Confirmatory Efficacy of Cognitive Enhancement Therapy for Early Schizophrenia: Results From a Multisite Randomized Trial

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Objective: Cognitive enhancement therapy (CET) is an 18-month comprehensive cognitive remediation intervention designed to improve cognition and functioning among patients with schizophrenia. The current study sought to confirm previously observed benefits of CET on cognitive and behavioral outcomes in the early course of the condition in a large multisite trial.

Methods: Overall, 102 outpatients with early-course schizophrenia were randomly assigned to 18 months of CET (N=58) or enriched supportive therapy (EST; N=44). Participants completed cognitive, social adjustment, and symptom assessments at baseline and at 9 and 18 months. Composite indices were calculated for these outcomes. Mixed-effects models investigated differential changes in outcomes between CET and EST. Because of a high attrition rate, sensitivity analyses of data from treatment completers (N=49) were conducted.

Results: The effects of CET on improved overall cognition were confirmed and tentatively confirmed for social cognition in both intent-to-treat and completer analyses, and beneficial effects on attention/vigilance were also observed. An effect of CET on social adjustment was not confirmed in the analyses, because both CET and EST groups had considerably improved social adjustment. Although not statistically significant, the between-group effect size for CET's effect on social adjustment doubled from the intent-to-treat (Cohen's d=0.23) to completer analyses (Cohen's d=0.51) (p=0.057). Both groups displayed similar symptom improvements.

Conclusions: CET effectively improved cognition among patients with early-course schizophrenia. The functional benefits of CET appeared to increase with treatment retention. Further research is needed to understand predictors of attrition and mechanisms of change during CET for this population.

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Cognitive impairments are hallmarks of schizophrenia (1, 2) and are barriers to functional recovery from this condition (3, 4). The impact of pharmacotherapies on cognition of patients with schizophrenia has been limited (5), and cognitive remediation interventions therefore remain the most promising approaches for improving cognition and functioning among such patients (6–8). Nearly two decades of research have established evidence for beneficial and durable effects of cognitive enhancement therapy (CET) (9) on cognition and functional recovery in the early (10, 11) and chronic (12, 13) stages of the condition and among individuals with comorbid substance misuse (14). CET is a comprehensive, 18-month intervention that integrates computer-based neurocognitive training with structured social-cognitive groups (9). The effects of CET in early-course schizophrenia have yet to be replicated and may

HIGHLIGHTS

- Cognitive enhancement therapy (CET) is a promising cognitive remediation intervention for early-course schizophrenia, and confirmatory evidence of its effects would further support the use of CET for the treatment of patients with cognitive and functional impairments.
- This study sought to confirm previously observed cognitive and behavioral effects of CET on patients with early-course schizophrenia with a larger multisite design.
- The results of the current trial confirmed the overall cognitive benefits of CET and tentatively confirmed improved social cognition among patients with early-course schizophrenia.
- The results add to evidence that CET is an effective intervention for patients with early-course schizophrenia, particularly when the full CET treatment is provided.

reduce long-term disability. Confirmatory evidence of CET's efficacy is critical for the continued advancement of treatment for early-course schizophrenia.

The early stage of schizophrenia is hypothesized to be an optimal therapeutic window for cognitive remediation, given that treatments may capitalize on neuroplasticity reserves (15, 16). Nearly a dozen clinical trials have indicated that cognitive remediation is efficacious for early-course schizophrenia (8). Findings suggest that, compared with individuals with chronic schizophrenia, those in the early stage of the disease may have greater improvements in cognition and functioning after cognitive remediation (17, 18), highlighting the potential of these interventions to expedite recovery and prevent long-term disability. In 2009, Eack and colleagues (10) reported the results of a randomized controlled trial (RCT) of 58 individuals with early-course schizophrenia (mean±SD illness duration=3.2±2.2 years) randomly assigned to 2 years of either CET (N=31) or an enriched supportive therapy (EST; N=27) comparison intervention. Compared with patients treated with EST, those treated with CET had significantly greater improvements in neurocognition (Cohen's d=0.46), social cognition (Cohen's d= 1.55), social adjustment (Cohen's d=1.53), and psychiatric symptoms (Cohen's d=0.77).

