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Internet-delivered computerized cognitive & affective remediation training for the treatment of acute and chronic posttraumatic stress disorder: Two randomized clinical trials

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A B S T R A C T

Treatment of posttraumatic stress disorder (PTSD) is time and cost-intensive. New, readily implementable interventions are needed. Two parallel randomized clinical trials tested if cognitive/affective computerized training improves cognitive/affective functions and PTSD symptoms in acute (N = 80) and chronic PTSD (N = 84). Adults age 18–65 were recruited from an Israeli hospital emergency room (acute) or from across the United States (chronic). Individuals were randomized to an active intervention (acute N = *50,* chronic N = 48) that adaptively trains cognition and an affective positivity bias, or a control intervention (acute N = 30, chronic N = 36) of engaging computer games. Participants, blind to assignment, completed exercises at home for 30 min/day over 30 days (acute) or 45 min/day over 45 days (chronic). Primary outcomes were computerized cognitive/affective function metrics. Secondary outcomes were Clinician-Administered PTSD Scale (CAPS) total scores. In chronic PTSD, the active arm demonstrated facilitated speed of fearful face identification (F = 20.96, q < 0.001; d = 1.21) and a trend towards improvement in total PTSD symptoms (F = 2.91, p = 0.09, d = 0.47), which was due to improvement in re-experiencing symptoms (F = 6.14, p = 0.015; d = 0.73). Better cognitive performance at baseline moderated the training effect and was associated with more favorable improvements on both metrics. Cognitive and affective training does not have widespread benefit on symptoms and cognitive/affective functions in PTSD. Future studies targeting re-experiencing *a priori*, stratifying on cognitive capacity, and with modified methods to infer on mechanisms and optimized training parameters may be warranted. ClinicalTrials.gov Identifiers: NCT01694316 & NCT02085512.

1. Introduction

Posttraumatic stress disorder (PTSD) is a prevalent public health issue (Kessler et al., 1995) that is persistent (Kessler et al., 2017) and functionally impairing (Norman et al., 2007). Though efficacious treatments for PTSD exist, not all individuals will respond favorably (Cusack et al., 2016). Of established treatments, medications show small effect sizes (Hoskins et al., 2015) while trauma-focused psychotherapies have moderate effect sizes (Cusack et al., 2016). Nevertheless, many individuals do not seek or complete treatment (Spoont et al., 2014), and up to one half of completers continue to have residual symptoms (Bradley et al., 2005). Novel treatment options are needed for these and other individuals not responding or lacking access to first-line interventions.

Cognitive and affective training is an inexpensive and scalable treatment modality that may hold promise as a novel treatment. This approach employs repeated engagement with computerized tasks to engage specific cognitive or affective processes and trains them by adaptively modulating task difficulty levels to be slightly above current performance. Training cognitive and affective processes may exert beneficial effects on training targets and related cognitive/affective capacities. It may also improve symptoms, as impaired cognitive and

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affective functions may promote symptom maintenance, or, when trained above baseline to capacity, may promote remission. If efficacious, this approach has the distinct advantages of reducing healthcare provider, patient, and financial burden, being easily deliverable, being an enjoyable and convenient option, and having minimal side effects.

Computerized training regimens for affective disorders have typically targeted a cognitive or affective deficiency believed to relate to maintenance of symptoms. In anxiety disorders, there is an established attention bias towards disorder-relevant threatening stimuli (Pergamin-Hight et al., 2015), and prior studies have attempted to alter this bias through attention bias modification training (Cristea et al., 2015; Hakamata et al., 2010). In PTSD, although evidence for attention bias modification efficacy is mixed (Badura-Brack et al., 2015; Kuckertz et al., 2014; Schoorl et al., 2013), findings suggest modifying attention to negative or threatening stimuli via computerized training may be a viable treatment target.

Individuals with PTSD demonstrate impaired cognition (Aupperle et al., 2012a; Schuitevoerder et al., 2013; Scott et al., 2015), which predicts poorer outcomes to established treatments, e.g., psychotherapy (Falconer et al., 2013; Nijdam et al., 2015; Wild and Gur, 2008). Thus, investigators have employed computerized protocols to train cognitive functions in PTSD (Bomyea et al., 2015), in which improvements may have therapeutic effects on symptoms. In one study (Bomyea et al., 2015), a component of cognitive function was trained in PTSD using a computerized task, which was found to reduce PTSD re-experiencing symptoms and improve working memory. These findings illustrate the potential for adaptive computerized training to be beneficial for both cognition and symptoms in PTSD.

