert Figure 12 here

DISCUSSION

The results suggested that CICT is a feasible method for reducing disability in adults with brain fog and cognitive dysfunction due to PASC. All the benchmarks for adherence, acceptability, and safety were met. All but one among those who received CICT completed at least 29 hours of treatment. The same number completed at least 70% of their homework. All the Immediate-CICT participants or a family caregiver, when a participant rating was not available, reported that CICT was highly beneficial. Only one Immediate-CICT participant reported that CICT was excessively difficult. No participant who started CICT dropped out. There were no adverse events.

Of note, CICT, compared to TAU, resulted in very large improvements in performance of cognition-based activities in daily life. All Immediate-CICT participants reported clinically meaningful improvements on the COPM Performance scale; no TAU participants did so. Skeptics might argue the substantial advantage in favor of CICT on the primary outcome was due to the operation of demand characteristics, e.g., the desire of CICT participants to please experimenters. However, the changes in employment observed suggest otherwise: 80% of Immediate-CICT participants who had not retired prior to COVID-19 onset resumed a full set of work duties after treatment; none did so after TAU. Even though employment was assessed by self-report, return-to-work might be considered a “hard” endpoint because of its binary nature and description of a state-of-the-world (as opposed to an internal state). An advantage for CICT over TAU was also observed on the SDMT, which is an objective cognitive-processing-speed test. We highlight that the findings about efficacy summarized in this paragraph are preliminary. Additional testing of CICT in large-scale trials is needed before definitive conclusions can be made.

Immediate-CICT participants, compared to TAU participants, reported very large reductions in brain fog and fatigue and large reductions in depressive symptoms. One possible

interpretation of the results is that CICT benefited IADL, employment, and brain fog by improving participants' mood. Another possibility is that CICT produced improvements in both sets of variables by targeting a common mechanism or targeting multiple mechanisms. Testing which of these possible explanations is correct would be of interest for future studies. Regardless, CICT produced improvements here in both everyday function and three of the four self-reported Long COVID symptoms assessed.

Lessons for Future Trials, Constraints on Generality, and Other Study Limitations

Two-of-nine TAU participants withdrew before Baseline 2 testing, which may have inflated the advantage observed for CICT. Three additional TAU participants withdrew before crossover to CICT. The pattern of changes after CICT in the remaining four, however, was similar to that for Immediate-CICT participants (see **SUPPLEMENT**). The pattern of drop-out suggests that a credible placebo-control or active-comparison condition may be needed in future trials to reduce drop-out in the control arm. This pattern also advocates against a crossover procedure in future trials.

The enrollment rate of 0.8 participants per month, which would be inadequate to support a large-scale trial, suggests that future trials need to budget for a robust recruitment effort. This intramurally-funded, early-phase RCT relied largely on referrals from clinicians. Future trials might consider mining health system records, social media advertising campaigns, and community outreach, which might be of particular value for recruiting participants from ethnic groups that were under-represented in this trial (see next paragraph). The large proportion of candidates who did not have sufficient impairment to qualify for this trial suggests that it is important that recruitment materials highlight the criteria for cognitive impairment and express the criteria in terms candidates can understand. Other measures that future trials might take to support enrollment, based on the small but not negligeable proportion excluded here for scheduling issues and transportation problems, are offering flexible scheduling of treatment and testing sessions, including hours in the evenings and weekends, and subsidized transportation.

An alternate approach would be to offer CICT on a tele-health basis, which would eliminate the need to travel to a treatment facility on multiple occasions (Uswatte et al., 2021; Wadley et al., 2006).

Another question for a future trial is what elements of CICT are necessary. CICT is a complex intervention with three components-- SOPT, in-lab IADL training, and the Transfer Package-- each of which has multiple elements (see **INTRODUCTION** and **Interventions** section). The literature provides some guidance about what to test. Unlike in older adults without cognitive impairment at baseline (see **INTRODUCTION**), transfer of SOPT gains to other domains has not been observed when SOPT has been tested in adults with slowed cognitive processing speed and brain fog due to multiple sclerosis and HIV (Chiaravalloti et al., 2022; Vance et al., 2024). Because these trials did not combine in-lab IADL training or a Transfer Package or similar elements with SOPT, their findings suggest that one or both of these elements may be necessary for production of robust real-world changes in populations with cognitive impairment. A widely-cited components analysis in adults with chronic stroke of upper-extremity CIMT, which features in-lab training on everyday motor activities and a motor Transfer Package (see **INTRODUCTION**), found that the motor Transfer Package was necessary for production of both improvements in use of the hemiparetic arm in daily life and increases in the amount of grey matter in brain regions controlling movement of that arm (Gauthier et al., 2008; Taub et al., 2013). These prior findings suggest, as a first step, a future RCT with a factorial design that tests the independent and joint contributions of in-lab IADL training and the cognitive Transfer Package to real-world outcomes over and above SOPT alone. If some elements of CICT were found to be unnecessary, these elements could be eliminated, which would reduce the time and skill level required to deliver the intervention.

The small (n=14) and ethnically homogenous (93% European American) sample enrolled raises questions about the generality of the findings. Future trials might consider tailoring their recruitment strategies to ethnic groups who are under-represented here. The

preponderance of females (*n*=10) in the sample is typical of the target population (Graham EL et al., 2021; Jaywant et al., 2024); females appear to be at higher risk of developing Long COVID because of unique features of their immune system (Graham EL et al., 2021).

Another feature of this trial that limited the generality of the findings was our use of cutoffs on the MoCA rather a measure of perceived cognitive function to identify candidates with cognitive impairment. We chose a performance test, i.e., the MoCA, because we thought that in the event we observed advantages for CICT, the presence of objective impairment helped to reduce the salience of interpretations contending that the results were simply due to alleviating psychological distress. In addition, we thought it would be difficult to detect any improvements on our in-lab, cognitive performance tests because of the ceiling effects likely to be present in a sample without objective cognitive impairment. The downside of this decision was that we excluded individuals with substantial cognitive difficulties per self-report but without objective cognitive impairment, which is not uncommon in Long COVID brain fog (Bland et al., 2024; Whitaker-Hardin et al., 2025). Testing CICT in this population would be of considerable interest for a future trial.

Although the differences were not statistically significant, the Immediate-CICT group was younger and had long COVID for a shorter period than the TAU group. In addition, none in the CICT had been hospitalized while two in the TAU group had. This pattern might suggest that the CICT group was less impaired than the TAU group and, hence, had a greater capacity to respond to treatment. However, other data indicate that these demographic and medical history differences were unlikely to have influenced the study findings. More proximal indicators of baseline function than these demographic and medical history variables suggest that the two groups were very similar at baseline in their symptom profile and, hence, capacity to respond to treatment. Inspection of **Table 1**, which now includes baseline values of the outcome measures, reveals that the two groups' mean baseline scores were very similar, i.e., within one unit of each other, on the measures of brain fog, cognitive impairment, IADL performance, employment,

fatigue, and anxiety. Modest differences, which were smaller than what is considered clinically meaningful and were in opposite directions, were present on the measures of depressive symptoms and cognitive processing speed. The CICT group had more severe depressive symptoms than the TAU group. The TAU group processed information more slowly than the CICT group.

Other important limitations were the absence of long-term follow-up, blinding, and control for placebo effects. A shortcoming of our inclusion criteria was that we did not formally assess the presence of brain fog. We did not do so because norms were not available for adults with Long COVID or adults without neurological injury on the MCS, our brain fog outcome measure. Instead, we directed our referral sources to recommend candidates with brain fog, which resulted in a sample that, except for one participant in the CICT group with an initial MCS score 1.2 out of 10, had brain fogs symptoms at baseline at best a little less than half the time (range = 4.4-9.1; IQR = 5.5 to 6.8). A shortcoming of our outcome assessment was that we did not directly measure post-exertional malaise (PEM), which is an out-of-proportion loss of stamina and onset of fatigue following the exertion of physical, cognitive, or emotional effort (Cotler et al., 2018). The large reductions in fatigue present after CICT, high CICT adherence rates observed, high acceptability ratings, and absence of drop-outs among those who received CICT, suggest that PEM, which is a common Long COVID symptom, was not triggered frequently by CICT (Graham et al., 2022). Two factors that may have contributed to the latter were the (a) organization of SOPT and in-lab IADL training following shaping principles, which support gradual increases in exercise intensity and length, and (b) scheduling of training sessions to meet individual participants' needs, including their stamina (Skinner, 1938, 1968; Taub E et al., 1994). A shortcoming of the cognitive outcome assessment was use of the MoCA, which was designed for use as a screening tool (Nasreddine et al., 2005).

CONCLUSIONS

Adults with mild cognitive impairment and dysfunction in IADL associated with Long COVID adhered to the CICT protocol and were highly satisfied with their outcomes from CICT. These preliminary findings warrant confirmation in a large-scale RCT.