Although promising, the results of this initial trial of CET for early-course schizophrenia were based on a modest sample size of patients with schizophrenia at a single study site. The current study sought to confirm the previously observed positive cognitive and behavioral impacts of CET on patients with early-course schizophrenia in a larger two-site clinical trial. On the basis of findings from previous trials, we hypothesized that CET-treated participants would have significantly greater improvements in the primary outcomes of cognition and social adjustment compared with patients in an active supportive therapy.

METHODS

Procedures

This two-site (Boston and Pittsburgh), 18-month RCT of CET (N=58) versus EST (N=44) for treatment of patients with early-course schizophrenia was conducted over a period ranging from June 2012 to May 2018. The study was reviewed and approved annually by Beth Israel Deaconess Medical Center and University of Pittsburgh institutional review boards. Participants were recruited from several well-established outpatient treatment programs for early-course schizophrenia in both Pittsburgh (N=53) and Boston (N=49). Before study enrollment, all participants provided written informed consent. Potential participants were screened for inclusion criteria (see below), with final eligibility confirmed in videotaped interview consensus meetings (12). Eligible participants were then randomly assigned by an independent data manager by using a computer-generated randomization procedure. Participants were randomly assigned on a within-site basis with a higher ratio assigned to CET to facilitate the formation of the social-cognitive groups. Participants completed assessments at baseline and at 9 and 18 months.

Participants

In total, 102 outpatients participated in this study, of whom 58 were randomly assigned to receive CET and 44 to receive EST. Inclusion criteria for this study were a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder confirmed by the Structured Clinical Interview for the DSM-IV-TR (SCID) (19) and consensus diagnostic meetings, including study clinicians and raters that utilized all clinical data from study assessments and patient psychiatric records; onset of psychotic symptoms within the past 10 years; clinically stable positive symptoms for at least 2 months before enrollment; adherence to prescribed antipsychotic medication as determined by the clinical team; age 18–55 years; IQ score ≥80; ability to read and speak fluent English; and significant social and cognitive disability determined by the Cognitive Style and Social Cognition Eligibility Interview (10, 12, 14). There is not yet consensus on the definition of early-course schizophrenia, with duration of the illness ranging from 1 to 10 years in the literature (20). The sample was considered early course with an average duration of schizophrenia of 3.7±2.3 years, and most of the participants were ill <5 years (N=78, 76%). These durations were similar to those of the sample in the previous early-course CET trial (10), who had an illness duration of 3.2±2.2 years, with 78% (N=45) of the sample being ill for <5 years.

Participants were excluded if they had significant neurological or medical disorders producing cognitive impairments, persistent suicidal or homicidal ideation or behavior, substance abuse or dependence meeting *DSM-IV* criteria within the past 3 months confirmed by the SCID (19), or any MRI contraindications, such as ferromagnetic objects in the body. A diagram of participant flow through the trial is presented in an online supplement to this article. The overall attrition rate was high (i.e., 49%). Treatment groups had similar attrition rates (CET, 50%, and EST, 48%), and did not significantly differ by study site (Boston, 55%, and Pittsburgh, 43%). Because of the high level of attrition, sensitivity analyses were performed to test for any potential differences in the findings between the intent-to-treat sample (N=102) and those who completed treatment (N=49).

Treatments

Participants received antipsychotic medications approved for schizophrenia or schizoaffective disorder prescribed by a psychiatrist throughout the trial. Antipsychotic dose and adherence did not significantly differ between the CET and EST groups at baseline or any other time point.

CET. CET consists of 60 hours of weekly computer-based neurocognitive training to improve attention, memory, and problem-solving and 45 small-group sessions to improve

social cognition. Designed as a recovery-phase intervention, CET is both active and performance-based, targeting illness-related developmental impairments in cognition that are barriers to patients' functional recovery (21). To encourage socialization, neurocognitive training is implemented in participant pairs and conducted by a CET therapist or coach. The weekly 1-hour neurocognitive training sessions begin with Ben-Yishay et al.'s orientation remediation module to improve different aspects of attention and processing speed (22). After approximately 3 months of attention training, three to four pairs of participants combine to form a social-cognitive group. The 1.5-hour weekly social-cognitive group sessions use experiential learning opportunities to teach a wide range of social-cognitive abilities designed to enhance social wisdom and interpersonal success. CET groups are conducted by at least two master's-level or higher therapists. Neurocognitive training in memory and problem-solving using Bracy's PSSCogReHab software (23) proceeds concurrently with the social-cognitive groups after attention training and throughout the remainder of treatment. A complete description of the curriculum is given in the CET manual (9).