However, there are several barriers to wide-scale implementation. First, adherence to a training regimen delivered remotely in real-life settings, e.g., the participant's home, has not been assessed. Second, prior studies have employed training paradigms that target only specific biases or cognitive functions (Badura-Brack et al., 2015; Bomyea et al., 2015). Maximal therapeutic efficacy may be afforded by adaptively training multiple cognitive and affective processes in tandem. Third, no studies have investigated efficacy of cognitive/affective training in the acute phase of the disorder, i.e. 1–3 months post-trauma. This is important given the current paucity of effective interventions for preventing disorder progression (Shalev et al., 2011, 2012). Finally, characteristics moderating training effects have not yet been established, which is crucial for informing efforts to identify individuals appropriate for this intervention.

Here, we report findings from two randomized clinical trials assessing efficacy of internet-delivered cognitive and affective remediation training in two samples: a) trauma survivors with acute PTSD recruited in an emergency department; and b) trauma survivors with chronic PTSD remotely recruited from across the U.S. Our goals were as follows: 1) determine adherence to and engagement with an internet-delivered intervention; 2) establish efficacy of the intervention in improving cognitive and affective functioning (primary outcomes) and reducing (or preventing progression of) PTSD symptoms (secondary outcomes). Our intervention trained two broad constructs relevant to the expression and maintenance of PTSD: cognitive capacities (Aupperle et al., 2012b); and affective biases towards negative, threatening, or trauma-related stimuli (Armstrong et al., 2013; Naim et al., 2015; Olatunji et al., 2013; Thomas et al., 2013; Todd et al., 2015). We also conducted exploratory analyses to test: a) baseline moderators of the training effect on PTSD symptoms, focusing on demographic, clinical, and cognitive measures that have previously been found to moderate or predict PTSD treatment outcome; and b) whether improvement in training task performance mediated improvements in outcome measures, thereby providing candidates for key psychological process changes that may underlie intervention effects.

We expected dropout rates would be similar to that observed for electronically-delivered psychotherapy, i.e. around 33% (Fernandez et al., 2015), and would not differ by treatment arm. We also expected adherence to the protocol (i.e. training the requisite time each day for an adequate number of sessions) would occur at rates between 50 and 80% of study completers, given estimates from prior cognitive training studies (Meesters et al., 2018; Tedim Cruz et al., 2014). Given prior findings in PTSD (Bomyea et al., 2015; Kuckertz et al., 2014), we expected combined cognitive training and affective training to demonstrate benefits on both cognitive and affective functions as well as PTSD symptoms.

2. Methods

Complete details of the methods are available online in the Supplemental Methods. The following is an abbreviated description.

2.1. Study 1 (acute PTSD)

2.1.1. Participants

Participants were English or Hebrew-speaking trauma survivors ($N = 80$ exposed to car, work, or home accidents, burns, terrorist or physical attacks, or large scale disaster), ages 18–65, admitted to a hospital emergency department in Jerusalem following a traumatic event. Participants currently taking a benzodiazepine and/or in ongoing psychotherapy were excluded, but those with a current stable antidepressant regimen (i.e., at least 6 weeks) were permitted to participate(see Table 1).

2.1.2. Procedure

All procedures were carried out in accordance with the latest version of the Declaration of Helsinki and were approved by the Shaare Zedek Medical Center Helsinki Committee. Informed consent was obtained from all participants after the nature of the procedures had been fully explained. Participants identified via self-report measure, the PTSD Check List (PCL) (Weathers et al., 2013b), shortly post-trauma to be at high risk of PTSD development were invited to participate in the study. Participants were assessed with the Clinician-Administered PTSD Scale (CAPS) (Weathers et al., 2013a) and Structured Clinical Interview for DSM-IV (First et al., 2002) to establish diagnoses, and those not having exclusion criteria (open head injury, coma, pre-existing PTSD, lifetime psychotic illness or obsessive-compulsive disorder (OCD), suicide risk, substance dependence) completed an online cognitive and affective assessment battery and were then randomized separately by gender with a 5:3:2 allocation ratio to the combined cognitive/affective training intervention ($N = 50$) or one of two control groups: daily computer games ($N = 30$) that are fun and engaging but do not train any cognitive or affective functions (games), or daily reading of internet news and lifestyle articles of their choice ($N = 17$; reading). Our primary analysis focuses on utilizing the games control condition for comparison to active, since: a) it most effectively controls for the non-specific elements of the training; and b) it is congruent with the study in the chronic sample, which only utilized the games control condition. Subjects completed 30 consecutive days of daily training over 4–5 weeks for 30 min each day. Experimenters tracked engagement with daily exercises and offered reminder phone calls and e-mails as needed to maintain adherence. Once the training period was complete, the same assessments were repeated.

2.1.3. Outcome assessment

To address our aims, we utilized the post-treatment assessment time point as the primary outcome assessment (rather than a six month follow-up).