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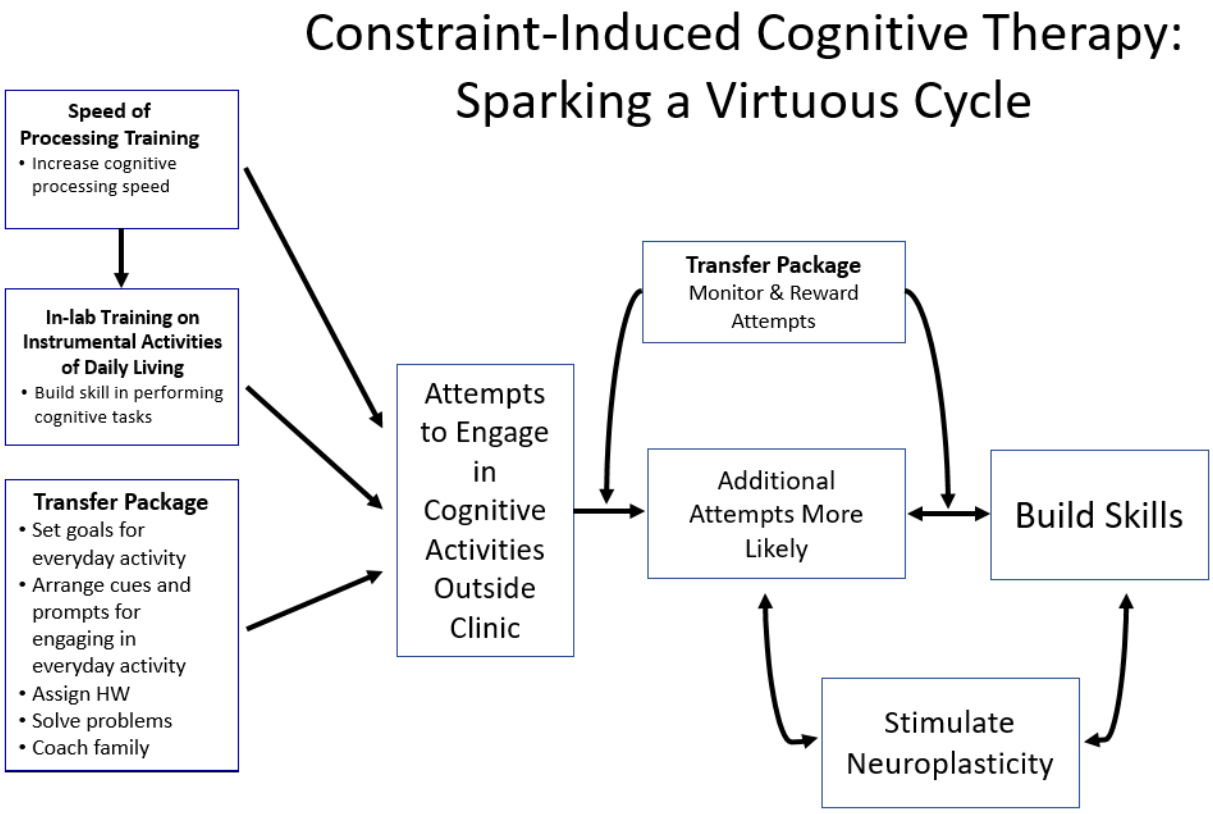

Figure 1. A Conceptual Model of How Constraint-Induced Cognitive Therapy (CICT) Operates. The three components of CICT are listed in the boxes on the left-hand side of the figure. We hypothesize that all three components promote attempts to perform cognition-based tasks outside the treatment setting. Moving from left to right, we hypothesize elements of the Transfer Package (i.e., the Cognitive Task Activity Log, Inventory of New Cognitive Activities, and Home Skill Assignment; see **Table 2**) permit therapists to monitor and reward attempts when they occur (Uswatte et al., 2010). Rewarding behavior increases its frequency (Skinner, 1938, 1968). Repetition builds skill and stimulates brain plasticity (Ungerleider et al., 2002). Skill building and neuroplasticity support each other, which we hypothesize, in turn, makes attempts at cognition-based tasks less effortful and thereby more frequent—kicking off a virtuous cycle (Kleim et al., 1998; Uswatte et al., 2010).

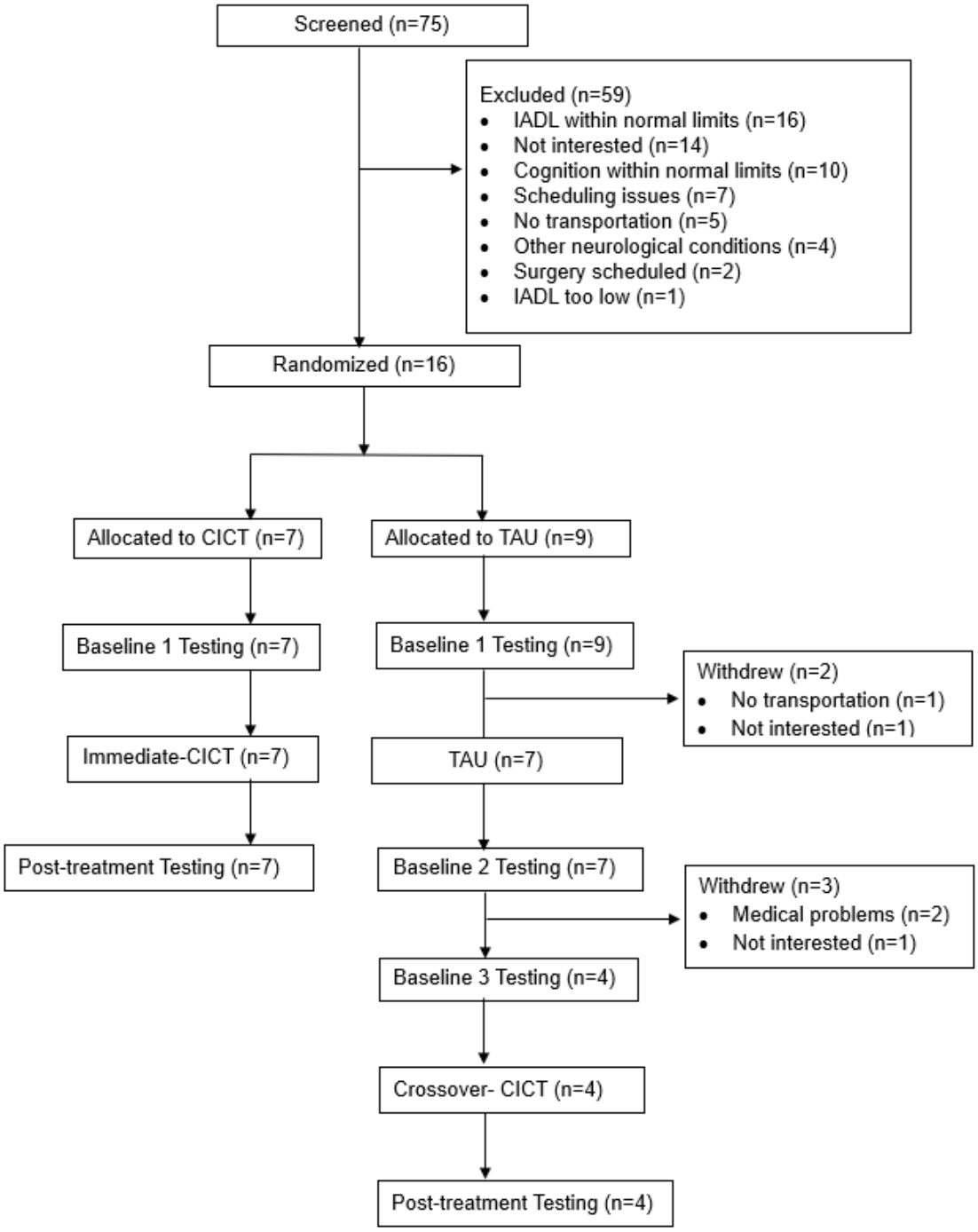

Figure 2. Flow of Participants in the Trial. Candidates were initially screened by telephone. If they had persistent Long COVID symptoms, were more than 3-months post-infection, were community residents, have reliable transportation, were medically stable, and did not have pre-existing brain injuries, they were invited to an onsite screening examination. In addition, candidates were asked during the telephone interview if there was someone who observed how they performed daily activities on a regular basis, and if that person could come to at least half of the treatment sessions. If yes, we encouraged candidates to invite this person to attend

testing and treatment sessions with them. At the onsite screening examination, candidates completed the informed consented process and were tested for presence of mild or moderate cognitive impairment and difficulty performing instrumental activities of daily living. If both were present and a candidate gave consent, the candidate was enrolled, randomized to either Immediate-CICT or TAU, and scheduled to complete Baseline 1 testing. Immediate-CICT participants, after Baseline 1 testing, received CICT and completed Post-treatment testing. TAU participants, after Baseline 1 testing, were permitted to receive any treatment available from healthcare providers in the community before completing Baseline 2 testing. Then, after an approximately 3-month interval, TAU participants completed Baseline 3 testing, were crossed over to CICT, and completed Post-treatment testing. CICT = Constraint-Induced Cognitive Therapy; TAU = treatment-as-usual.