EST. EST is a weekly, 1-hour, individualized psychotherapy approach that utilizes components of the basic and intermediate phases of personal therapy (24) and was used as an active comparison treatment to account for the nonspecific effects of CET (e.g., psychoeducation and provision of a skilled empathic therapist). EST incorporates psychoeducation, illness management, and healthy coping strategies in the context of a supportive therapeutic environment. EST is divided into two phases, which are sensitive to each participant's stage of recovery. Phase 1 concentrates on general psychoeducation, the role of stress in the illness, and techniques to minimize or avoid stressful situations. In phase 2, a personalized approach is used to help participants recognize their early cues of distress and to develop healthy coping strategies. Each phase of treatment is provided for approximately 9 months for a total of 18 months.

The same clinicians provided both CET and EST to minimize the possibility of therapist effects. Given that CET and EST are manualized, such that CET sessions are held approximately 2.5 hours per week once the social-cognitive groups begin, and that EST sessions are conducted 1 hour per week, we did not attempt to artificially match treatment hours. As predicted, given the CET group and computer sessions, the CET and EST groups significantly differed in the number of attended sessions (71.1±57.7 and 25.3±20.6 sessions, respectively, $p<0.001$). This difference did not moderate differential change at 18 months for any primary or secondary outcome, indicating that a response to CET was not associated with significantly more attended CET sessions relative to fewer attended EST sessions. Fidelity to the treatments was monitored throughout the study via random review of audio and video recordings of sessions by three authors (S.S.H., D.P.G., S.M.E.).

Measures

At each time point (i.e., baseline and at 9 and 18 months), the participants completed a comprehensive battery of cognitive and behavioral assessments conducted by assessors blind to treatment assignment. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (25) is the standard cognitive assessment for clinical trials of cognitive enhancers and was used to evaluate cognition. MCCB assesses overall cognition and the domains of processing speed, attention/vigilance, working memory, verbal learning, visual learning, problem-solving, and social cognition. The MCCB produces T-scores scaled to a mean±SD of 50±10 corrected for age and sex, as recommended by Kern et al. (26), with higher scores indicating better cognitive performance. The overall cognitive composite and cognitive domains were considered primary outcomes. A social adjustment composite was also created to avoid excessive univariate inference testing by converting individual measure scores to a common z-metric, averaging scores, and then scaling them to T-scores of 50±10. Scale items were reverse coded, as necessary, such that higher scores represented better outcomes. The social adjustment composite was considered a primary outcome and included the domains of global functioning, social functioning, independent living, and employment assessed with the following scoring instruments: Major Role Adjustment Inventory (27), Social Adjustment Scale-II (28), Global Assessment of Functioning (29), and the Strauss-Carpenter Outcome Scale (items 2 and 3 [30]). The secondary symptom outcome composite was calculated with the same method as the social adjustment composite and included measures of positive and negative symptoms, depression, anxiety, and general psychopathology. (A complete description of the study measures can be found in the online supplement.)

Data Analysis

To examine the differential effects of CET versus EST on outcomes, we implemented intent-to-treat linear mixed-effects models with random slope and intercept parameters in R by using the nlme package (31). Significant group × time interactions were the effects of interest. Study site was included as a confounding variable in all models. Sex was a potential confounding variable because of slight but significant differences between the two treatment groups. However, sex was unrelated to primary study composites at baseline and over time. To retain statistical power and not introduce bias due to unnecessary overadjusting (32), sex was not included as a confounding variable. Analytic models used the restricted maximum likelihood procedure for estimation (33), and missing longitudinal data were handled at the time of parameter estimation with a standard expectation-maximization approach (34). Imputation of any missing baseline scores was conducted with the Amelia

package for R (35). Effect sizes were calculated as Cohen's d with Hedges' formula (36) for mixed-effects models. Sensitivity analyses of treatment completers (N=49) were conducted with the same strategy. Because of the confirmatory nature of this trial, all reported p values for mixed-effects models were one tailed in both intent-to-treat and completer analyses (37). Exploratory post hoc effect sizes rather than inference tests (38) were calculated for the individual measures of the social adjustment and symptom composites because they were not primary outcomes (see the online supplement). The Benjamini-Hochberg (39) method of p value adjustment was applied to demographic and MCCB subdomain analyses.