2.1.3.1. Primary outcomes: cognitive and affective functions. Cognitive and affective function was assessed using the internet-based Webneuro assessment battery (Silverstein et al., 2007). Cognitive tests measured sustained attention, working memory, task shifting, inhibition, processing speed, executive function, verbal learning, and verbal

Table 1
Participant demographics and characteristics at baseline.

Measure	Acute PTSD (n = 80)		Statistics	Chronic PTSD (n = 84)		Statistics
	Active (n = 50)	Control (n = 30)		Active (n = 48)	Control (n = 36)	
Age (yrs)	35.08 (10.13)	37.87 (13.01)	$t = -1.07$, $p = 0.29$	41.50 (13.33)	38.50 (14.37)	$t = 0.93$, $p = 0.36$
Gender (M/F)	24 male/26 female	12 male/18 female	$\chi^2 = 0.48$, $p = 0.49$	23 male/25 female	17 male/19 female	$\chi^2 = 0.01$, $p = 0.95$
Ethnicity	Caucasian (n = 50)	Caucasian (n = 30)	N/A[a]	American Native (n = 1) Asian (n = 1) African-American (n = 2 Caucasian (n = 37)) Mixed/Other (n = 7)	American Native (n = 1) Asian (n = 1) African-American (n = 6) Caucasian (n = 22) Mixed/Other (n = 6)	$\chi^2 = 4.26$, $p = 0.37$
Education (yrs)	14.29 (3.50)	15.15 (3.79)	$t = -0.97$, $p = 0.33$	14.58 (2.12)	14.28 (1.61)	$t = 0.72$, $p = 0.47$
Psychiatric Medications	No medications (n = 50) SSRIs/SNRIs (n = 0) Benzos (n = 0)	No medications (n = 29) SSRIs/SNRIs (n = 1) Benzos (n = 0)	N/A[a]	No meds (n = 26) SSRIs/SNRIs (n = 13) Benzos (n = 9)	No meds (n = 11) SSRIs/SNRIs (n = 15) Benzos (n = 10)	$\chi^2 = 4.66$, $p = 0.10$
CAPS Total Score	61.88 (17.07)	61.97 (19.45)	$t = -0.02$, $p = 0.98$	68.56 (14.13)	66.29 (18.10)	$t = 0.63$, $p = 0.53$
CAPS Reexperiencing	9.90 (4.63)	10.57 (4.55)	$t = -0.38$, $p = 0.71$	15.81 (7.41)	17.90 (7.07)	$t = -1.22$, $p = 0.23$
CAPS Avoidance	14.28 (4.63)	13.63 (5.07)	$t = 0.26$, $p = 0.80$	29.95 (8.17)	28.13 (8.99)	$t = 0.91$, $p = 0.37$
CAPS Hyperarousal	10.62 (3.92)	10.63 (3.88)	$t = 0.05$, $p = 0.96$	23.64 (5.24)	21.18 (6.23)	$t = 1.87$, $p = 0.07$
BDI Total Score	21.33 (10.15)	20.60 (9.65)	$t = 0.31$, $p = 0.76$	31.30 (8.49)	28.53 (10.55)	$t = 1.33$, $p = 0.19$
Current MDD	36 yes, 14 no	18 yes, 12 no	$\chi^2 = 1.23$, $p = 0.27$	28 yes, 20 no	19 yes, 17 no	$\chi^2 = 0.26$, $p = 0.61$
Current Panic	1 yes, 49 no	1 yes, 29 no	$\chi^2 = 0.14$, $p = 0.71$	10 yes, 38 no	6 yes, 30 no	$\chi^2 = 0.23$, $p = 0.63$
Current Agoraphobia	1 yes, 49 no	1 yes, 29 no	$\chi^2 = 0.14$, $p = 0.71$	7 yes, 41 no	5 yes, 31 no	$\chi^2 = 0.01$, $p = 0.93$
Current SAD	6 yes, 44 no	1 yes, 29 no	$\chi^2 = 1.76$, $p = 0.18$	20 yes, 28 no	12 yes, 24 no	$\chi^2 = 0.61$, $p = 0.44$
Current GAD	1 yes, 49 no	1 yes, 29 no	$\chi^2 = 0.14$, $p = 0.71$	8 yes, 40 no	8 yes, 28 no	$\chi^2 = 0.41$, $p = 0.52$

Unless otherwise noted, numbers refer to measure means and standard deviations are included within parentheses after the mean; [a]In these cases a statistical test was not possible due to a lack of variance or a zero value for one or more of the categories; BDI = Beck Depression Inventory; Benzos = benzodiazepines; CAPS = Clinician Administered PTSD Scale for DSM-IV; F = female; GAD = generalized anxiety disorder; M = male; MDD = major depressive disorder; SAD = social anxiety disorder; SNRI = serotonin and norephinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; yrs = years.

memory. Affective tasks measured facial affect recognition, memory for affective faces, emotional conflict, and emotional conflict regulation.

