ORIGINAL ARTICLE

Cognitive Enhancement Therapy for Schizophrenia

Effects of a 2-Year Randomized Trial on Cognition and Behavior

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Background: Deficits in social cognition and neurocognition are believed to underlie schizophrenia disability. Attempts at rehabilitation have had circumscribed effects on cognition, without concurrent improvement in broad aspects of behavior and adjustment.

Objective: To determine the differential effects of cognitive enhancement therapy (a recovery-phase intervention) on cognition and behavior compared with state-of-the-art enriched supportive therapy.

Design: A 2-year, randomized controlled trial with neuropsychological and behavioral assessments completed at baseline and at 12 and 24 months.

Setting: An outpatient research clinic housed in a medical center's comprehensive care service for patients with severe mental illness.

Patients: A total of 121 symptomatically stable, non–substance-abusing but cognitively disabled and chronically ill patients with schizophrenia or schizoaffective disorder.

Interventions: Cognitive enhancement therapy is a multidimensional, developmental approach that integrates computer-assisted training in neurocognition with social cognitive group exercises. Enriched supportive therapy fosters illness management through applied coping strategies and education.

Main Outcome Measures: Six highly reliable summary measures—Processing Speed, Neurocognition, Cognitive Style, Social Cognition, Social Adjustment and Symptoms—were tested using analysis of covariance and linear trend analysis.

Results: At 12 months, robust cognitive enhancement therapy effects were observed on the Neurocognition and Processing Speed composites ($P<.003$), with marginal effects observed on the behavioral composites. By 24 months, differential cognitive enhancement therapy effects were again observed for the 2 neuropsychological composites and for Cognitive Style ($P=.001$), Social Cognition ($P=.001$), and Social Adjustment ($P=.01$). As expected, no differences were observed on the residual Symptoms composite. Effects were unrelated to the type of antipsychotic medication received. Enriched supportive therapy also demonstrated statistically significant within-group effect sizes, suggesting that supportive psychotherapy can also have positive, although more modest, effects on cognitive deficits.

Conclusion: Many cognitive deficits and related behaviors of patients with stable schizophrenia are improved when sufficient exposure to relevant rehabilitation is provided.

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SCHIZOPHRENIA IS A LEADING cause of disability throughout the world.[1] Numerous, but often cross-sectional, studies have now shown correlations between neurocognitive deficits and behavior.[2] Concurrent impairment in social cognition has also been proposed as an important rate-limiting factor to recovery.[3-6] These observations have stimulated various neurocognitive rehabilitation approaches.[7-18] Sample sizes have been small (30-90 individuals), and many have included severely impaired, hospitalized patients. Treatment exposure has been limited (median, approximately 4 months), and no trial has exceeded 9 months. Successful attempts to improve neuropsychological (NP) test performance have been reported,[19-21] as has some evidence of generalization to untrained NP tests.[12,16,22,23] However, concurrent effects on broad aspects of functioning and behavior have been viewed as small and lacking generalization.[15,18]

Cognitive enhancement therapy (CET) was developed and piloted in the early to middle 1990s as an integrated approach to the enhancement of neurocognitive and social cognitive abilities. It at-

Table 1. Eligibility Criteria

Criterion	Description	Entry Score, mean (SD)	
		EST Group	CET Group
	Cognitive Style Deficits*		
Impoverished style		7.2 (2.8)	8.2 (3.1)
Impairment	Poverty of speech production, amotivation, reduced or flat affect, little preference for relevant/irrelevant information		
Disability	Effortful planning or problem solving, difficulty initiating behavior, effortful recall of information		
Social handicap	Language does not express needs, preferences, or opinions; lacks credible account of behavior; low stamina, withdrawn, disinterested, apathetic, inactive		
Disorganized style		8.7 (2.9)	8.2 (3.0)
Impairment	Ineffective inhibition; spontaneous, labile affect; loose ideational content; poor attention; poverty of speech content		
Disability	Chaotic or imprecise planning, difficulty terminating behavior, difficulty staying on track, failure to "chuck" or categorize memory stores		
Social handicap	Inappropriate responses not self-edited, difficulty using language coherently, hard to follow train of thought, impulsive, readily changes plans or goals		
Rigid style		7.0 (2.4)	7.6 (3.3)
Impairment	Fixed, inflexible, ideational content; restricted cognitive schema; constrained affect; obsessive, repetitive thinking		
Disability	Plans, goals, and problem solving limited by inflexible thinking		
Social handicap	Behavior restricted by preoccupation with details, tends toward stereotyped views, single-minded pursuit of inappropriate goals or career objectives		
Total		**22.9** (4.5)	**24.0** (4.6)
	Social Cognitive Deficits†		
Vocational ineffectiveness	Unemployed or working below potential; reduced work stamina; unable to establish or maintain a routine; unable to use feedback from coworkers, supervisor, or authority figures; unrealistic or absent career goals		
Interpersonal ineffectiveness	Lack of empathy, flexibility, or reciprocity, unable to negotiate conflicts, express needs, act wisely, or take perspectives		
Lack of foresight	Unable to assess long-term consequences of behavior (good or bad), difficulty forming long-range plans	16.4 (2.6)	16.9 (2.7)
Gist extraction deficits	Difficulty understanding formal or informal rules of conduct as social contexts change, unable to assess central point or norm of social situation		
Adjustment to disability	Unable to temporarily revise expectations, failure to understand or accept residual limitations imposed by illness		

Abbreviations: CET, cognitive enhancement therapy; EST, enriched supportive therapy.
*Required a score of 7 or higher on any style to enter (1 = rare, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe; score range, 3 to 15 for 3 items in each style).
†Required a score of 12 or greater to enter (1 = rare, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe; scale range, 5 to 25 for 5 items).

tempts to capitalize on a presumed neuroplasticity reserve believed to respond to enriched cognitive experiences.[24] Cognitive enhancement therapy is a recovery-phase intervention for symptomatically stable schizophrenic outpatients with reduced relapse risk (who nevertheless remain socially and cognitively disabled), an increasing population in the modern era of atypical antipsychotic medications.[25] A 2-year, randomized study was undertaken between January 1995 and February 2002, together with a 1-year follow-up. This article describes the results of the 2-year controlled trial.