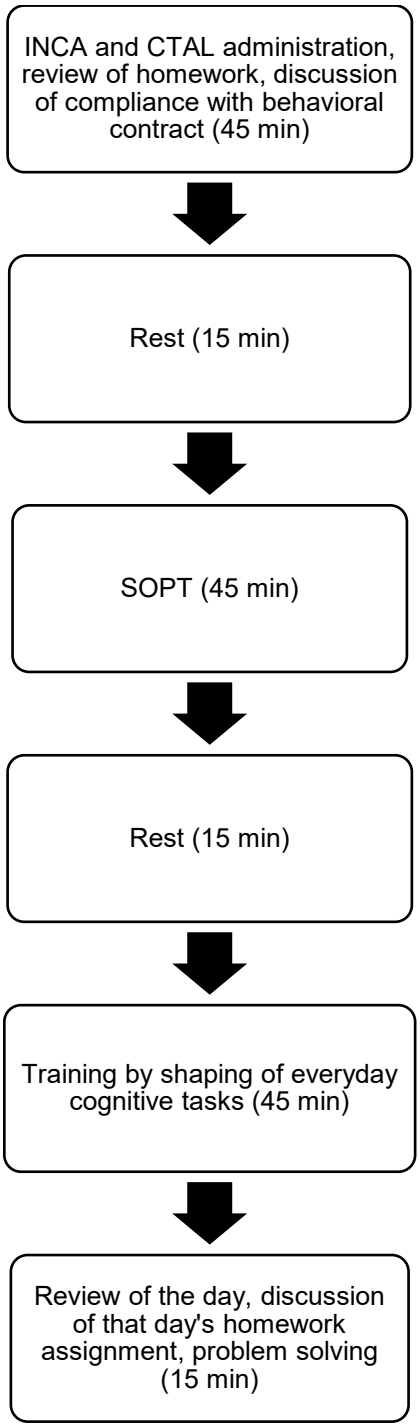

Figure 3. **Typical Constraint Induced Cognitive Therapy Session Schedule.** CTAL indicates Cognitive Task Activity Log; INCA, Inventory of New Cognitive Activities; SOPT, Speed of Processing Training.

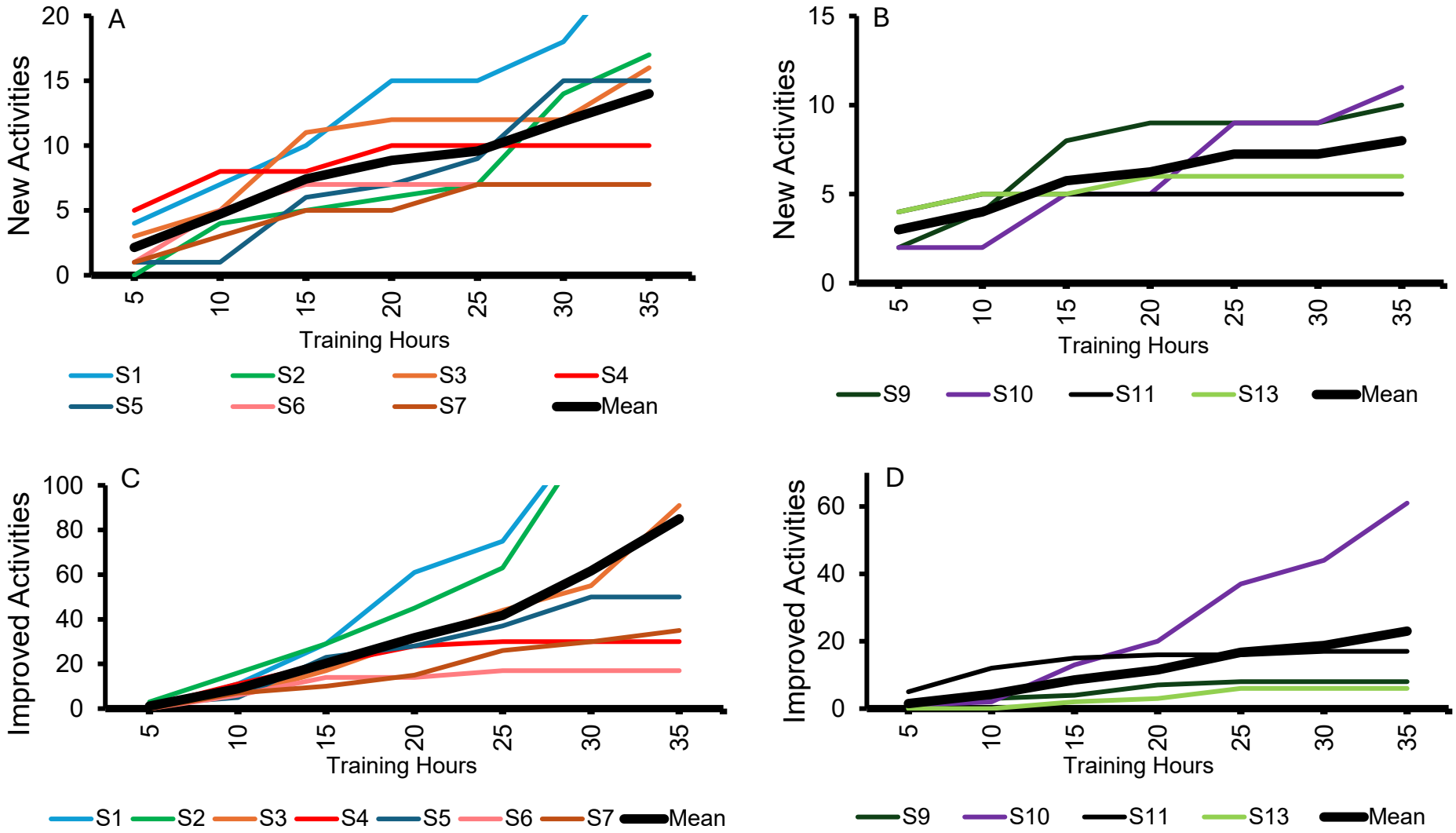

Figure 4. Everyday Cognition-based Activities Assessed with the Inventory of New Cognitive Activities (INCA). A. The number of activities resumed in the Immediate-CICT group that participants had ceased post-COVID. **B**. The number of activities resumed in the Crossover-CICT group that participants had ceased post-COVID. **C**. The number of activities improved during in the

Immediate-CICT group. The lines for S1 and S2 are cut off because they extend beyond the range that it is possible to graph without obscuring the others' data. The number of improved activities at the end of therapy for S1 and S2 were 192 and 180, respectively. **D**. The number of activities improved during Crossover-CICT.

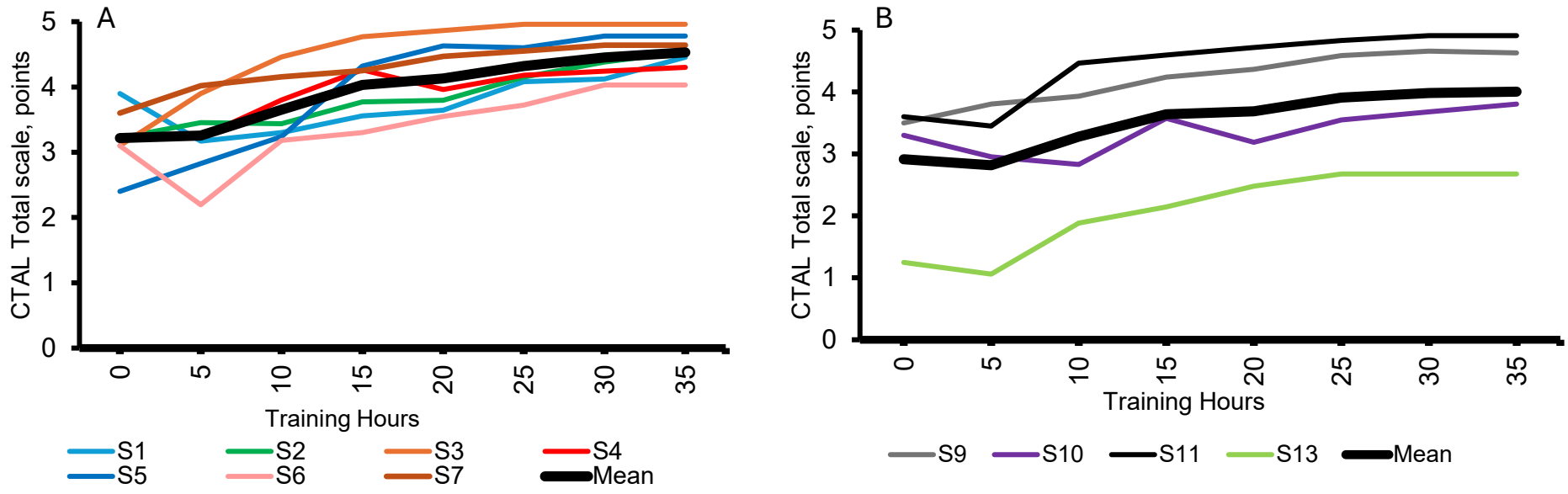

Figure 5. Engagement in IADL Outside the Treatment Setting. The Cognitive Task Activity Log (CTAL) indexes how independently and well respondents carry out 24 cognition-based activities outside the treatment setting. A 0 indicates that an activity was not done at all; a 5 indicates that the activity was completed normally. A ceiling effect restricted the observation of improvement for several participants; three of the seven had test scores above 4 midway through therapy. **A**. Engagement in IADL Outside the Treatment Setting by Immediate-CICT Group. **B**. Engagement in IADL Outside the Treatment Setting by Crossover-CICT Group