2.1.3.2. Secondary outcomes: PTSD symptoms. PTSD symptom severity was quantified using the CAPS for DSM-IV. Due to the short duration intervention, symptom scores utilized for assessing treatment efficacy were quantified over the past week. Other assessments included the SCID and the Beck Depression Inventory (Beck et al., 1996).

2.1.4. Cognitive/affective remediation training intervention

The intervention consisted of daily 30-min sessions for 30 days. On each training day, participants were given access to a battery of 8 tasks accessible via an online survey page, which routed via single sign-on to the game hosts. Participants were instructed to train each task for 3–4 min, the order of which was pseudo-randomized across training sessions. Tasks trained selective attention, working memory, task shifting, processing speed, and positive emotion recognition/resisting negative emotion distraction. This approach allowed for a variety of training experiences and diminished boredom. All tasks included "game-like" features, i.e. they were visually engaging and motivating, and provided feedback about performance. Difficulty level increased as performance improved.

2.1.5. Computer games and reading conditions

Participants engaged in a pre-selected panel (which remained the same each day) of daily computer games freely available and hosted via online gaming sites. These games had fun and engaging graphics, provided feedback, etc., like the training tasks, but did not train any specific cognitive or affective function.

2.2. Study 2 (chronic PTSD sample)

2.2.1. Participants

Participants ($N = 84$), ages 18–65, were recruited through advertisement from across the U.S. to participate in a computerized intervention study. Individuals were required to meet either full or partial diagnostic criteria for PTSD (sub-threshold severity on either Criterion C or Criterion D, but required to meet all other diagnostic criteria) in the DSM-IV diagnostic framework (APA, 2000) as assessed by the CAPS. As only 5 of 84 individuals were sub-threshold, we refer to this sample as the "chronic PTSD" sample for ease of communication. Participants currently taking a benzodiazepine and/or in ongoing psychotherapy were excluded, but those with a current stable antidepressant regimen (i.e., at least 6 weeks) were permitted to participate. When the trial commenced, participation was originally limited to veterans. However, this eligibility criterion was changed about 6 months later to allow non-veterans to participate. This facilitated more rapid recruitment and greater generalizability of findings.(see Table 1)

2.2.2. Procedure

All procedures were carried out in accordance with the latest version of the Declaration of Helsinki and were approved by the Stanford University Institutional Review Board. Informed consent was obtained from all participants after the nature of the procedures had been fully explained. Participants were initially screened for probable PTSD via online survey using modified probes from the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) and then completed the PCL and BDI. Those participants with a score of 45 or more on the PCL (probable PTSD) were invited to undergo online and cognitive/affective assessment and then clinical assessment with the CAPS and SCID by telephone or videoconference. After assessment and eligibility determination (no current or recent substance dependence, neurological disorder, suicide risk, history of psychosis, bipolar, or OCD), participants were randomly assigned in a parallel design to one of two groups: cognitive/affective remediation training ($N = 48$) or control games ($N = 36$). Participants were asked to practice assigned exercises once a day for 35–45 min for a total of 45 days. Experimenters tracked daily participant engagement, and participants were contacted by phone or e-mail if they missed more than two consecutive training days. At the end of the 45-day training period, participants were invited to retake assessments.

2.2.3. Outcome assessment

As in the acute PTSD sample, we utilized the post-treatment assessment time point as the primary outcome assessment.

2.2.3.1. Primary outcomes: cognitive and affective functioning. Participants completed an English language version of the same aforementioned internet-based cognitive and affective battery (Silverstein et al., 2007).

2.2.3.2. Secondary outcomes: PTSD symptoms. Same as the acute PTSD sample.

2.2.4. Cognitive/affective remediation training intervention

On each training day, participants were instructed to train each of 11 tasks (those utilized in Study 1 with one substituted cognitive task and 3 additional affective tasks not included in Study 1 due to English language content) for 3–4 min. The substituted cognitive task trains task shifting, while three additional affective games trained attention towards positive affective stimuli, identification of emotional faces, and identification of complex emotional stimuli.

2.2.5. Computer games comparator condition

In contrast to the acute PTSD sample, only engaging computer games was offered as a control arm. Administration and tracking of engagement was the same as in the acute sample.

2.3. Statistical analyses

2.3.1. Assessing training effects on outcomes

For both studies, intervention effects on primary and secondary outcomes ($p < 0.05$ criterion) were assessed using a longitudinal linear mixed model analysis in line with the intent-to-treat principle. False discovery rate (FDR) correction was utilized to control for Type I error inflation arising from multiple cognitive and affective outcomes.

2.3.2. Assessing improvement on training task performance

To verify learning occurred over the training regimen, we tested whether participants in the training arm demonstrated significant improvement in task performance over time, and using linear mixed models we estimated individual intercept and slope parameters for each participant's starting point and rate of improvement on each task over time, respectively.