METHODS

PATIENTS

Initially, 132 outpatients who satisfied *DSM-III-R* or *DSM-IV* criteria for schizophrenia or schizoaffective disorder and who currently satisfied *Research Diagnostic Criteria for a Selected Group of Functional Disorders*[26] were enrolled. (Another 12 referred patients were not enrolled because of mental insufficiency or organicity.) Referrals came from the University of Pittsburgh Medical Center's Comprehensive Care (outpatient) Service, a local mental health center, and a University of Pittsburgh Medical Center satellite clinic following a preliminary population screen of potentially eligible patients. Most patients (76%) were in full or partial remission of positive psychotic symptoms at baseline. For individuals with persistent positive symptoms, stability criteria indicated no serious effect on daily activities. By design, most patients (88%) were more than 1 year past their last hospitalization (median, 46 months) and thus were at reduced risk of relapse.[27] Eight of the 132 patients (4 CET recipients and 4 enriched supportive therapy [EST] recipients) withdrew consent before treatment exposure. After assessment, 3 additional patients were judged to be ineligible by reason of mental insufficiency (IQ <80) or organic brain disorder. The final study sample contained 121 patients who met the criteria for cognitive disability, which consisted of the impairments, functional disabilities, and social handicaps associated with 1 of 3 dysfunctional cognitive styles,[28] and the criteria for social cognitive disability (**Table 1**). The styles are continuous rather than categorical: 91% of patients met the criteria for a single style (33% were impoverished, 41% were disorganized, and 17% were rigid) and 9% for multiple styles. These eligibility criteria were assessed during a videotaped, semistructured interview. Patients were fluent in English, aged 18

Table 2. Characteristics of 121 Patients With Schizophrenia or Schizoaffective Disorder

Characteristic	Value
Sex, M/F, %	59/41
Age, mean (SD), y	37.3 (8.9)
Race, %	
White	89
African American	11
Length of psychotic illness, mean (SD), y	15.7 (9.3)
Previous hospitalizations, mean (SD), No.	5.96 (5.97)
Cumulative hospitalization, mean (SD), mo	13.9 (4.5)
Time since last worked, median, y	4*
Estimated WAIS IQ (2 performance and 2 verbal tests), mean (SD)	97.2 (11.5)
Residence, %	
Parental	44
Conjugal	10
Extended family	2
Alone	44
Marital status, %	
Never married	82
Currently married	7
Previously married	11
Education, %	
High school or less	25
Attempted college	44
Completed college	31
Highest occupation, %	
Unskilled position	45
Semiskilled or skilled	32
Student, homemaker, other	23
Diagnosis, %	
Paranoid schizophrenia	56
Schizoaffective disorder	30
Other schizophrenia	14

Abbreviation: WAIS, Wechsler Adult Intelligence Scale.
*Twenty-five percent of patients had not worked in more than 10 years.

to 60 years, treated with a Food and Drug Administration–approved antipsychotic medication, and free of serious alcohol or drug abuse in the preceding 6 months, with an IQ of 80 or greater. Final eligibility was determined by team consensus after a review of all diagnostic, historical, and interview materials. **Table 2** describes the sample characteristics. Before intake, patients provided a signed informed consent form, and the study was reviewed annually by the University of Pittsburgh institutional review board.

DESIGN

Patients were randomized by the project statistician (R.U.) to receive CET or EST and were treated under these conditions for 2 years. To more rapidly form the 11 CET social cognitive groups, 67 patients were randomized to the CET condition and 54 to the EST condition. Ten patients (6 CET recipients and 4 EST recipients) who experienced an interim relapse (n=5) or medical illness (n=5) were given a brief "timeout," were stabilized, and were readmitted to their assigned treatment group. Fourteen patients (12%) terminated treatment early: 8 patients between 4 and 6 months (4 EST recipients and 4 CET recipients) and 6 patients at 12 months (4 EST recipients and 2 CET recipients). Four of these patients became medication refractory (2 EST recipients and 2 CET recipients) and 7 withdrew consent (3 EST recipients and 4 CET recipients); 1 EST patient became alcohol dependent and 2 EST patients died (cancer and heart disease). All 121 patients met the criteria for minimum treatment exposure and were included in the intent-to-treat analyses at 12 months. Before analyzing data, it was deemed inappropriate to carry forward to 24 months the ratings of the 4 CET and 4 EST patients who terminated treatment between 4 and 6 months.