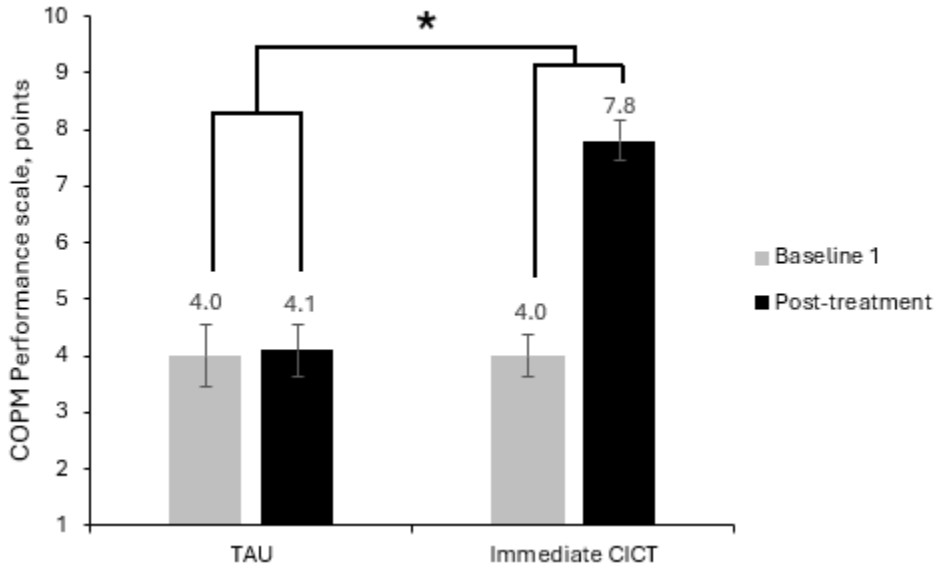

Figure 6. Performance of Everyday, Cognition-based Activities Before and After Immediate-Constraint-Induced Cognitive Therapy (CICT) and Treatment-as-Usual (TAU). The Canadian Occupational Performance Measure (COPM) Performance scale measures how well participants perform five self-selected cognition-based activities (1 = not able; 10 = able to do it extremely well). Horizontal bars represent standard errors. All Immediate-CICT participants had clinically meaningful improvements; no TAU participants did.

*$p < .001$

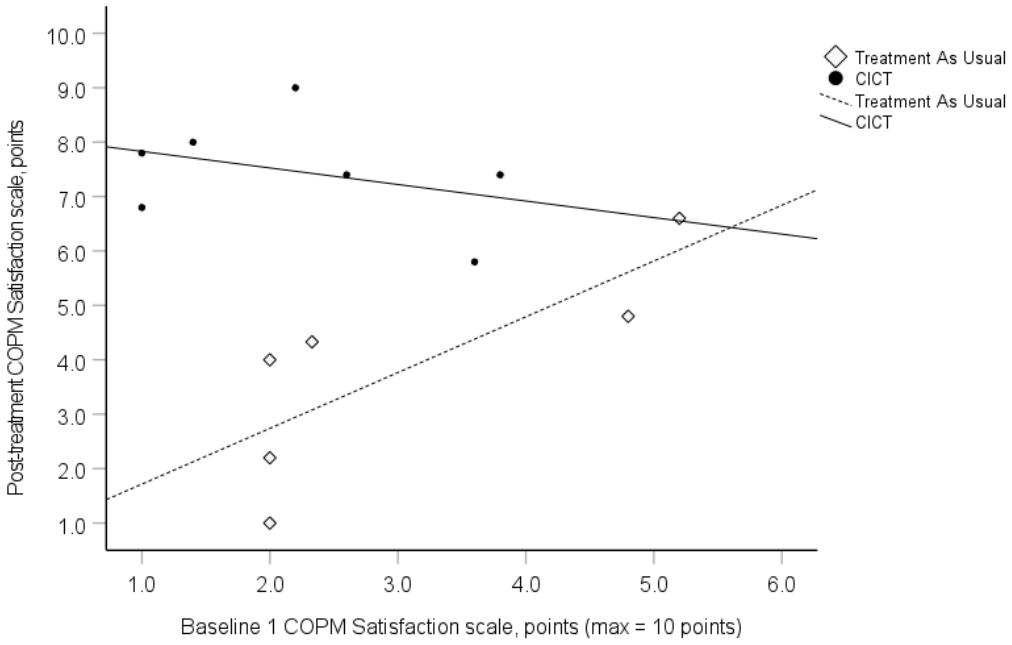

Figure 7. Satisfaction with Performance of Everyday Cognition-based Activities. The Canadian Occupational Performance Measure (COPM) Satisfaction scale measures how satisfied participants are with the performance of 5 self-selected, cognition-based activities. All of the Immediate-Constraint-Induced Cognitive Therapy (CICT) participants had clinically meaningful improvements; only two of six Treatment-As-Usual (TAU) participants with COPM data did. A scatterplot rather than a bar graph is drawn because an interaction between group assignment and baseline COPM Satisfaction scores was present (see text).

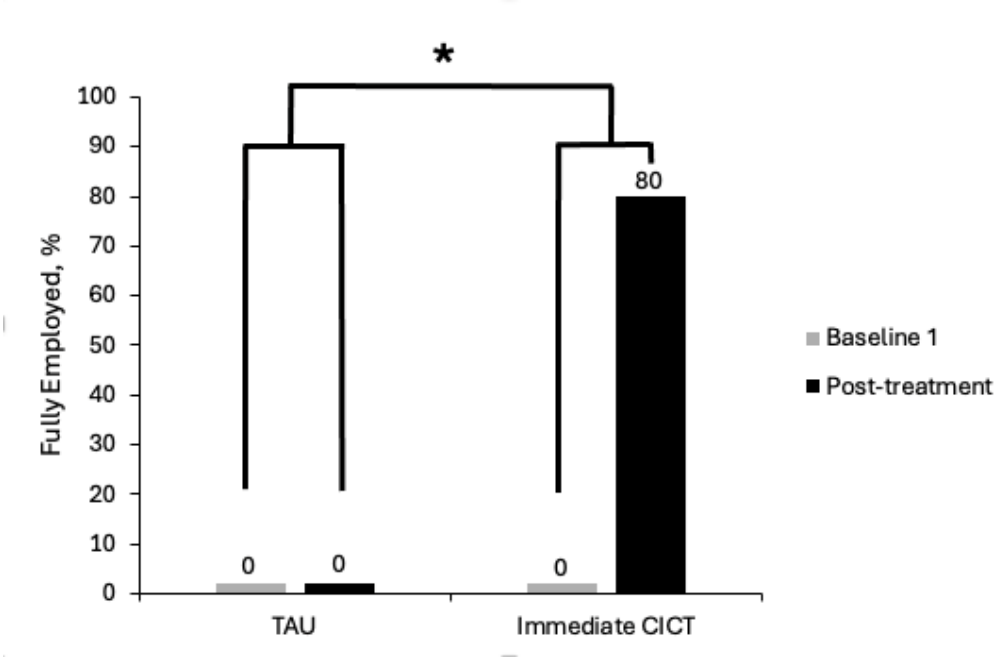

Figure 8. Participants' Employment Status Before and After Immediate-Constraint Induced Cognitive Therapy (CICT) and Treatment-as-Usual (TAU). The numbers indicate the percentage of individuals who were fully employed at Baseline 1 and Post-Treatment.

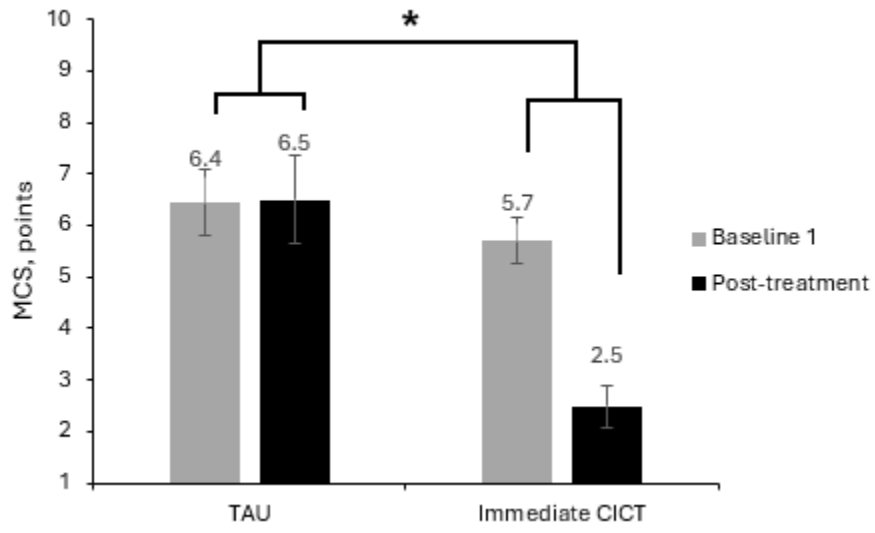

Figure 9. Brain Fog Symptom Frequency Before and After Immediate-Constraint Induced Cognitive Therapy (CICT) and Treatment-as-Usual (TAU). The Mental Clutter Scale (MCS) measures how frequently participants experience eight brain fog symptoms (1 = not at all, 10 = all the time). Horizontal bars represent standard errors.