2.3.3. Assessing baseline moderation of training effects

Exploratory moderation analyses focused on the following variables shown in prior studies to moderate or predict PTSD treatment outcome: age (Norr et al., 2018), depression severity (Cloitre et al., 2017), PTSD symptom severity (Cloitre et al., 2016), emotion regulation (Cloitre et al., 2016), and delayed verbal memory (Nijdam et al., 2015). As logical controls to establish specificity of some of the aforementioned variables, i.e. related characteristics that may account for observed effects, we also examined participant gender, regular psychiatric medication use (yes/no), years of education, and overall cognitive performance.

2.3.4. Assessing mediation of training effects on outcomes by training task performance improvements

To link improvements in specific trained processes to improvements in outcome measures, we conducted an exploratory analysis to test whether learning during training mediated improvements in outcome

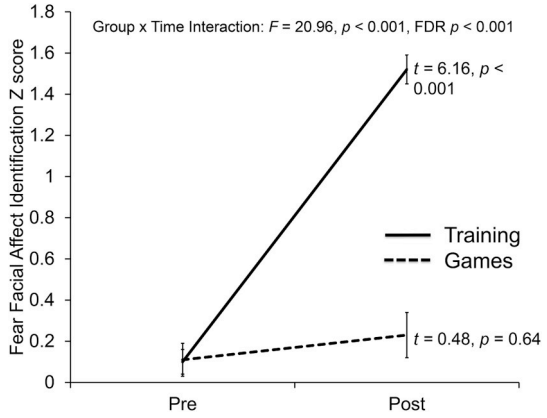

Fig. 1. Cognitive/Affective Training Improves Speed of Fearful Facial Affect Identification in Chronic PTSD. Figure depicts the predicted mean values for the age and gender-corrected Z scores for fearful facial affect identification reaction times from the linear mixed model at pre and post assessment time points for the active ($N = 48$) and control arms ($N = 36$). T-statistics and p values indicate are the statistics for the within-group parameter from the linear mixed model specifying trajectory of change over time. Error bars indicate ± 1 standard error. FDR = false discovery rate.

measures. For those metrics showing a significant differential change from pre-to-post treatment, the random effect slope estimates from 2.3.2 (individual participant improvement in performance on each training task) were carried to a second-level analysis to test whether training task performance improvements mediated the effect of time on the outcome measure of interest.

2.4. Power calculation

Power was estimated based on training effects on cognitive and affective functions in the active compared to control arm from a pilot sample (N = 13 randomized to each arm). The study was designed to provide sufficient power to detect a difference in cognitive and affective outcomes by treatment arm, but not to detect moderation or mediation effects or training effects on symptoms.

3. Results

3.1. Participant rates of completion and adherence

See Supplemental Results for complete details.

3.1.1. Acute PTSD

In brief, dropout rates were 24% (12 of 50) in the active arm and 20% (6 of 30) in the control games arm. Of those remaining in the protocol, rates of adherence to completing the minimal adequate "dose" (at least 20 training sessions) over the 30-day training period were 71% in the active arm (27 of 38) and 92% in the control arm (22 of 24). Rates of dropout and number of training sessions completed did not differ between arms. There were no adverse events reported.

3.1.2. Chronic PTSD

In brief, dropout rates were 35% (17 of 48) in the active arm and 33% (12 of 36) in the control games arm. Of those remaining in the protocol, rates of adherence to completing the minimal adequate "dose" (completing at least 30 training sessions) over the 45-day period were 77% in the active arm (24 of 31) and 75% in the control arm (18 of 24). Rates of dropout and number of training sessions completed did not differ between arms. There were no adverse events reported.

3.2. Primary outcomes: cognitive and affective functions

See Supplemental Results and Tables S1 and S2 for complete results.

3.2.1. Acute PTSD

After FDR correction, the only metric displaying a significant differential effect by treatment arm was reaction time to happy facial affect identification (treatment arm × time interaction $F = 12.24$, $p = 0.001$, FDR-corrected $p = 0.037$; Cohen's $d = 0.90$) (Fig. S3). This interaction was driven entirely by the control arm. Individuals in the active intervention displayed equivalent performance at pre- and post-treatment on happy facial affect processing speed (within-group trajectory of change: $t = 0.86$, $p = 0.392$), while individuals in the control games displayed a substantial increase in reaction times (within-group trajectory: $t = -3.25$, $p = 0.002$). *Post-hoc* exploration of this effect (see Supplemental Methods) showed greater reaction time increases in the control arm were associated with worsening of PTSD numbing symptoms. For completeness, we also examined the active arm vs. the reading control arm effect on these metrics. We detected no statistically significant differential changes on primary outcomes.