TREATMENTS

Cognitive enhancement therapy theory and practice are described in detail elsewhere.[5,28] This therapy was influenced by the holistic program for traumatic brain-injured patients developed by Ben-Yishay and colleagues,[29] the integrated cognitive approach of Brenner et al,[8] and a contemporary theory of human cognitive development.[30] Cognitive enhancement therapy attempts to facilitate the attainment of adult social cognitive milestones, such as perspective taking and social context appraisal,[31,32] by shifting an alleged early developmental reliance on effortful, serial, and verbatim (concrete) cognitive processing[33] to a more "gistful," spontaneous abstraction of social themes through structured but unrehearsed in vivo social interactions. Cognitive enhancement therapy is a small-group approach that combines approximately 75 hours of progressive software training exercises in attention, memory, and problem solving with 1.5 hours per week of social cognitive group exercises (approximately 56 sessions). A group (6 patients) began to meet 4 to 6 months after the initiation of attention training. Software exercises required that patients work in pairs, offer mutual support and encouragement, respond to online Socratic coaching, and use the cueing and fading of prompts until the principles underlying test performance were mastered. Three attention training components of Ben-Yishay's Orientation Remediation Module[34] were used (the Attention Reaction Conditioner, Zero Accuracy Conditioner and Time Estimates) that are graduated in difficulty and designed to enhance vigilance, selective attention, the ability to shift between auditory and visual modalities, and rapid decision making. Attention training was followed by 7 memory routines and ultimately 7 problem-solving exercises from the Bracy PSSCogReHab program[35] that represented the Trail Trace, Spatial Memory (sequenced and objects and location), Recall Recognition, Visual/Spatial Memory, Paired Associates and Verbal Memory (categories) exercises. The goal was to develop memory skills through the enhancement of a categorizing capacity, an abstracting attitude, cognitive flexibility, and decision making. Problem-solving exercises included Designer Patterns, Numbers Manipulation I and II, Reversals, Logicmaster, Deduction, and Checker Exchange. These engaging exercises targeted analytic logic, effortful decision making, strategic and foresightful planning, and the intuitive thinking that supports social cognition.

The group curriculum[28] contained activities such as categorization exercises; formation of gistful, condensed messages; solving of real-life social dilemmas; abstraction of themes from the editorial pages of *USA Today*; appraisal of affect and social contexts; initiating and maintaining conversations; play writing; and the center stage exercises Introduce Yourself/Friend adapted from the curriculum of Ben-Yishay.[36] Sessions typically contained a homework review, a psychoeducation topic, an exercise by a patient or pair, feedback from other patients and coaches, and a new homework assignment based on the education topic. Although a group contained patients with different cognitive deficits, relative emphasis was placed on the prominent cognitive style deficit of a patient. To provide the best test of CET and EST, most CET patients (74%) were treated by 3 psychologists (S.F., D.G., and A.G.) who, by inclination and training, were disposed toward cognitive interventions. Two master's-level psychiatric nurses (S.C. and A.L.D.), each with 9 years' experience providing personal therapy (PT),[37,38] on which EST was based, treated most EST patients.

A review of patient performance on each core exercise indicated that all CET patients improved over baseline before proceeding to a new exercise. All patients except 1 with early treatment termination completed the 3 attention exercises, and more than 90% of all memory exercises and problem-solving routines were completed. Excluding 6 early terminators (who accounted for most noncompliance and missing data), the 61 CET recipients who completed 2 years of treatment kept a mean (SD) of 91.3% (4.4%) of their scheduled or rescheduled appointments per therapist. Missed group sessions were reviewed on videotape, and missed computer sessions were rescheduled. Cognitive enhancement therapy was an open, structured, manual-guided intervention that was supervised by 2 CET designers (G.E.H. and S.F.). Computer performance data and adherence to a written group agenda served to ensure fidelity.

Enriched supportive therapy included most practice principles of the basic and intermediate phases of the demonstrably effective PT approach.[37,38] The intent was to provide a stringent test of CET. Enriched supportive therapy encouraged illness self-management through the control of subjective cues of distress that might lead to destabilization or social dysfunctioning. Phase 1 provided psychological and material support, psychoeducation regarding the nature and treatment of schizophrenia, resumption of instrumental tasks, role restructuring, and basic skills training in stress avoidance. Phase 2 included a personalized education concerning vulnerability to stress, adjustment to disability, identification of early signs of decompensation, and stress management strategies. (These EST components were also made available to CET patients through the group curriculum.) Strategies related to social cognition, such as perspective taking, criticism management, and most PT Advanced-Phase techniques, were strictly avoided. Enriched supportive therapy was intended to be applied weekly in phase 1 and biweekly in phase 2. No attempt was made to match EST to CET hours. (Artificially increasing the hours of a control intervention has been shown to have an adverse effect,[17] and hours of psychosocial treatment have most often not been associated with greater effects in large, well-controlled, multisite studies.[39-41]) A mean (SD) of approximately 90.8% (6.1%) of scheduled or rescheduled sessions per therapist were kept by the 46 EST patients who completed 2 years of treatment. Enriched supportive therapy was a manual-directed, office-based intervention supervised by a codesigner of the PT approach. Random audiotaped sessions were scale rated for fidelity during the initial years of study. Cost considerations and the absence of therapist drift led to discontinuation of monitoring in the final year of grant support.

MEDICATION

All patients were administered a Food and Drug Administration–approved antipsychotic medication. Medication was not controlled, and compliance was high among all patients, as intended. At baseline, 33.5% of patients received clozapine, 28.9% received an atypical antipsychotic medication (mostly risperidone or olanzapine), and 35.5% received a conventional neuroleptic, typically at the minimum effective dose. By 2 years, these percentages had changed to 41.6%, 33.6%, and 24.8%, respectively. Analyses of medications at baseline and at 1 and 2 years revealed no treatment group differences in either the type or dose of medication or in compliance. Thus, the differential psychosocial treatment effects reported herein cannot be attributed to medication differences. Medication was prescribed by an experienced research psychiatrist (H.P.).

ASSESSMENTS

Partially correlated behavioral assessments of social cognition, cognitive style, symptoms, and adjustment were selected (or developed) before the study that reflected the observations of clinicians, patients, and family members. Neuropsychological tests of attention, memory, and problem solving were chosen that had historically indicated schizophrenia cognitive impairment.[42,43] Neuropsychological testing was administered under highly standardized conditions by a psychometrician (R.Z.), who was uninvolved with treatment, and served as a more objective, longitudinal outcome measure on which patients had not been trained.