**p < .001*

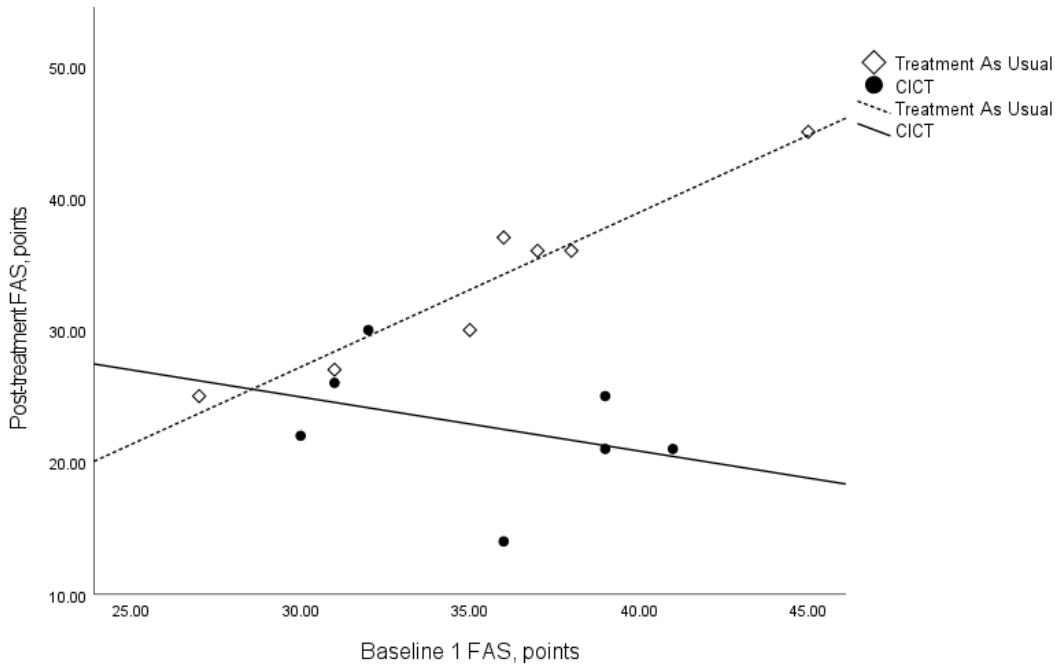

Figure 10. Fatigue Symptom Severity. The Fatigue Assessment Scale (FAS) was used to assess fatigue symptom severity. On the FAS, respondents are asked to rate how frequently 10 symptoms are experienced using a 5-point scale (1 = never, 5 = always). The test score is the sum of the item scores. Six of seven Immediate-Constraint-Induced Cognitive Therapy (CICT) participants had clinically meaningful improvements; only two of seven Treatment-As-Usual (TAU) participants did. A scatterplot rather than a bar graph is drawn because an interaction between group assignment and baseline FAS scores was present (see text).

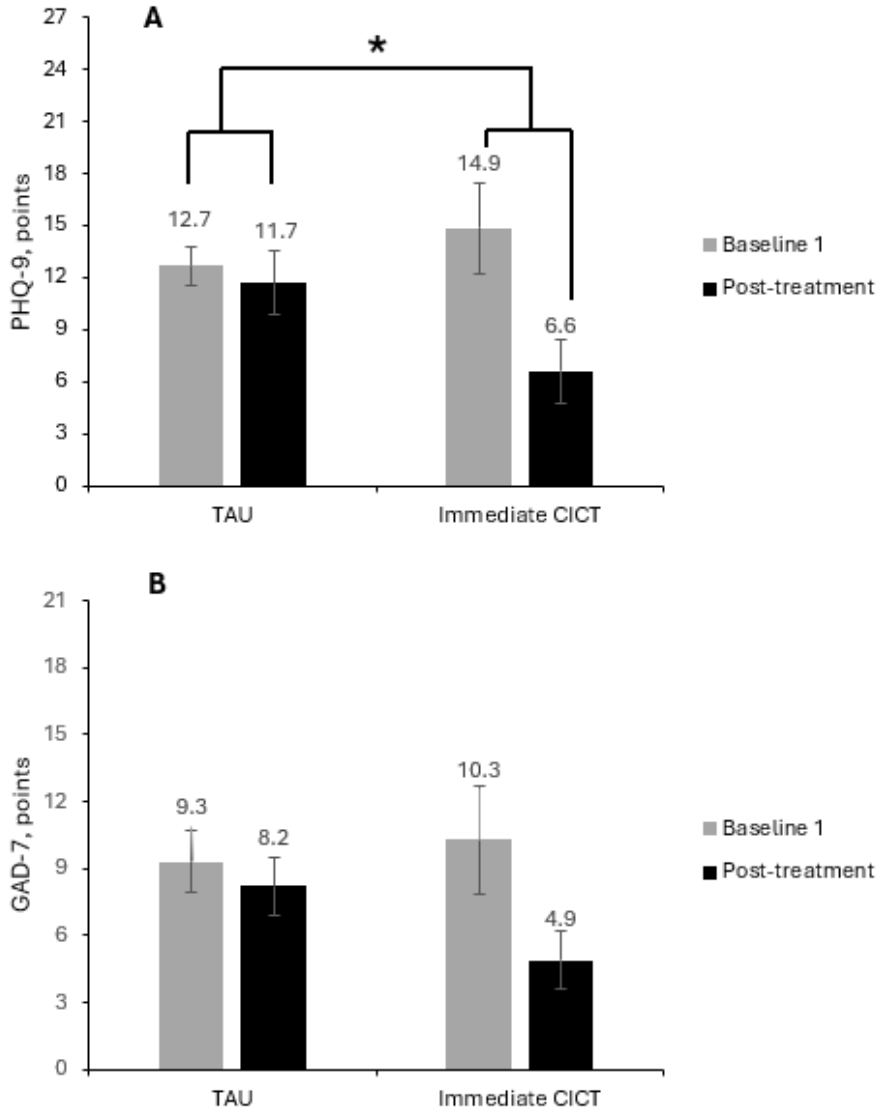

Figure 11. (A) Depressive and (B) Anxiety Symptom Severity Before and After Constraint-Induced Cognitive Therapy (CICT) and Treatment-As-Usual (TAU). The Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) were used to assess depression and anxiety symptom frequency, respectively. The PHQ-9 lists nine symptoms; the GAD-7 lists seven. On both surveys, respondents rate how frequently the symptoms are experienced using 4-point scales (0, never; 3, nearly every day). The test score is the sum of the item-scores. Panel A plots raw scores as opposed to ranks (see next section). Four of seven Immediate-CICT participants had clinically meaningful improvements in depressive symptoms; only two of seven TAU participants did. Five of seven Immediate-CICT participants had clinically meaningful improvements in anxiety symptoms; only two of seven TAU participants did.

*$p < .05$

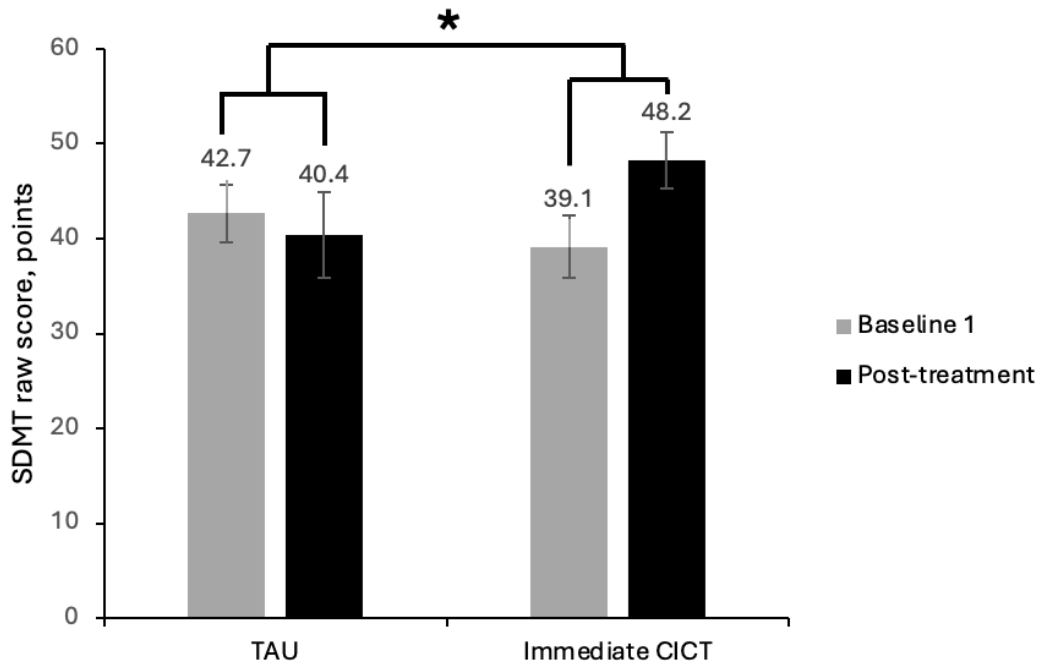

Figure 12. **Cognitive Processing Speed Before and After Immediate-Constraint-Induced Cognitive Therapy (CICT) and Treatment-As-Usual (TAU).** The Symbol Digit Modalities Test (SDMT) was used to assess cognitive processing speed. The total score is the number of symbols that are coded correctly in 90 s (max = 110). Raw as opposed to rank scores are plotted.