RESULTS

Table 1 presents participants' baseline characteristics across study sites and treatment groups. Overall, the participants were in their mid-20s (24.8±5.4 years), and most were male (N=76, 75%), had been ill for 3.7±2.3 years, and had some college education (N=69 of 94, 73%). Most participants (>75%) had a schizophrenia diagnosis, and about one-half had a history of substance misuse. The CET group had significantly more men than the EST group, but the two treatment groups were otherwise well matched across the demographic characteristics. The overall sample of the current study was similar to that in the previous CET trial (10) on several key demographic characteristics, including age (25.9±6.3 years), sex (N=40, 69% male), illness duration (3.2±2.2 years), and education (N=39, 67% with some college) of the previous sample.

As shown in Table 2, for the intent-to-treat, mixed-effects analyses, CET had beneficial effects on overall cognition relative to EST both at 9 months (Cohen's d=0.44, p=0.003, one tailed) and the end of treatment at 18 months (Cohen's d=0.35, p=0.022, one tailed), confirming the efficacy of CET

TABLE 1. Baseline characteristics of patients with early-course schizophrenia treated with cognitive enhancement therapy (CET) or enriched supportive therapy (EST)[a]

	CET (N=58)		EST (N=44)				Boston site (N=49)		Pittsburgh site (N=53)			
Variable	N	%	N	%	p^b	p_{adj}	N	%	N	%	p^b	p_{adj}
Age (M±SD)	23.9±4.1		25.9±6.7		.062	.574	23.7±4.5		25.7±6.1		.068	.330
Sex (male)	48	83	28	64	.039	.574	41	84	35	66	.068	.330
Racial minority group	24	41	20	45	.692	.916	23	47	21	40	.549	.741
Race-ethnicity												
African American	13	22	11	25			6	12	18	34		
White	34	59	24	55			26	53	32	60		
Hispanic	0	—	1	2			0	—	1	2		
Asian	4	7	1	2			3	6	2	4		
Hawaiian/Pacific Islander	1	2	0	—			1	2	0	—		
More than one race	2	3	5	11			7	14	0	—		
Other	4	7	2	5			6	12	0	—		
IQ score (M±SD)[c]	108.1±9.6		107.5±11.5		.794	.918	109.4±9.8		106.4±10.8		.153	.578
Education (some college)[d]	42	76	27	69	.483	.918	31	76	38	72	.815	.816
Employed[e]	14	25	17	39	.136	.839	13	27	18	34	.520	.748
Illness length (M±SD years)[f,g]	3.8±2.2		3.6±2.4		.621	.918	3.4±2.4		3.9±2.2		.293	.676
Schizophrenia diagnosis	48	83	34	77	.616	.918	41	84	41	77	.464	.748
Past substance use disorder	28	48	22	50	1.00	1.00	26	53	24	45	.552	.748
Antipsychotic medication dose (M±SD, CPZ equivalent)[h]	442.0±367.0		412.5±284.1		.664	.918	459.1±365.5		403.7±301.6		.413	.723
Antipsychotic medication adherence[e,i]	43	75	32	73	.820	.918	41	85	34	64	.022	.150
MCCB overall cognition composite (M±SD)[j]	34.4±11.3		38.0±11.8		.119	.839	36.5±10.0		35.5±13.0		.664	.778
Social adjustment composite (M±SD)[k]	49.4±9.6		50.8±10.5		.491	.918	53.2±9.6		47.1±9.5		.002	.023
Symptom composite (M±SD)[k]	50.1±10.4		50.3±10.0		.920	.973	52.6±9.7		48.0±10.3		.021	.150