Before analysis, highly reliable, multivariately derived indices of psychosocial behavior and cognitive functioning were constructed. These "composites" provided protection against the potential error contained in extensive univariate testing that could not be realistically accommodated with Bonferroni corrections. Within each domain, we first selected measures that at face value represented hypothesized outcomes. Following suggestions for constructing summary scores[44] and approaches that would increase power by reducing within-group variance,[45] stringent reliability criteria were applied. Candidate variables for a composite had to satisfy test-retest reliability criteria of 0.40 or greater, using the time series panel method across baseline and 1 and 2 years[46]; mean interitem correlations within a composite of 0.30 or greater; mean item-total score correlations of 0.50 or greater (with no item <0.30), and an $\alpha \geq .80$ for the composite itself. **Table 3** describes the composites and their reliabilities. The (Bracy) version of the Continuous Performance Test[59] used by us and the measure of Gist Extraction Deficits failed retest reliability. Also, the Brief Psychiatric Rating Scale Thought Disorder factor, the Major Role Adjustment Inventory Relationships in the Home and Sexual Relationships measures also failed retest reliability because of low variance. Although they satisfied retest reliability criteria, all family measures and most patient measures showed inadequate internal consistency within the assigned composite (or any other composite). Similarly, the Benton Verbal Fluency Test[60] was insufficiently correlated with other neurocognitive measures and was also excluded.

NEW MEASURES

During pilot studies (36 patients and 6 raters), ongoing revisions of new instruments were made until interrater reliability coefficients were 0.77 or greater, with insignificant rater F ratios. The Cognitive Styles Eligibility Criteria (Table 1) were derived from studies[61-63] of acute schizophrenia symptoms reflecting impoverishment (negative symptoms), disorganization, and reality distortion. (During remission, the latter construct seemed to represent a type of rigid, inflexible cognition.[28]) These styles reflected the cognitive processes with which patients approached instrumental and relationship tasks. Selected NP and neurobiological data support the validity of the constructs.[61,62,64-66] The styles serve to reduce the heterogeneity in schizophrenia diagnosis[62] and, we believed, the diverse adaptations to cognitive impairments.[28] Clinician retest reliability coefficients were 0.78, 0.64, and 0.69 for the 3 styles, with high independence of styles (intercorrelations ≤ 0.10). The associated Cognitive Styles Inventory was a 46-item micromeasure of the 3 styles, which were also well discriminated.

Social cognition was a more difficult concept to measure, with more than 100 definitions available.[67] We abandoned selected "proxy" measures, previously developed on low-functioning, hospitalized patients (eg, the Social Cue Recognition Test[68]), that showed a ceiling effect among our stable outpatients. We attempted to distinguish social cognition (awareness of relationship aspects) from social adjustment (instrumental role performance or capacity). We relied on the Social Cognition Profile, a 50-item checklist of relevant behaviors gleaned from the literature, for example, Selman

Table 3. Composite Components and Reliability Values

Variable	Retest Reliability
Processing Speed: α = .83; Mean Interitem *r* = 0.50; Mean Item-Total *r* = 0.63	
Simple reaction time: fixed ISI[34]	0.65
Simple reaction time: variable ISI[34]	0.63
Visual spatial scanning[35]: time to detect embedded stimulus	0.68
Choice reation time: dominant hand[35]	0.61
Choice reaction time: nondominant hand[35]	0.49
Neurocognition: α = .89; Mean Interitem *r* = 0.36; Mean Item-Total *r* = 0.56	
Verbal memory	
WMS[47] A & B: immediate recall	0.73
WMS[47] A & B: delayed recall	0.75
CVLT[48] list A	
Total recall 1-5	0.75
CVLT short-term/free recall	0.73
CVLT long-term/free recall	0.74
Working memory	
WAIS[49] Digit Span	0.81
Language	
WAIS[49] Vocabulary	0.88
Cognitive flexibility/problem solving	
Trails B[50]	0.60
WAIS Picture Arrangement	0.70
WCST[51]	
Categories achieved	0.57
Perseverative errors	0.76
Nonperseverative errors	0.52
% Conceptual response	0.68
Psychomotor speed/vigilance	
WAIS[49] Digit Symbol	0.84
Symptoms: α = .83; Mean Interitem *r* = 0.32; Mean Item-Total *r* = 0.52	
Clinician	
BPRS[52] withdrawal retardation factor	0.63
BPRS anxiety depression factor	0.62
BPRS hostility factor	0.57
Wing Negative Symptom Scale[53] total	0.69
Degree of illness global	0.69
Raskin Depression Scale[54] total	0.50
Patient Subjective Responses Questionnaire[55] factors	
Energy	0.50
Sluggish	0.41
Anxious	0.51
Dysthymic	0.57
Feels good	0.49
Feels bad	0.50
Everyday worries	0.61
Self-esteem	0.62

(continued)

Table 3. Composite Components and Reliability Values (cont)