*$p < .05$

Table 1. Participant Demographic, COVID-19 Characteristics, Baseline 1 Scores and CICT Treatment Characteristics

Characteristic	Immediate-CICT (n=7)	TAU (n=7)	All (N=14)
Age, years	45 (15.2)	56.4 (6.9)	50.7 (12.8)
Sex			
Male	1	3	4
Female	6	4	10
Ethnicity			
European American	6	7	13
African American	1	0	1
Education	15.7 (2.3)	15.2 (2.3)[a]	15.5 (2.2)
Months since COVID-19 onset	7.4 (2)	12.9 (7)	10.1 (6.5)
Hospitalized due to COVID-19	0	2	2
Performance of Everyday Cognition-based Activities, COPM			
Performance scale, points	4 (1.2)	4.1 (1.4)	4 (1.2)
Satisfaction scale, points	2.2 (1.2)	3.4 (1.7)	2.9 (1.5)
Employment Status			
Employed, full duty set	0	0	0
Employed, limited duty set	1	0	1
Unemployed	4	5	9
Retired	2	2	4
Long COVID Symptom Frequency			
Brain fog, MCS, points	6.4 (1.6)	5.7 (2.3)[c]	6.1 (1.9)
Fatigue, FAS, points	35. 4 (4.4)	35.6 (5.7)	35.5 (4.9)
Depressive, PHQ-9, points	14.9 (6.9)	12.71 (2.9)	13.8 (5.2)
Anxiety, GAD-7, points	10.3 (6.4)	9.3 (3.6)	9.8 (5)
Cognitive processing speed, SDMT	39.1 (12.1)	42.7 (7.5)[c]	40.8 (10)
Cognitive function, MoCA, points	23.6 (1.8)	25 (1.6)[c]	24.2 (1.8)
CICT training duration			
Hours, *M* (*SD*), min-max	34.8 (3.1), 30.8-39.8	32.2 (4.6), 26.5-35.8[b]	33.8 (3.7), 26.5-39.8

Sessions, *M* (*SD*), min-max	12 (1.8), 9-15	11 (1), 10-12[b]	11.5 (1.6), 9-15
Days from first to last session, *M* (*SD*), min-max	27 (13.5), 10-52	31.3 (12.5), 15-41[b]	28.6 (12.7), 10-52

Abbreviations: CICT, Constraint-Induced Cognitive Therapy; TAU, treatment-as-usual.
Values are *M* (*SD*) or counts at Baseline 1, unless otherwise specified. There were no significant between-group differences for any characteristics.
[a] Years of education were missing for two TAU participants.
[b] Three TAU participants dropped out before crossover to CICT. Hence, crossover-CICT data were only available for four.
[c] One participant did not complete the measure at Baseline 1.
[d] One subject was excluded from the calculation of the MoCA average score because their Baseline 1 MoCA score was an outlier. Their score fell below the lower bound of the Inter-quartile Range minus 1.5 times the Inter-quartile Range (Tukey, 1977). Another perspective is that all the other participants had scores in the mild cognitive impairment range (18-26), while this participant had a score in the moderate range (10-17) (Sun & Genton, 2011). The average MoCA values for the TAU group and for both groups with the participant included were [*M* (*SD*)]:, 23.7 (3.7) and 23.6 (2.8), respectively.

Table 2. Elements of the Cognitive Transfer Package

Transfer Package Element	Description
Behavioral Contract	At the outset of treatment, trainers negotiate a "contract" with participants and their family members or other informal caregivers, if available, about their responsibilities, as well as the responsibilities of the treatment team. This written agreement specifies activities with important cognitive components that are important to participants and commits participants to attempt these activities outside the treatment setting and to attend and engage in all training sessions. The agreement, in addition, specifies when support from a family member, if available, is needed to carry out an activity safely.
CTAL and INCA	The CTAL and INCA, which are completed at the beginning of each training session, collect information about the performance of everyday activities with important cognitive components outside the treatment setting by participants (see **Feasibility** section of the **SUPPLEMENT**). These structured interviews serve as occasions to (a) reward participants with verbal praise for attempts to carry out cognition-based activities in daily life and (b) support problem solving by participants and their family caregivers, when relevant, regarding perceived and actual barriers to doing so.
Home Skill Assignment	At the end of each training session, participants, with support from family caregivers, if needed, are asked to carry out up to 10 cognition-based tasks at home before the next session. The tasks are selected from a bank developed by this lab; the list is refreshed, as needed, at each session. Participants check off the activities carried out on the form provided to them, plus enter when the activities were carried out and comment on any difficulties encountered. Examples of tasks are: prepare a meal, sort mail, write emails, play board games, count calories, make a grocery list, make a budget for the week, pay a bill, and organize closet. Completion of the activities assigned is reviewed at the outset of each training session.
Problem Solving	Throughout each session, but particularly during the CTAL and INCA interviews and review of home skill assignments, trainers support problem solving by participants regarding any perceived or actual barriers to the performance of cognition-based tasks in daily life. The problem-solving procedures are based on the "goal-plan-do-check" procedure employed by Skidmore and colleagues (Skidmore et al., 2011).
Family Engagement	Trainers coach family caregivers, if available, to (a) permit clients to carry out tasks independently when safe to do so, (b) provide clients with supervised practice in the home, and (c) prompt clients to perform IADL at home.
Follow-up Program	Trainers give participants an individualized program of 10 to 15 tasks to practice for a total of 30-60 minutes a day at home at the end of the last training session. Follow-up telephone calls are scheduled weekly for the first month after treatment. During each call, trainers conduct the CTAL and INCA interviews, review and encourage compliance with participants' home programs, and modify the programs as needed, e.g., replacing easy with difficult tasks. As in training sessions, the CTAL and INCA interviews are occasions to reward participants with verbal praise for engaging in cognition-based activities and to support problem solving by participants regarding any barriers to doing so.

Abbreviations: CTAL, Cognitive Task Activity log; INCA, Inventory of New Cognitive Activities; IADL. Instrumental Activities of Daily Living

SUPPLEMENT

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

G. USWATTE, E. TAUB, K. BALL, B. MITCHELL, J. BLAKE, S. MCKAY, F. BINEY, O. IOSIPCHUK, P. HEMPFLING, E. HARRIS, A. DICKERSON, K. LOKKEN, A. J. KNIGHT, V. W. MARK, S. AGNIHOTRI, & G. CUTTER.

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.

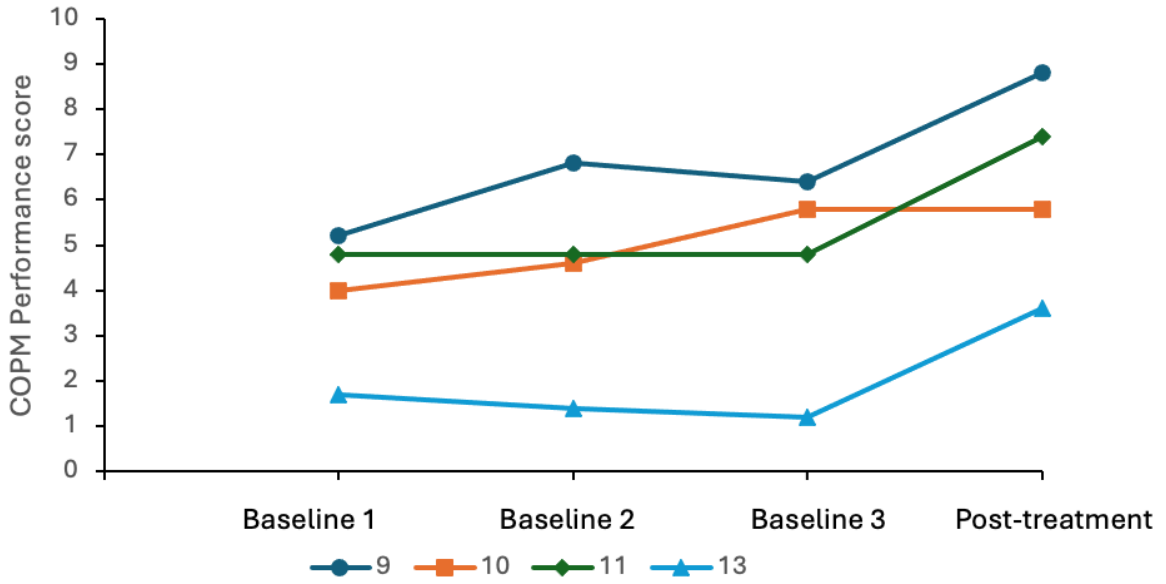

Figure s2. Canadian Occupational Performance Measure (COPM) Performance Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All but one showed improvement after crossover to CICT.