3.2.2. Chronic PTSD

Only one metric displayed a differential change across arms from pre-to post-treatment and survived correction for multiple comparisons. This was reaction time to fearful facial affect identification ($F = 20.96$, $p < 0.001$, FDR-corrected $p < 0.001$; $d = 1.21$). Individuals in the active intervention displayed a large reduction in reaction times, i.e. quicker responses, in identifying fearful facial affect (within-group trajectory of change: $t = 6.16$, $p < 0.001$), while individuals in the control games maintained equivalent performance (within-group trajectory of change: $t = 0.48$, $p = 0.64$) (Fig. 1). Changes in fearful facial affect processing speed were not correlated with changes in total PTSD symptoms, nor were they correlated with improvements in PTSD symptom dimensions (all $p's > 0.17$).

3.3. Secondary outcomes: PTSD symptoms

3.3.1. Acute PTSD

Although both groups demonstrated a significant reduction in PTSD symptoms (CAPS total scores) ($F = 58.11$, $p < 0.001$), there was no significant differential symptom reduction by treatment arm ($F = 0.30$, $p = 0.58$; $d = 0.06$). There was also no significant effect of treatment arm on symptom reductions for re-experiencing ($F = 1.20$, $p = 0.275$; $d = 0.12$), avoidance/numbing ($F = 0.80$, $p = 0.37$; $d = 0.02$), or hyperarousal domains ($F = 0.76$, $p = 0.39$, $d = 0.33$). For completeness, we likewise compared the active arm vs. the reading control arm. We detected no statistically significant differential changes on PTSD total symptoms or symptom dimensions.

3.3.2. Chronic PTSD

Both arms displayed a significant attenuation of PTSD symptoms ($F = 77.66$, $p < 0.001$), and there was a statistical trend towards a more prominent reduction in total PTSD symptoms in the training arm relative to the control games ($F = 2.87$, $p = 0.09$; $d = 0.47$). Given prior findings for computerized training evoking a domain-specific reduction in re-experiencing symptoms (Bomyea et al., 2015), we tested whether this trend-level effect is capturing a change in re-experiencing symptoms specifically. A follow-up mixed model revealed a significant treatment arm x time effect on re-experiencing symptoms ($F = 6.14$, $p = 0.015$; Bonferroni-corrected p = 0.045; $d = 0.73$), with those in the training arm displaying more prominent reductions in PTSD re-experiencing symptoms ($t = -5.98$, $p < 0.001$) relative to those in the control games ($t = -2.11$, $p = 0.038$) (Fig. 2). Neither avoidance/numbing symptoms ($F = 1.35$, $p = 0.25$) nor hyperarousal symptoms ($F = 0.34$, $p = 0.56$) showed any evidence of differential change between groups (Fig. 4).

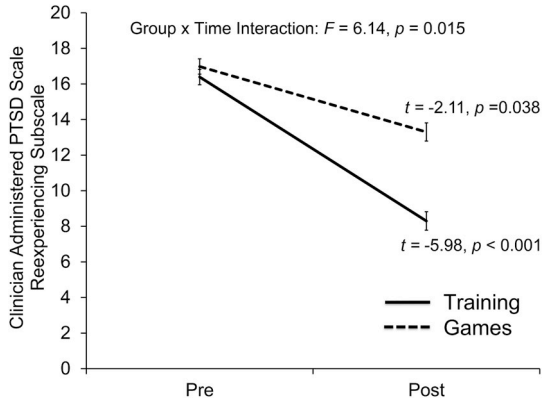

Fig. 2. Cognitive and Affective Remediation Training Attenuates Reexperiencing Symptoms in Chronic PTSD. Figure depicts the predicted mean values for the Clinician-Administered PTSD Scale Reexperiencing subscale scores from the linear mixed model at pre and post assessment time points for the training arm ($N = 48$) and control games arm ($N = 36$). T-statistics and p values indicate are the statistics for the within-group parameter from the linear mixed model specifying trajectory of change over time. Error bars indicate ± 1 standard error.

3.4. Assessing performance improvement on training tasks

Since the chronic PTSD sample displayed training effects attributable to the training arm, we assessed whether participants improved performance on the training tasks. We considered this a logical necessity for training effects on outcomes to be interpretable. Linear mixed models of session data in the training arm showed the expected improvement over time across all training tasks (all fixed effect coefficients of Time indicated performance improvements and were statistically significant with $p's < 0.021$).

3.5. Exploratory analyses of treatment moderation, mediation, and within-arm outcome prediction

3.5.1. Acute PTSD

As this sample did not show significant or trend-level group x time effects on outcomes attributable to the training arm, we did not pursue these analyses.