Variable	Retest Reliability
Cognitive Style: α = .81; Mean Interitem *r* = 0.35; Mean Item-Total *r* = 0.53	
Clinician eligibility criteria	
Impoverished style	0.73
Disorganized style	0.65
Rigid style	0.69
Total: impairment, disability, social handicap	0.64
Highest cognitive style score	0.58
Clinician cognitive style inventory	
Problems getting started	0.77
Problems staying focused	0.72
Problems changing ideas	0.69
Social Cognition: α = .85; Mean Interitem *r* = 0.42; Mean Item-Total *r* = 0.60	
Clinician social cognition profile	
Tolerant factor	0.64
Supportive factor	0.74
Perceptive factor	0.70
Self-confident factor	0.58
Clinician eligibility criteria	
Vocational ineffectiveness	0.69
Interpersonal ineffectiveness	0.56
Lack of foresight	0.47
Adjustment to disability	0.55
Social Adjustment: α = .90; Mean Interitem *r* = 0.46; Mean Item-Total *r* = 0.60	
Clinician ratings: major role adjustment inventory[56]	
Employment	0.72
Relationships outside of home	0.57
Major role performance	0.43
Overall functioning	0.61
Global Assessment Scale[57]	0.57
Social Security (employability) criteria[58]	
Mental ability	0.62
Daily living activities	0.78
Social functioning	0.67
Instrumental task performance	0.69
Global work readiness	0.69

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CVLT, California Verbal Learning Test; ISI, interstimulus interval; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale.

and Schultz.[69] A principal components analysis of the item correlations across rating periods (using >1500 ratings from patients, families, and clinicians) yielded 4 factors with loadings greater than 0.40 and few split-loaded items. Although the factor structure was nearly identical across different observers (specific variance), when scored, the patient and family factors were highly redundant (common variance). However, the clinician factors were well discriminated. The Social Cognitive Deficit Eligibility Criteria (Table 1) represented our judgment of functionally incapacitating deficits. Because few patients worked full time, we scaled the 4 criterion areas (50 items) used by the Social Security Administration[58] for determining employment disability (see Social Adjustment in Table 5). Component areas met high interrater (>0.77), retest (>0.62), and internal consistency (>0.87) criteria. Information on these scales is available from one of us (G.E.H.). The results provided herein represent initial validity data.

As expected, selected behavioral composites were moderately correlated across periods (Cognitive Style and Symptoms, r=0.25; Social Adjustment and Social Cognition, r=0.50; and Cognitive Style and Social Cognition, r=0.44), indicating some redundancy but nevertheless unique variance. The Neurocognition and Processing Speed composites were only modestly correlated at baseline (r=0.30). Each composite correlated higher with itself across periods than with any other composite.

STATISTICAL ANALYSIS

Composite scores were standardized according to a baseline mean (SD) of 50 (10). The regressed composite change scores between baseline and 1 and 2 years were tested using 2-tailed

Table 4. Treatment Effects on Composite Indices at 12 and 24 Months*

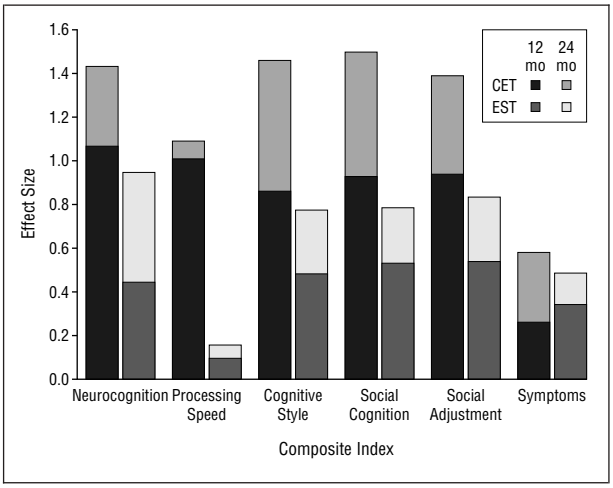
	12 mo (N = 121)				24 mo (N = 113)			
	Adjusted Posttreatment Mean				Adjusted Posttreatment Mean			
Composite	CET	EST	F Ratio	*P* Value	CET	EST	F Ratio	*P* Value
Processing Speed	43.3	49.4	20.25	<.001	42.4	48.9	20.24	<.001
Neurocognition	43.8	47.5	9.10	.003	41.5	44.4	5.74	.02
Symptoms	47.5	46.8	0.16	.69	44.2	45.3	0.24	.63
Cognitive Style	42.2	45.6	3.31	.07	34.2	41.7	10.94	.001
Social Cognition	41.6	45.2	3.78	.055	33.4	41.4	11.82	.001
Social adjustment	41.6	45.2	4.07	.046	36.5	41.9	7.00	.01

Abbreviations: CET, cognitive enhancement therapy; EST, enriched supportive therapy.

*Posttreatment means are based on regressed change scores (analysis of covariance) between baseline and 12 months and baseline and 24 months. Each composite was standardized to reflect pretreatment scores having a mean (SD) of 50 (10). Posttreatment means below 50 indicate improvement from baseline and are easily converted to standard deviations. The *df* range from 106 to 115 depending on the composite and period. Initial level served as the covariate. Residual SDs average 8.2 (range, 5.7-9.6) at 12 months and 9.1 (range, 5.9-11.0) at 24 months. Analysis of covariance factors included treatment, sex, and length of illness (≤15 vs >15 years), psychosis level (less than vs greater than mild), and IQ (≤98 vs >98) dichotomized at the baseline mean.

($P<.05$) analysis of covariance (ANCOVA) and confirmed by a linear trend analysis of treatment differences across 2 years. In addition to treatment and sex, length of illness (≤15 vs >15 years), baseline positive symptoms (less than mild vs greater than mild), and IQ (≤98 vs >98) dichotomized at the mean were entered as (moderator) factors; the baseline mean served as the covariate. Only the simple interactions of a moderator and treatment condition were examined. Univariate (ANCOVA) analyses were undertaken to identify the relative item contributions within the significant composites at 2 years.