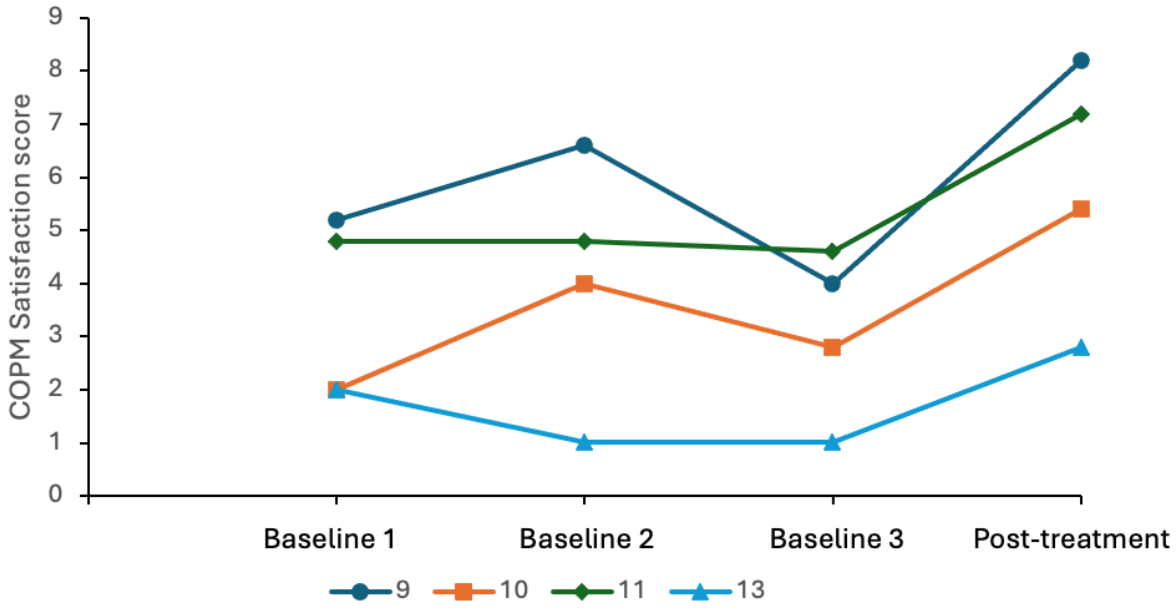

Figure s3. Canadian Occupational Performance Measure (COPM) Satisfaction Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All showed improvement after crossover to CICT.

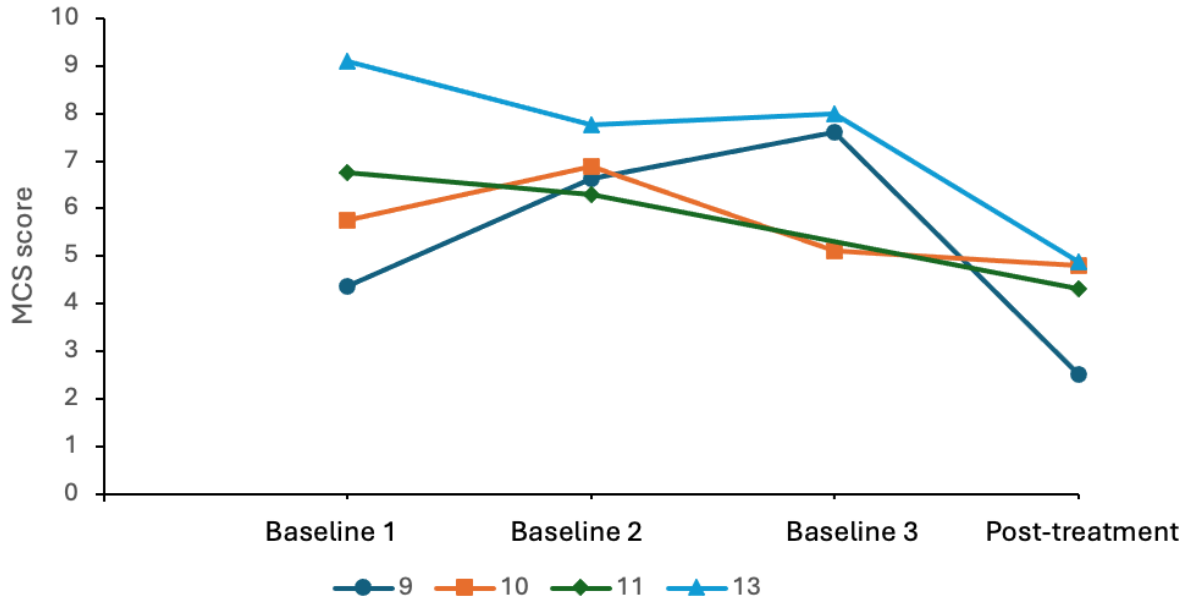

Figure s4. Mental Clutter Scale (MCS) Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All showed improvement after crossover to CICT.

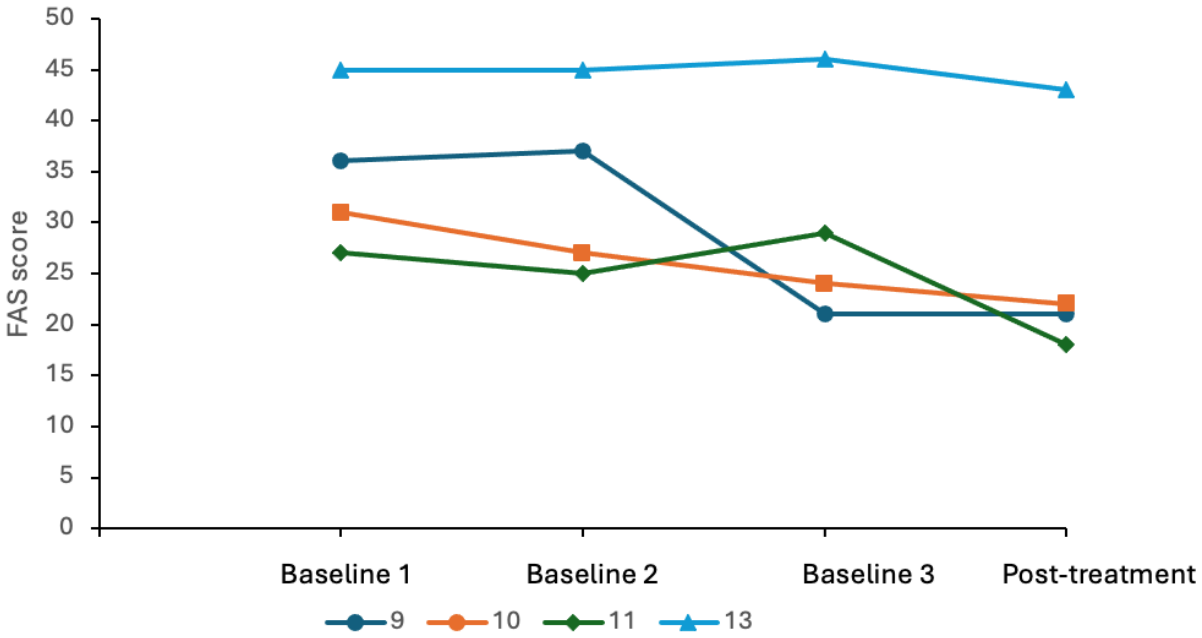

Figure s5. Fatigue Symptom Severity (FAS) Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to CICT. All but one showed improvement after crossover to CICT.

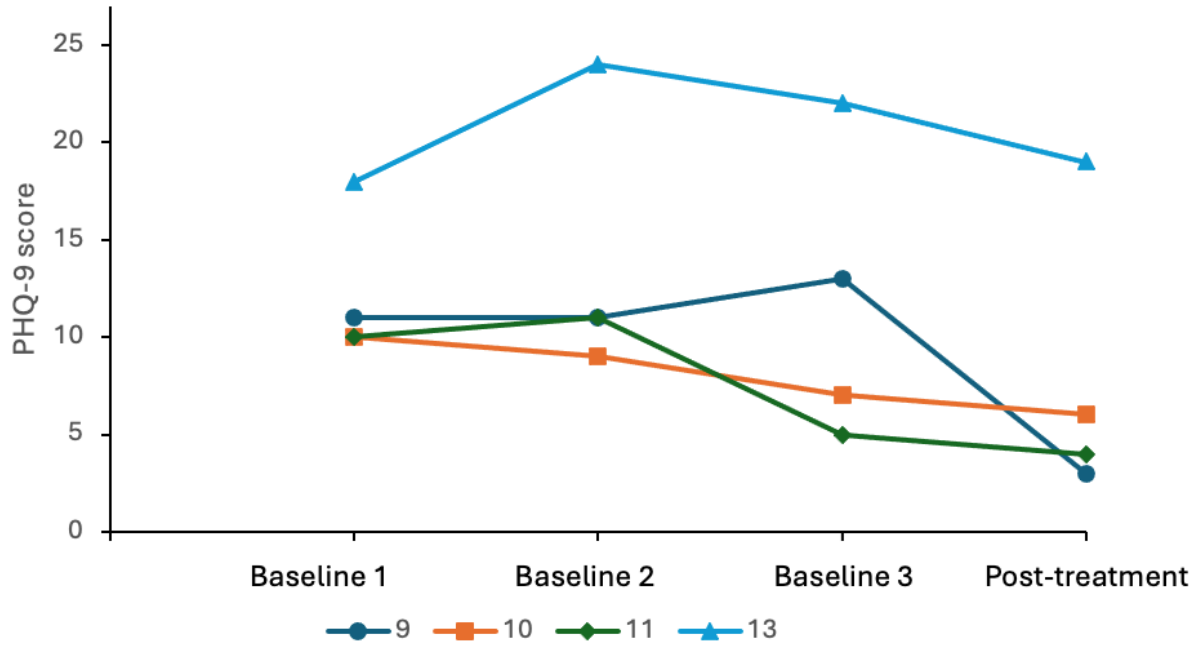

Figure s6. The Patient Health Questionnaire-9 (PHQ-9) Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All showed improvement after crossover to CICT.