3.5.2. Chronic PTSD

3.5.2.1. Baseline moderation by clinical, demographic, and cognitive measures. Two outcomes showed a significant group x time effect in this sample (fearful facial affect identification speed and PTSD re-experiencing symptoms), while CAPS total scores showed a group x time trend-level effect ($p = 0.09$). We thus tested if baseline demographic and clinical characteristics moderated the intervention effect on these metrics. See Supplemental Results for details. In brief, better overall baseline cognitive performance moderated the intervention effect on both fearful facial affect identification speed and PTSD total symptoms, with individuals in the training arm displaying better cognitive performance demonstrating larger improvements on both metrics (Fig. 3). Self-reported baseline use of cognitive reappraisal also moderated the intervention effect on total PTSD symptoms. Individuals in the training arm reporting less frequent use of cognitive reappraisal demonstrated greater improvements in PTSD symptoms (Fig. 4). To examine whether these two effects were related, we correlated baseline overall cognitive performance scores with self-reported use of cognitive reappraisal. The two measures were unrelated (Spearman's rho = -0.08, $p = 0.51$).

3.5.2.2. Baseline outcome prediction in the training arm by training task initial performance. See Supplemental Results and Tables S3–S5.

3.5.2.3. Mediation of training effects by improvements in daily training performance. See Tables S3–S5 for complete results. In brief, greater improvements over time on a task training divided attention mediated the training-related facilitation of fearful facial affect processing speed. There was no significant mediation of PTSD re-experiencing or total symptom changes.

4. Discussion

We found that computerized cognitive/affective training in PTSD demonstrates rates of dropout similar to those of electronically-delivered psychotherapy (Fernandez et al., 2015) and rates of treatment adherence similar to those observed in prior cognitive training studies (Meesters et al., 2018; Tedim Cruz et al., 2014). This suggests it is feasible to remotely deliver to individuals with acute and chronic PTSD in real-world settings. The pattern of findings provides initial evidence that adaptively training (at least certain) cognitive/affective functions in PTSD can exert downstream effects not specific to the capacity trained. This generalization effect is the ultimate goal of such training paradigms, and the current findings provided limited though potentially encouraging evidence to support further investigation. In aggregate, although an internet-delivered computerized cognitive and affective training intervention in PTSD is feasible, we cannot provide evidence for a substantial or widespread benefit on cognitive/affective functions and PTSD symptoms. However, training effects may be more substantial for a pre-selected population subset. Though the number of individuals completing the full protocol was sufficient to provide adequate two-sample *t*-test estimated power to detect effects on primary outcomes utilizing an FDR correction, which was implemented here, power analyses are currently not well implemented for the linear mixed model approach (Chi et al., 2018), which is the preferred analytic approach for randomized clinical trials (Raudenbush and Liu, 2000). Though we therefore cannot definitively conclude that this study provided power comparable to that estimated by power analyses, the fact that sample sizes far exceeded the number necessary to detect two-sample *t*-test FDR-corrected effects based upon preliminary data effect size estimates provides confidence that both studies were adequately powered. This does not preclude the possibility, however, that future larger studies may better determine if the changes observed here are a subset of potentially more prominent and widespread benefits, as these studies were not designed to provide sufficient power to detect training effects on symptoms, for example.

There are several limitations to this study. First, we did not select individuals for the training intervention based upon cognitive or affective impairment, which may have resulted in inefficient treatment targeting. Second, acute and chronic PTSD samples received slightly different versions of the training battery (English language content on some tasks was unable to be modified). Furthermore, training period duration varied slightly between samples, as pilot data suggested different rates of study disengagement.

In summary, we recommend the following in guiding future research efforts in this area: a) focus efforts on chronic PTSD and re-experiencing symptoms, specifically, as a primary outcome; b) stratify individuals on overall cognitive capacity at baseline and prior to randomization to verify training effects are moderated by this intrinsic capacity; c) examine various durations of training (daily session lengths and training periods) to determine optimal parameters; d) incorporate repeated cognitive, affective, and symptom assessments throughout training periods to better establish temporal precedence for causal inference of intervention mechanisms; and e) target one or more closely-related cognitive or affective capacities with training to better isolate specific mechanisms of symptom change.