At baseline, the CET and EST groups were not different on any of the demographic or historical variables examined or on the ANCOVA composites or composite items except for the following 4 variables: EST assignees were rated on 3 variables as being less withdrawn, being more socially engaged, and having a higher Global Assessment Scale score by clinicians. Recipients of CET had a somewhat higher estimated average IQ than EST patients (99 vs 95) on the combined Wechsler Adult Intelligence Scale (WAIS) subtests.



Effect sizes of cognitive enhancement therapy (CET) and enriched supportive therapy (EST) at 12 and 24 months by composite index.

RESULTS

MULTIVARIATE MAIN EFFECTS

Table 4 describes the treatment effects on the 6 composites at 1 and 2 years. At 12 months, a robust effect of CET is observed on Processing Speed and Neurocognition, with marginal CET effects observed on the behavioral domains of Cognitive Style, Social Cognition, and Social Adjustment. No effect was seen on the Symptoms composite, as expected. By 2 years, all composites reflected significant differential improvement for CET recipients except for Symptoms. (Linear trend analysis of treatment differences across 2 years yielded the same results.) Effects of CET are broadly applicable to patients because there were no significant (moderator) ANCOVA or linear trend interactive effects with treatment.

Effects of CET were unrelated to the receipt of an atypical antipsychotic medication. A 6-factor ANCOVA that entered baseline drug type as an additional moderator (clozapine, atypical antipsychotic, or conventional antipsychotic) revealed no treatment interactions. Drug type had a significant main effect on Cognitive Style and Social Adjustment at 2 years, but not in the expected direction.[70] These effects indicated greater improvement overall among patients receiving the minimum effective dose of a conventional antipsychotic agent.

EFFECT SIZES

Effect sizes can provide a better indication of clinical significance than *P* values.[44] The **Figure** illustrates treatment effect sizes (Cohen d) that are appropriately calculated on the basis of variance associated with the actual regressed change scores tested by ANCOVA[71] rather than baseline variance. (Within and between groups, an effect size >0.40 is significant at the $P=.05$ level, with $n=50$ per group.)

By 2 years, effect sizes for CET exceeded 1 SD for all composites except Symptoms. Large effect size differences (>0.50) between treatments favoring CET occur on the Processing Speed (0.92) and Neurocognition (0.63) composites at 1 year and again on all composites at 2 years except Symptoms. Recipients of EST also show clinically meaningful change by 2 years on many composites, particularly Neurocognition (0.94), an unexpected effect for a psychotherapy that was devoid of tar-

Table 5. ANCOVA Results at 24 Months on Composite Component–Adjusted Posttreatment Means*

	Baseline (Raw) Mean		24-mo Adjusted Mean			
	CET Group	EST Group	CET Group	EST Group	F Ratio	*P* Value
Processing Speed						
Simple reaction time/fixed interstimulus interval, ms	251	246	203	246	15.39	<.001
Simple reaction time/variable interstimulus interval, ms	264	268	230	266	12.04	.001
Choice reaction time/dominant hand, ms	421	433	380	430	16.45	<.001
Choice reaction time/nondominant hand, ms	546	561	500	570	8.06	.006
Visual spatial scanning: time to detect embedded stimulus, s	4.38	4.73	4.06	4.24	1.26	.26
Neurocognition						
Verbal memory, No. of words						
WMS: immediate recall	20.6	21.0	25.8	23.4	5.35	.02
WMS: delayed recall	16.4	15.7	21.7	19.1	3.66	.06
CVLT List A						
Total recall 1-5	47.1	47.7	55.6	51.4	3.72	.06
Short-term/free recall	9.6	9.9	12.0	10.7	6.41	.01
Long-term/free recall	10.0	10.0	12.3	11.1	5.97	.02
Other memory						
WAIS Digit Span score	10.3	9.9	10.6	10.6	0.23	.63
Language						
WAIS Vocabulary score	10.4	9.7	10.4	10.5	0.19	.66
Cognitive flexibility/problem solving						
Trails B, s	77.3	85.2	65.2	65.9	0.03	.87
WAIS Picture Arrangement score	8.5	7.7	9.2	9.2	0.03	.96
WCST categories achieved score†	0.67	0.53	0.87	0.72	3.98	.05
WCST Perseveration errors score	16	20	12	12	0.37	.54
WCST Nonperseveration errors score	14	18	9	12	4.30	.04
WCST % conceptual response	66	60	76	72	1.76	.19
Psychomotor speed/vigilance						
WAIS Digit Symbol score	7.97	7.50	8.76	7.98	5.68	.02
Cognitive Style						
Clinician global measure score (eligibility criteria) (range, 3-15)						
Impoverished style	8.2	7.2	5.5	6.7	9.69	.002
Disorganized style	8.2	8.7	5.7	7.2	7.69	.007
Rigid style	7.6	7.0	5.9	7.2	6.46	.01
Total score: impairment, disability, social handicap (range, 9-45)	24.0	22.9	17.2	20.5	10.80	.001
Highest cognitive style score	11.0	10.4	7.5	9.1	14.28	<.001
Clinician cognitive style inventory score (1 = almost never, 2 = sometimes, 3 = often, 4 = usually, 5 = almost always)						
Problems getting started (eg, lacks initiative, energy, motivation, opinions, abstract thinking; effortful thinking)	2.5	2.3	1.7	2.0	10.73	.001
Problems staying focused (eg, changes mind quickly, disorganized speech, affectively labile, imprecise planning)	2.4	2.5	1.8	2.1	4.01	.048
Problems changing ideas (eg, inflexible or repetitive thinking, closed to suggestions, rigid goals and opinions)	2.2	2.2	1.9	2.1	1.53	.22

(continued)

geted cognitive strategies. However, Processing Speed was unaffected by EST. As suggested elsewhere,[72] a psychotherapeutic approach could lower the stress (arousal) that might exacerbate NP deficits.