[a] CPZ, chlorpromazine; MCCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery; p_{adj}, false-discovery rate adjustment method, two tailed.
[b] Values of independent-samples t tests or Fisher's exact tests, two tailed.
[c] Measured with Wechsler Abbreviated Scale of Intelligence 2nd Edition (WASI-II).
[d] Based on a total sample of 94 with available data (CET, N=55; EST, N=39).
[e] Based on a total sample of 101 with available data (CET, N=57; EST, N=44).
[f] Based on a total sample of 101 with available data (CET, N=58; EST, N=43).
[g] Since the onset of psychotic symptoms.
[h] Based on a total sample of 98 with available data (CET, N=55; EST, N=43).
[i] Estimated by clinical team.
[j] Age- and sex-corrected T-score with a mean±SD of 50±10, with higher scores indicating better cognition (26).
[k] T-score with a mean±SD of 50±10, with higher scores indicating better outcome.

for improving overall cognition (see the online supplement for trajectory plots). The effects of CET on improved social cognition (d=0.52, p=0.033, one tailed) and attention/vigilance (d=0.46, p=0.017, one tailed) were also significant at 18 months (Figure 1 and online supplement). The p values for social cognition and attention/vigilance did not remain statistically significant after adjustment for multiple comparisons. No statistically significant difference in the social adjustment effect between the treatment groups was observed, and both groups had medium-to-large improvements in social adjustment (Table 2 and Figure 2, panel A). With regard to social adjustment domains (see online supplement), CET's largest effect was on major role adjustment relative to EST. Finally, no significant group × time interaction was observed for the symptom composite, with both groups having moderate improvements (Table 2 and Figure 2, panel A). The sizes of beneficial effects of CET on symptom measures were small to medium and were primarily observed for negative symptom measures (see online supplement).

Examination of treatment completers at 18 months clarified the effects of CET compared with EST on social adjustment; the effect size of CET on this domain (Cohen's d=0.51) was more than double that of the intent-to-treat analysis (Cohen's d=0.23) and nearly reached the standard threshold for statistical significance (of p<0.05; p=0.057, Table 2 and Figure 2, panel B). Effects on cognition and symptoms were similar to those found in the intent-to-treat analyses (Table 2 and online supplement).

DISCUSSION

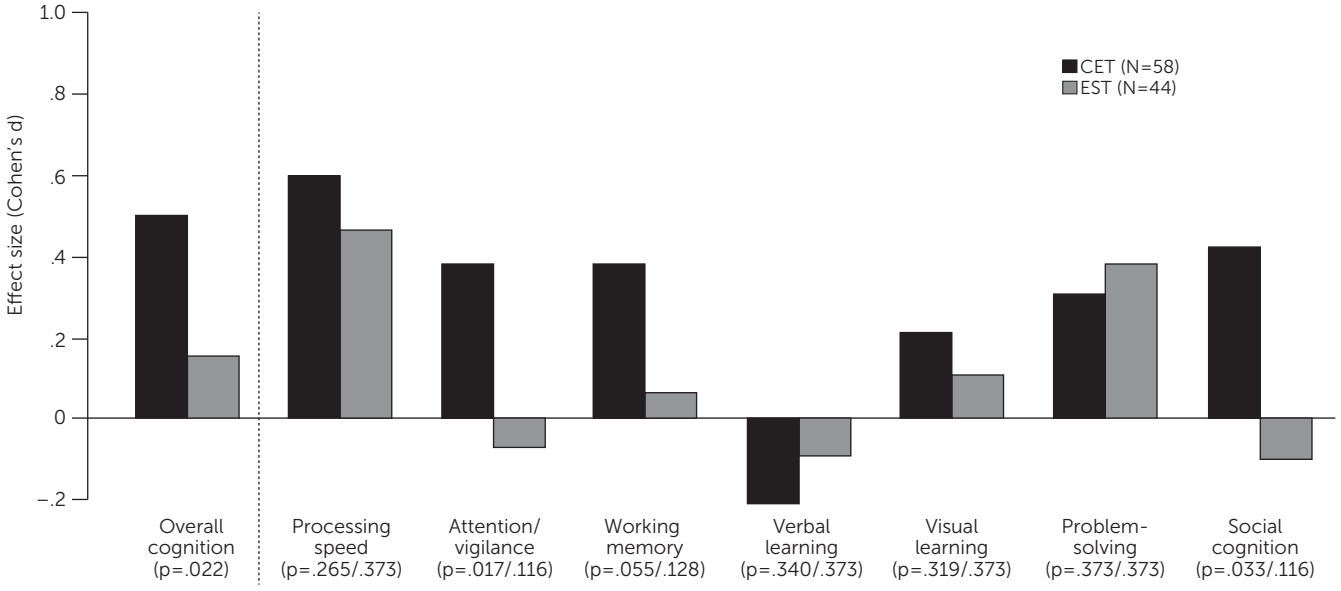
This large multisite RCT sought to confirm the previously reported beneficial effects of CET on cognition and social adjustment of patients with early-course schizophrenia (10).