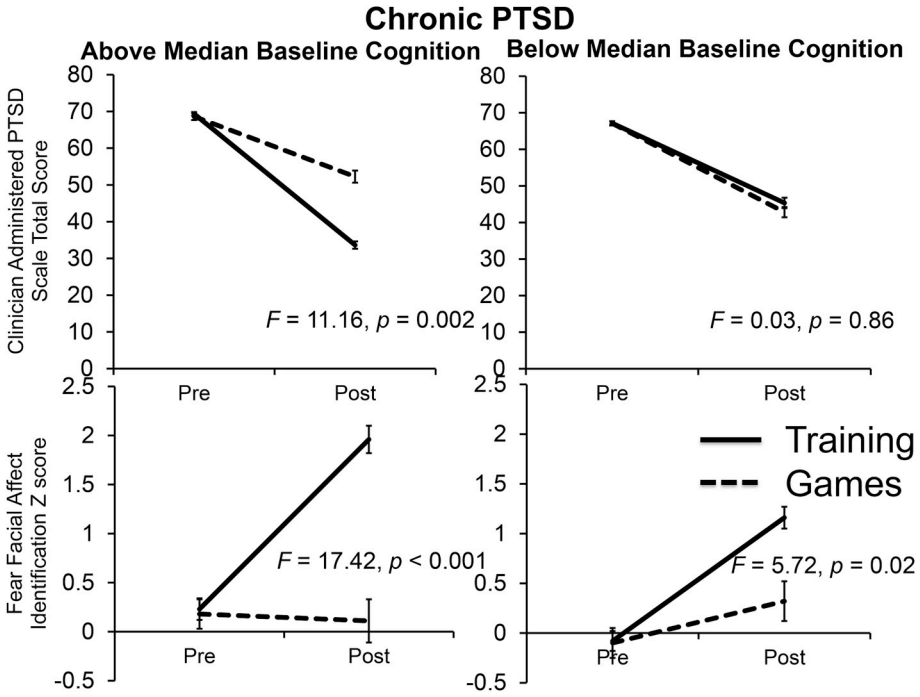

Fig. 3. Baseline Cognitive Function Moderates the Effect of Cognitive and Affective Remediation Training on Affective and Symptom Changes in Chronic PTSD. Figure depicts the predicted mean values (derived from the respective linear mixed models) at pre and post assessment time points for the Clinician-Administered PTSD Scale total scores (top row) and the fearful facial affect identification reaction time Z scores (bottom row) separately by individuals based upon above or below median overall cognitive performance composite scores at baseline in the chronic PTSD sample (N = 48 active, N = 36 control). The treatment arm x time statistics are displayed by median split for illustrative purposes. Note that symptom reductions and fearful facial affect identification reaction time improvements are more prominent for individuals in the training intervention when displaying better cognitive performance at baseline.

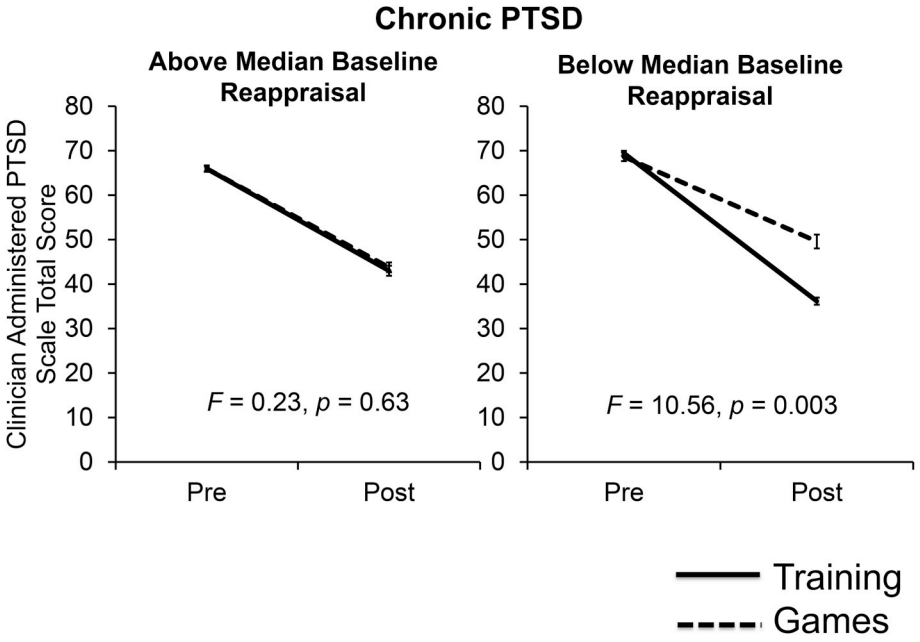

Fig. 4. Baseline Usage Frequency of Reappraisal Moderates the Effect of Cognitive and Affective Remediation Training on PTSD Symptom Change in Chronic PTSD. Figure depicts the predicted mean values (derived from the linear mixed model) at pre and post assessment time points for the Clinician-Administered PTSD Scale total scores separately by individuals based upon above or below median self-reported usage of cognitive reappraisal at baseline in the chronic PTSD sample (N = 48 active, N = 36 control). The treatment arm x time statistics are displayed by median split for illustrative purposes. Note that symptom reductions are more prominent for individuals in the training intervention when reporting less frequent usage of cognitive reappraisal at baseline.

Author disclosures

The authors declare no competing financial interests relevant to this research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.05.007.

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