UNIVARIATE MAIN EFFECTS

The contribution of the 45 component items to significant composite effects at 2 years are presented in **Table 5**. Various measures of reaction time, except for the embedded stimulus test, show uniform contributions to the Processing Speed effect. Verbal memory improvement accounts for most change in Neurocognition, with some evidence of improved cognitive flexibility and problem solving. The WAIS Digit Symbol (an indicator of psychomotor speed, cognitive flexibility, and vigilance) also contributes. Regarding Cognitive Style, impoverished cognition improves most and rigid thinking improves least, with disorganization showing intermediate improvement. Differential improvement in Social Cognition is uniform across the composite measures except for the Support factor. Few measures of Social Adjustment achieve statistically significant levels of differential improvement, with measures of improved work capacity indicating relatively greater improvement than actual role performance.

UNIVARIATE TREATMENT INTERACTIONS

There were 9 significant interactions with treatment ($P \leq .05$). Among patients who were ill for less than 15 years, CET recipients improved more than EST recipi-

Table 5. ANCOVA Results at 24 Months on Composite Component–Adjusted Posttreatment Means* (cont)

	Baseline (Raw) Mean		24-mo Adjusted Mean			
	CET Group	EST Group	CET Group	EST Group	F Ratio	*P* Value
Social Cognition						
Clinician social cognition profile score‡ (1 = almost never, 2 = sometimes, 3 = often, 4 = usually, 5 = almost always)						
Tolerant factor (eg, tolerant, nonjudgmental, reasonable, accepting, respectful, cooperative)	3.4	3.2	3.9	3.5	9.38	.003
Supportive factor (eg, supportive, empathic, concerned, helpful, reciprocal, friendly)	2.7	3.0	3.5	3.3	1.98	.16
Perceptive factor (eg, foresightful, self-aware, insightful, gistful, resourceful, independent)	2.5	2.5	3.3	3.0	5.66	.02
Self-confident factor (eg, confident, self-accepting, comfortable, assertive, joyful, involved)	2.4	2.5	3.1	2.8	4.93	.03
Social cognitive deficits score (eligibility criteria) (1 = rare, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe)						
Vocational ineffectiveness	3.90	3.87	3.06	3.53	6.14	.02
Interpersonal ineffectiveness	3.37	3.31	2.45	2.98	11.76	.001
Lack of foresight	3.60	3.40	2.44	3.13	13.38	.001
Adjustment to disability	2.78	2.56	1.50	2.23	10.43	.002
Social Adjustment						
Major role adjustment inventory score						
Employment (1 = paid FT/PT employment, 2 = FT/PT volunteer, 3 = unemployed)	2.95	2.71	2.13	2.56	3.60	.06
Relationships outside of home (1 = very compatible, gets along well; 2 = moderately compatible; 3 = neutral, tolerated, does not seek out others; 4 = moderately incompatible; 5 = very incompatible)	2.33	2.19	1.85	2.04	1.83	.18
Major role performance (1 = markedly higher than best previous performance, 2 = moderately higher, 3 = slightly higher, 4 = equal to best performance, 5 = slightly below, 6 = moderately below, 7 = markedly below best performance)	5.80	5.60	3.87	4.59	3.66	.06
Overall functioning (compared with the average [similar] nonpatient) (1 = markedly above average, 2 = slightly above average, 3 = equal, 4 = slightly below, 5 = markedly below average)	4.64	4.56	4.13	4.27	0.85	.359
Global Assessment Scale score	54.2	58.5	66.8	62.9	3.28	.073
Social Security employability criteria score (1 = almost never, 2 = sometimes, 3 = often, 4 = usually, 5 = almost always)						
Mental ability (eg, concentrate on task >1 h, remember details, organize thinking)	3.01	3.20	3.93	3.56	8.23	.005
Daily living activities (eg, independently clean home, shop, cook, secure residence, pay bills, use public transportation)	3.28	3.25	3.96	3.77	1.45	.232
Social functioning (eg, compatible, conversant, socially engaged, does leisure activities)	2.45	2.68	3.41	3.14	3.45	.067
Instrumental task performance (eg, follow instructions, keep to a schedule, take few timeouts, maintain endurance and focus)	2.33	2.32	3.27	2.92	4.27	.042
Global work readiness (ability to assume FT work or school) (1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = very good)	1.75	1.65	2.68	2.26	4.60	.035

Abbreviations: ANCOVA, analysis of covariance; CVLT, California Verbal Learning Test; FT, full-time; PT, part-time; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale.

*Average *df* = 1,109.

†Because of skewness, the WCST categories achieved measure was transformed. A higher score indicates more categories.

‡Examples include items that loaded at 0.60 or greater from factor analysis.

ents on measures of social functioning, the WAIS Digit Symbol Test, and impoverished cognition. Among patients who were ill for more than 15 years, CET recipients improved more than EST patients on simple reaction time. Patients in the CET group with fewer positive symptoms at baseline improved more than less symptomatic EST patients on the Global Assessment Scale, Wisconsin Card Sorting Test % Conceptual Level Response, and Impoverished cognition. Recipients of CET with a higher IQ improved more on Trails B than EST patients with a higher IQ, and CET patients with a lower IQ increased their WAIS Vocabulary score more than EST patients with a lower IQ. There were no significant interactions with sex.

COMMENT

After 2 years of treatment, CET demonstrated significant differential effects on all domains of behavior and cognition tested except residual symptoms, the latter likely speaking to the clinical stability of patients at baseline and the efficacy of PT in symptom management.[38] Modest CET effects on the behavioral composites at 1 year possibly reflect minimal exposure to the CET social group

curricula. At the moment, it is unclear how the cognitive changes are causally "linked" to changes in behavior.[73] Mediator analyses[74] that should help clarify causal links are planned.