TABLE 2. Effects of cognitive enhancement therapy (CET) and enriched supportive therapy (EST) on cognitive and behavioral composite indices

Outcome	CET		EST							Cohen's d[e]
	M[a]	SE	M[a]	SE	F[b]	p[c]	t	df[d]	p[c]	
Intent-to-treat sample (CET, N=58; EST, N=44)										
Cognition composite[f]										
Baseline	34.4	1.5	38.0	1.7			—	—	—	—
Month 9	38.4	1.6	37.1	1.9	4.38	.007	2.81	106	.003	.44
Month 18	40.1	1.8	39.8	2.0			2.04	106	.022	.35
Social adjustment composite[g]										
Baseline	49.5	1.3	51.0	1.4			—	—	—	—
Month 9	54.1	1.4	56.8	1.7	2.24	.056	−.78	107	.219	−.14
Month 18	56.3	2.0	55.5	2.3			.80	107	.214	.23
Symptoms composite[g]										
Baseline	50.2	1.3	50.4	1.5			—	—	—	—
Month 9	53.5	1.4	53.4	1.7	.09	.456	.20	107	.421	.04
Month 18	54.3	1.8	53.5	1.9			.43	107	.335	.11
Treatment completer sample (CET, N=26; EST, N=23)										
Cognition composite[f]										
Baseline	34.6	2.4	39.4	2.6						
Month 9	40.0	2.4	37.5	2.6	6.44	.001	3.44	88	<.001	.59
Month 18	41.3	2.5	40.6	2.6			2.58	88	.006	.45
Social adjustment composite[g]										
Baseline	47.1	1.8	50.4	1.8			—	—	—	—
Month 9	52.2	1.9	54.9	2.0	2.27	.054	.32	91	.376	.07
Month 18	54.5	2.4	53.4	2.5			1.60	91	.057	.51
Symptoms composite[g]										
Baseline	49.4	1.9	50.2	2.0			—	—	—	—
Month 9	53.2	1.8	52.8	1.9	.19	.412	.51	91	.305	.12
Month 18	54.0	2.0	53.1	2.1			.60	91	.275	.18

[a] Estimated marginal means.
[b] Test of slope differences across all time points between CET and EST.
[c] p values are one tailed and from mixed-effects models adjusted for differences among study location.
[d] df values are the same for both F and t values.
[e] Cohen's d values presented are between-group effect size of CET versus EST. Cohen's d intent-to-treat, within-group effect sizes were CET (month 9): cognition d=0.35, social adjustment d=0.48, symptoms d=0.32; CET (month 18): cognition d=0.50, social adjustment d=0.71, symptoms d=0.41; EST (month 9): cognition d=−0.08, social adjustment, d=0.62, symptoms d=0.29; and EST (month 18): cognition d=0.15, social adjustment d=0.48, symptoms d=0.30. Cohen's d completer within-group effect sizes were CET (month 9): cognition d=0.43, social adjustment d=0.58, symptoms d=0.39; CET (month 18): cognition d=0.55, social adjustment d=0.85, symptoms d=0.48; EST (month 9): cognition d=−0.16, social adjustment, d=0.51, symptoms d=0.28; and EST (month 18): cognition d=0.10, social adjustment d=0.34, symptoms d=0.30.
[f] Age- and sex-corrected T-score with a mean±SD of 50±10, with higher scores indicating better cognition (26).
[g] T-score with a mean±SD of 50±10, with higher scores indicating better outcome.