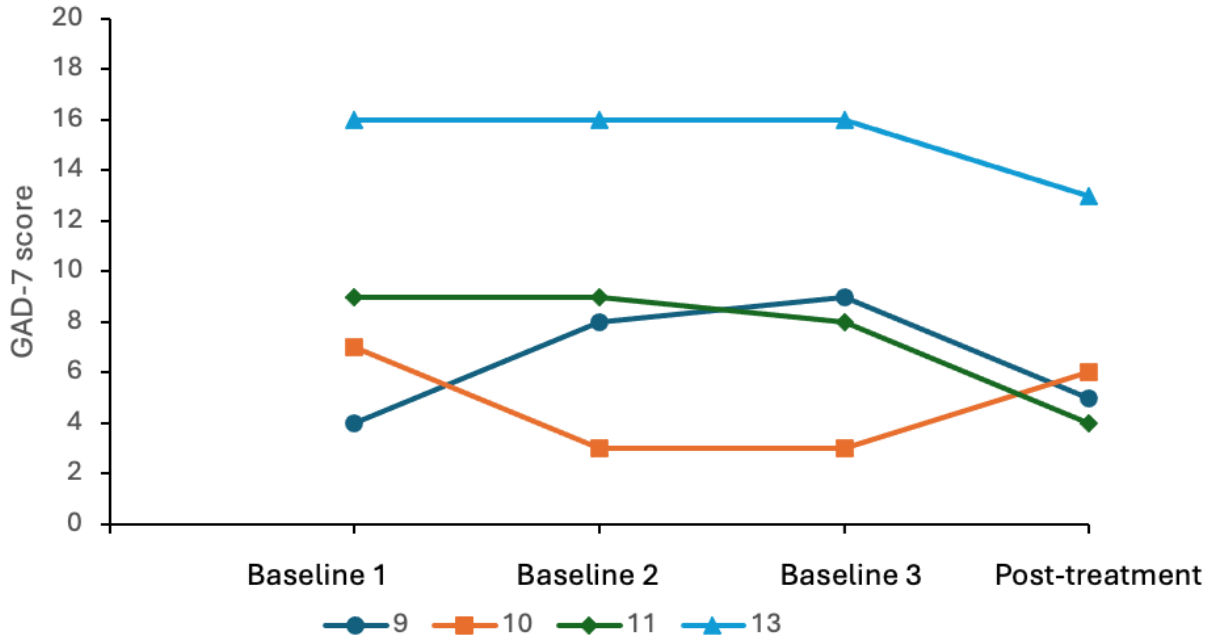

Figure s7. Generalized Anxiety Disorder-7 Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All but one showed improvement after crossover to CICT.

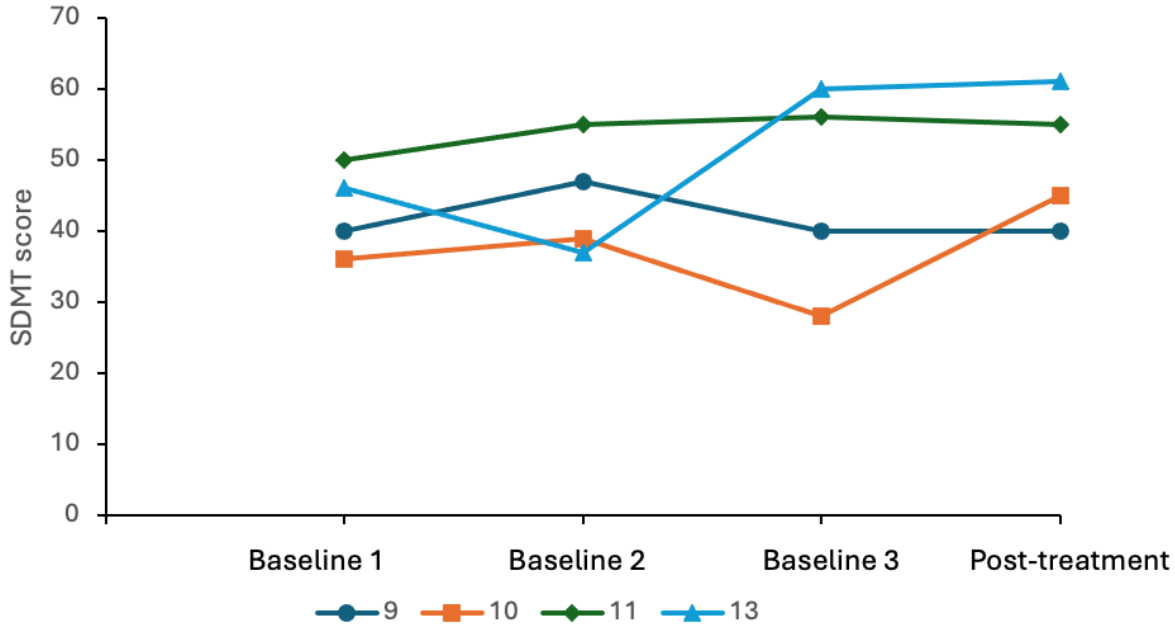

Figure s8. Symbol Digit Modalities Test (SDMT) Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). Half showed improvement after crossover to CICT.

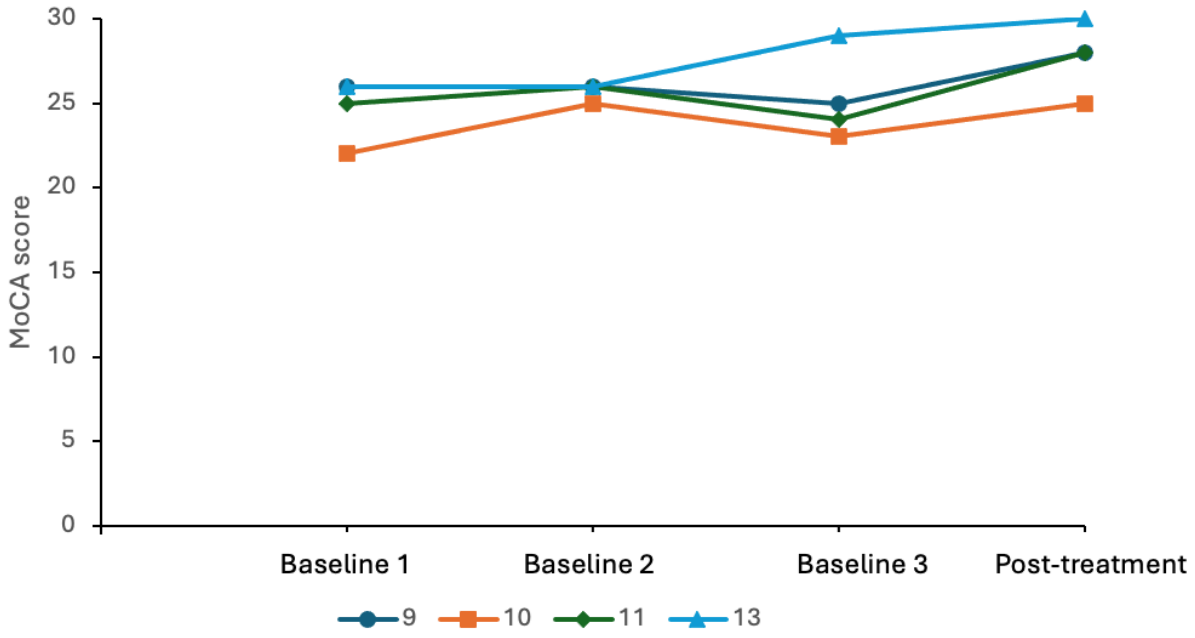

Figure s9. Montreal Cognitive Assessment Scores of Treatment-As-Usual (TAU) Participants Before and After Crossover to Constraint-Induced Cognitive Therapy (CICT). All showed improvement after crossover to CICT.

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