Processing speed is a primary mediator candidate because improvement was also observed immediately after training, was sustained over time, and was reserved exclusively for CET recipients. This result supports the observations of other researchers.[10,15,75] Verbal memory is another mediator candidate because it improved most in the first year among the neurocognitive measures and is thought to best predict functioning.[76] Computerized cognitive training may have been necessary for the differentially superior CET effects; however, substantive gains were also made by EST patients on neurocognition and behavior.

Intelligence is important for understanding treatment effects, particularly those involving cognitive deficits, because higher-IQ patients improved more than lower-IQ patients in both treatments on 12 measures. Although many patients with schizophrenia have a "below average" IQ, and some are alleged to experience a decline in IQ after schizophrenia onset, most are thought to remain within the range of "normal" intelligence and often recover intellectual functioning after successful treatment.[77] Much of the therapeutic pessimism concerning functional recovery in schizophrenia could be attributed to the minority of patients who have concurrent mental insufficiency (IQ <80), organic brain disorder, or persistent positive symptoms. In our experience, most patients with schizophrenia learn from developmentally appropriate experiences, including their "mistakes." Recommendation for a specific psychosocial intervention in schizophrenia can likely be best made in terms of patient characteristics: intelligence, length of illness, and phase of illness.[38]

There are potential limitations to our results. Most behavioral findings reflect the assessments of "unblinded" clinicians, although equally robust effects occurred on the blinded NP tests. The relative absence of strong effects in blinded psychosocial treatment trials could speak either to the control of a possible clinician bias or to the issue of questionable validity when assessments are decontextualized.[78] Studies are needed that evaluate the success of blinding psychosocial treatments and that establish the validity of blinded and clinician assessments against independent criteria (eg, NP tests and neuroimaging changes). Replication studies of CET might profitably blind ratings by using structured interview assessments, such as the Social Adjustment Scale II.[79] Otherwise, relevant and valid measures of social cognition among stable outpatients were not available at the start of the study and had to be constructed. Further development of these and other proxy measures is an important task.

There are clear reservations regarding the use of NP tests as longitudinal outcome measures,[80,81] a condition for which these tests were not designed. Schizophrenia cognitive deficits seem to be more generalized than focal[82,83]; thus, the specification and sequencing of training is uncertain. Neither is it clear whether a core cognitive deficit has been remediated (or compensated) or whether the improvement only reflects a tangential correlate of the deficit.[80] Practice effects are also possible, although it is unlikely that NP tests administered on an annual basis are greatly subject to this bias.[44] Increased comfort and familiarity with test procedures,[80] especially computerized tests, could have positively biased CET neurocognitive and processing speed performance given the extensive computer-based training provided. However, the most robust neurocognitive effects (Wechsler Memory Scale and California Verbal Learning Test memory effects and the WAIS Digit Symbol) were not computerized tests. By design, processing speed was a training goal. Otherwise, some researchers might argue for the dismantling of a multidimensional psychosocial treatment in search of the therapeutic component. However, attempts to deconstruct the software exercises and group components of the similarly organized Ben-Yishay program demonstrated that the whole was clearly superior to the component parts.[84]

Although the goal of the study was to improve social and nonsocial cognition, some researchers might cite the relative absence of robust CET effects on traditional "real-world" outcomes. Relapse (or days hospitalized) was not a hypothesized outcome because most patients were many years past their last psychotic episode. Expected[27,85] and observed relapses (9 EST and 3 CET patients) were quite low. Patients were older and ill for longer periods than in our previous studies,[86-89] and many had found their "niche," desiring an improved quality of life more than a job or return to school. Furthermore, most patients received disability benefits and the associated health insurance. Coupled with a difficult local labor market and the work disincentives of disability programs, many patients feared a loss of benefits if they increased part-time work or secured full-time, minimum-wage employment. (Our program did not provide job finding, training, or placement but relied on the referral of interested patients to the local Office of Vocational Rehabilitation.) Nevertheless, CET gains in adjustment were observed, an encouraging outcome given the stable pretreatment status of patients and the efficacy of EST. The CET trend in employment (Table 5) is attributed to the greater number of CET patients who found volunteer positions (26% of CET and 8% of EST patients) rather than paid employment. The CET gain in Major Role Performance (Table 5) reflects the observation that 60% of CET patients vs 42% of EST patients equaled or exceeded their best premorbid or previous functioning. The 3-year follow-up should provide a better assessment of adjustment effects.

Finally, CET results cannot be generalized to all patients with schizophrenia. It was designed as a recovery-phase intervention for stable, non–substance-abusing ambulatory patients with an IQ of 80 or higher. Behavioral, compensatory approaches[17] might be preferable for the more severely impaired or intellectually compromised subpopulations of patients. Cognitive behavior therapy, PT, skills training, and family psychoeducation seem to be more appropriate for those in the subacute, stabilization phase.[38] Although we lack data for a cost-benefit analysis, programs that rely on small-group rehabilitation approaches should find that CET is cost-effective. Most patients (87%) highly endorsed their CET experience. The stable patient with rehabilitation potential is

more likely to functionally improve after extended cognitive rehabilitation. In the era of managed cost, even expert consensus opinion[90] tends to disenfranchise this substantial segment of the schizophrenia population.

In conclusion, the cognitive disabilities of schizophrenia do not need to be the persistent deficits described in numerous naturalistic, longitudinal studies.[91,92] Instead, many of these disabilities are capable of improvement after adequate exposure to cognitive rehabilitation.

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