FIGURE 1. Intent-to-treat effect sizes of CET and EST at 18 months on the MATRICS Consensus Cognitive Battery[a]



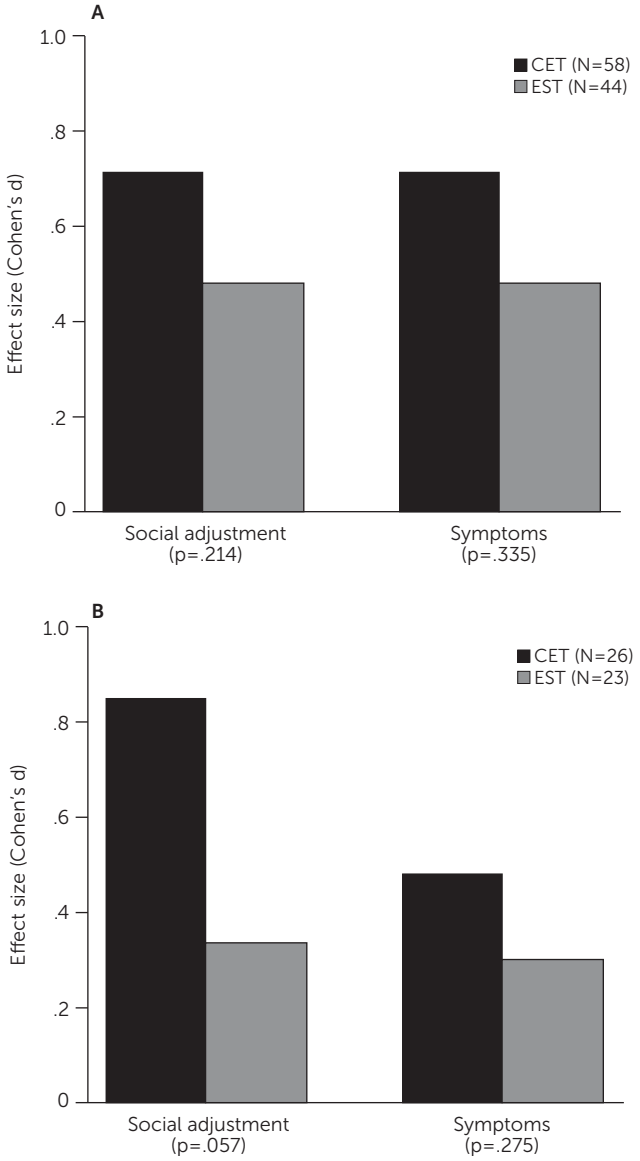
[a]N=102, p values are from mixed-effects models, are one tailed, and are given as unadjusted/adjusted with false-discovery rate. The vertical dotted line separates the overall cognition effect size from the subscale effect sizes. CET, cognitive enhancement therapy; EST, enriched supportive therapy.

Our results confirmed the overall cognitive benefits of CET and tentatively confirmed its social-cognitive benefits, relative to EST, in both intent-to-treat and treatment completer analyses. The beneficial effects of CET on social cognition were no longer statistically significant after the analyses were adjusted for multiple comparisons, but the significant unadjusted results aligned with those of the previous trial of CET for early-course schizophrenia (10). In both analyses, CET had a particularly positive effect on attention/vigilance. Effects on social adjustment were not confirmed in the intent-to-treat or treatment completer samples, because both groups had considerable improvements in functioning. Although the differential effect of CET on social adjustment did not meet the conventional threshold for statistical significance (i.e., $p<0.05$) in the completer analyses ($p=0.057$), the noticeable increase in the 18-month between-group effect size from the intent-to-treat (Cohen's $d=0.23$) to the treatment completer (Cohen's $d=0.51$) analyses suggest a functional advantage of completing the full CET treatment. Overall, these findings confirm the beneficial cognitive outcomes of CET for patients with early-course schizophrenia. CET also had a positive impact on social cognition and attention/vigilance. The social adjustment effect observed in the previous CET trial (10) was not confirmed, but our results indicate that the greatest functional benefits are likely gained among those who complete the entire CET treatment.

The results of this confirmatory trial add further evidence for the benefits of CET for patients with early-course schizophrenia and have important implications for advancing cognitive remediation approaches. It is particularly notable that CET's effects on social cognition were the largest among all its effects on cognition, consistent with findings of previous trials indicating that CET yields consistent and large improvements in this domain (10, 12, 14). The social-cognitive effect size was more modest in the current study, perhaps because of reliance on blinded performance-based assessments and the significant attrition rate. Neurocognitive gains were observed mostly in attention/vigilance, an observation that was different from the improvements mainly in verbal memory and problem-solving noted in the initial CET trial (10). These differences between our studies likely reflect the updated measurement battery to the MCCB, which includes attention/vigilance, not assessed in the initial trial, and both verbal and nonverbal working memory measures, of which our previous trial assessed only the former. Further, the problem-solving measures, which exhibited an effect in the initial trial, are not comparable to the measures in the MCCB used in the present study.

The findings regarding social adjustment effect sizes may reveal the importance of treatment engagement and exposure in translating cognitive benefits to meaningful functional improvements. CET begins with attention training for the first 3–6 months in participant pairs to encourage socialization, after which the social-cognitive groups are initiated and proceed concurrently with neurocognitive training. The social-cognitive groups focus not only on improving social cognition, but also on applying cognitive gains to daily life. Apparently, the later components of CET may be essential to achieving functional improvement through cognitive gains. Both social and nonsocial cognitive improvements during CET have been shown to mediate functional

FIGURE 2. Effect sizes of CET and EST at 18 months on the social adjustment and symptom composites[a]



[a]Panel A, effect sizes for intent-to-treat analysis sample (N=102); panel B, effect sizes for completers (N=49). p values are from mixed-effects models and are one tailed. CET, cognitive enhancement therapy; EST, enriched supportive therapy.

improvement in early schizophrenia (40, 41). Future research is needed to confirm that cognitive gains, especially during the later phase of CET, mediate functional improvement. It is noteworthy that the CET participants continued to make gains in the primary outcomes from 9 to 18 months (Table 2). These findings are consistent with previous meta-analytic evidence indicating that short-term neurocognitive training does little to improve functioning without integration into broader psychosocial treatments (7). The results of this confirmatory trial suggest a benefit of completing the full 18 months of CET rather than only half of the treatment. Future studies are needed to examine the minimal dosage of CET needed to achieve a significant functional benefit in early-course schizophrenia.

Several limitations of this study temper our conclusions. First, this study had a high attrition rate, which reduced statistical power to detect significant treatment effects at 18 months. Attrition is often greater in studies of early-course schizophrenia, a period of the condition during which patients are more ambivalent about treatment (42–45). The attrition rate of the previous CET trial was 21% (10), and the current trial had more than double this rate. The previous and current study samples were demographically similar, but rates of past lifetime substance misuse 3 months before study enrollment were noticeably higher in the current sample, which may have been related to the difference in attrition rates between the two studies. However, this was an anecdotal observation, and it will be important to further investigate factors that might explain the differences in attrition and findings between the two studies. In the current sample, completers and noncompleters significantly differed in age, IQ score, illness length, and antipsychotic medication dose (see the online supplement), likely indicating a selection bias. It is essential that future research identify approaches to promote engagement in longer-term treatments that could reduce disability.

Second, CET and EST are manualized and differ in clinician contact hours. Consequently, we were unable to match clinician contact between the two groups. To account for any potential clinician effects on differential change between CET and EST, the study was designed such that the same clinicians provided both treatments. As previously mentioned, the number of attended sessions did not influence changes in the outcomes. Third, the modalities of the treatments were different—CET is group based and EST is individual based. Exposure to the social context of a group in CET, in addition to computer-based neurocognitive training in pairs (46), could have contributed to some of the improvements in social cognition and functioning, and it will be important for future studies to examine the impact of group versus individual treatment on these domains. Finally, we did not examine CET-related mechanisms of cognitive and behavioral changes because the chief goal of this study was to confirm the previously observed cognitive and behavioral effects of CET for early-course schizophrenia. Confirmation of earlier observations of neurobiological mechanisms underlying the benefits of CET (47, 48) is a critical next step for advancing this intervention, and such confirmatory studies are forthcoming.

CONCLUSIONS

The findings of this study confirm the overall benefits of CET on cognitive function among individuals with early-course schizophrenia and tentatively confirm the social-cognitive benefits of this intervention, providing further

support for the use of CET to promote recovery among people with this condition. This work also highlights future opportunities to optimize CET for this population, including identifying mechanisms of change driving the major therapeutic elements and factors associated with treatment engagement.

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